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Does clinician preference affect the treatment of older women with operable breast cancer?

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Declaration

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Youth is full of sport, Age's breath is short,

Youth is nimble, Age is lame:

Youth is hot and bold, Age is weak and cold.

The Passionate Pilgrim by William Shakespeare (1564-1616)

The fewer the facts, the stronger the opinion.

Arnold H Glasgow (1905-1998)

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“An analysis of the decision-making preferences of older women with operable breast cancer in the UK” at 3rd Symposium on primary breast cancer in older women, 6th March 2015, Nottingham, UK.

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Abbreviations

ABS	Association of Breast Surgery
ADL	Activities of Daily Living
AI	Aromatase Inhibitor
ANC	Axillary Node Clearance
BCS	Breast Conserving Surgery
BCSS	Breast Cancer Specific Survival
CB	Clinical Benefit
CGA	Comprehensive Geriatric Assessment
CNS	Clinical Nurse Specialist
CR	Clinical Response
DCE	Discrete Choice Experiment
ER	Oestrogen Receptor
EUSOMA	European Society of Breast Cancer Specialists
HCP	Healthcare Professional
HER2	Human Epidermal Growth Factor Receptor 2
NCEI	National Cancer Equality Initiative
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Primary Endocrine Therapy
PFS	Progression Free Survival
PR	Partial Response
RCT	Randomised Controlled Trial

TAM	Tamoxifen
TNM	Tumour, Nodes, Metastases
TTP	Time to Progression
SD	Static Disease
SDM	Shared Decision-Making
SIOG	International Society of Geriatric Oncology
WLE	Wide Local Excision

Abstract

Background and Aims:

Primary endocrine therapy (PET) is a common alternative to surgery for frailer older women with operable, oestrogen sensitive breast cancer but may result in treatment failure, contributing to the poor outcomes seen in this age group. Criteria for patient selection for such treatment are lacking with no clear guidance and wide variance in clinician opinion about the appropriate use of the non-surgical option. There is debate about whether cancer specific and overall survival outcomes vary between treatment types with little high quality research published in the field. This mixed-methods study aimed to identify whether outcomes vary by treatment type and whether clinician preference contributes to the variation in treatment of older breast cancer patients in the UK and to explore some of the factors influencing clinician decision making.

Methods and Results:

This thesis used a range of methods to explore this issue including literature review and meta-analysis to assess published evidence of variance and its clinical impact, registry data analysis to assess the extent of the variance in current UK practice and whether this was significant when adjusted for case mix and then to explore the underlying reasons behind the variance using a combination of qualitative and questionnaire study of UK HCP in the field of breast care to determine why the variance exists.

Each of these components is summarised below:

A meta-analysis of data from six randomised controlled trials and 31 non-randomised studies demonstrated superior disease control and a likely survival benefit for surgery over PET in patients with predicted life expectancies of five years or more.

Analysis of cancer registry data on 17154 women over 70 with ER+ operable breast cancer between 2002 and 2010 demonstrated considerable variation in surgery rates at hospital level which persisted despite case mix adjustment.

Semi-structured qualitative interviews with 34 specialist healthcare professionals (HCPs) from 14 UK sites demonstrated a variety of factors HCPs consider when determining treatment. Opinion was divided regarding the best way to treat dementia patients and whether PET should be offered as a treatment option.

A questionnaire survey of Association of Breast Surgery members demonstrated that comorbidities were most important in determining treatment of older breast cancer patients. Opinion was divided

over the treatment of dementia patients. Only a quarter felt PET should be offered to all patients over 70 years.

A Discrete Choice Experiment contained within the questionnaire demonstrated five variables (age, co-morbidity, cognition, functional status and cancer size) were independently associated with treatment preference ($p < 0.05$) for surgery or PET.

Conclusions:

Meta-analysis of the published literature and registry data analysis corrected for case mix suggests that PET may result in inferior cancer specific and overall survival in older women. PET is however a valuable option in those with a short predicted life expectancy and case selection is therefore of critical importance in outcome optimisation. Analysis of registry data suggests that case mix does not fully explain treatment variation in older women with operable breast cancer which indicates that thresholds for selection vary widely and evidence based guidelines would be of value in standardising best practice. Clinicians vary in the factors they consider important in the decision making process and whether patients should be offered a choice of treatment themselves. This practice variance, coupled with the inferior outcomes associated with PET in poorly selected women could be a significant contributing factor to globally inferior breast cancer outcomes in older women. Clinical guidelines are urgently needed to address this variability.

Chapter 1: Introduction

1.1. Overview of breast cancer

1.1.1. Epidemiology

Breast cancer is the most common cancer in the UK [1], accounting for nearly a third of all new cancer diagnoses in women in England [2], with 42 489 new cases diagnosed in the UK in 2012 [1, 3]. The incidence of breast cancer is rising, and has increased by 90% between 1971 and 2010 [2], so that a woman now has a 1 in 8 chance of developing the disease over their lifetime [4]. Despite this rising incidence, mortality rates from breast cancer in England and Wales have fallen by 37% since 1971, with just over 10 144 deaths in 2013 [2, 5] (see figure 1.1, reproduced with data from the Cancer Research UK website [1]).

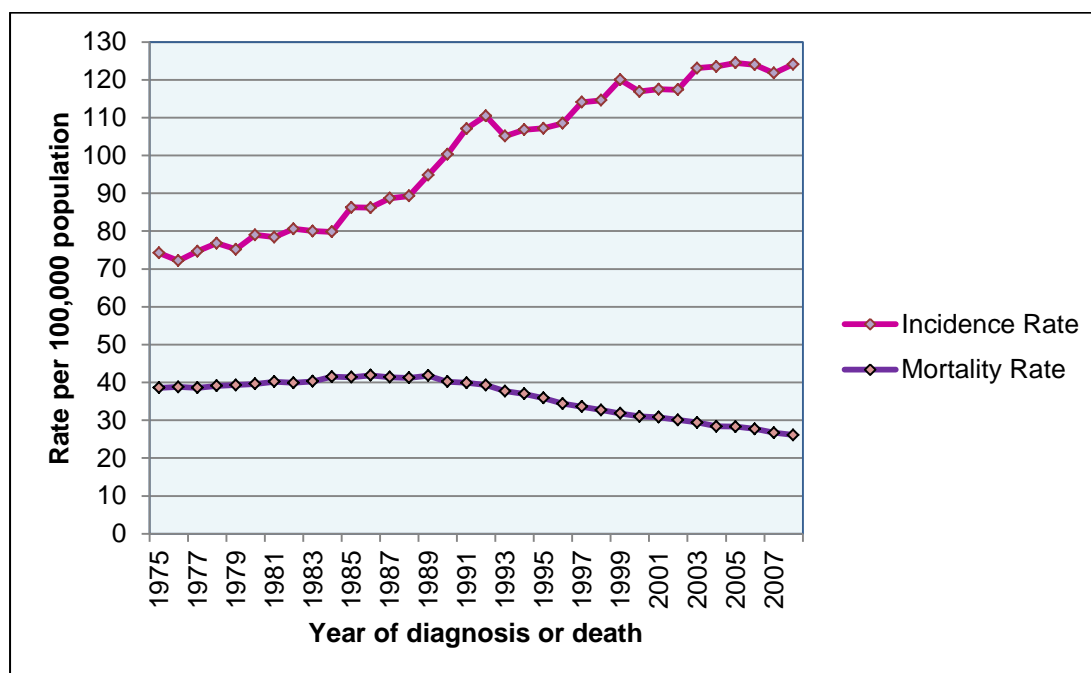


Figure 1.1: Age standardised breast cancer incidence and mortality rates in the UK 1975-2008 (reproduced from the Cancer Research UK website [1]).

1.1.2. Clinical presentation of breast cancer

1.1.2.1. Clinical features

Breast cancer may be symptomatic or asymptomatic at presentation. Around two thirds of patients are symptomatic at diagnosis, with the most common symptom being a painless breast lump in more than 80% of cases [6]. Other symptomatic presentations include:

- A palpable axillary mass (from involved lymph nodes);
- A change in size or shape of the breast;

- A change in nipple position, shape or becoming inverted;
- Skin changes with puckering, dimpling or *peau d'orange*;
- Nipple discharge;
- A rash or crusting over the nipple;
- Pain in the breast or axilla;
- Symptoms of metastatic disease which will vary depending on the site of spread, with common sites including the liver, bone and lungs. Around 4% of breast cancers will have signs or symptoms of metastases at the time of presentation [7].

The remaining one third of breast cancers in the UK are diagnosed among asymptomatic patients via the NHS breast screening programme.

1.1.2.2. Diagnosis

Symptomatic patients in the UK are referred from primary care into designated breast clinics within local hospitals [8]. Asymptomatic patients are referred from the NHS Breast Screening Programme into these same one-stop breast clinics. Diagnosis within these clinics are accomplished utilising a method of triple assessment [9]; that is:

- Clinical examination;
- Imaging (with mammography and/or ultrasound);
- Core biopsy and/or fine needle aspiration cytology.

Ultrasound assessment is particularly useful in women below the age of 35 years as they have denser breast tissue which makes mammography less sensitive [10].

During the initial assessment, patients with suspicious breast lesions will also undergo clinical and ultrasound assessment of the ipsilateral axilla to identify any abnormal lymph nodes – if found, these are subjected to image-guided core biopsy.

1.1.2.3. Staging

Breast cancer is staged according to three factors, the size of the tumour, the presence or absence of tumour cells within the local lymph nodes, and the spread of tumour cells to other parts of the body (metastases).

Staging provides information about the disease extent, prognosis and can guide clinicians on appropriate treatment.

Several staging systems are in operation, with the most common in the UK being the TNM (tumour, node, metastases) staging system [11] (see table 1.1).

Primary Tumour (T)		Lymph node status (L)		Metastases (M)	
T_x	Primary tumour cannot be assessed	N_x	Unable to assess lymph node status.	M_x	Unable to assess for metastases.
T₀	No evidence of primary tumour	N₀	No evidence of lymph node spread.	M₀	No evidence of metastasis.
T_{is}	Carcinoma in situ	N₁	Metastasis in moveable axillary lymph nodes.	M₁	Metastatic spread.
T₁	Tumour ≤2cm in greatest dimension	N₂	Metastasis in fixed axillary lymph nodes +/- internal mammary nodes.		
T₂	Tumour ≥2cm, <5cm.	N₃	Metastasis in supraclavicular lymph nodes +/- axillary/internal mammary nodes.		
T₃	Tumour >5cm.				
T₄	Tumour of any size with direct invasion into chest wall (T4a) or skin (T4b) or inflammatory cancer (c)				

Table 1.1: Abridged TNM staging system for breast cancer, 7th Edition [11].

1.1.3. Treatment options for operable breast cancer

Breast cancer management is complex and dependent on many factors. A detailed description of breast cancer management in its entirety is outside the scope of this thesis, however a brief overview of breast cancer management is presented below.

1.1.3.1. Surgery

Surgery is the cornerstone of treatment for women with early breast cancer and is usually the first line treatment option [9]. The primary aim of surgical management is local disease control (i.e. removal of the tumour) and secondarily to provide accurate assessment of disease stage to guide further therapies.

Surgery to the breast

Surgery to the breast usually involves either breast conservation, e.g. wide local excision (WLE) or mastectomy. Breast conservation surgery (BCS) is accompanied by post-operative radiotherapy of the remaining breast tissue. A meta-analysis of the long-term results of six randomised controlled trials has demonstrated that patients treated with BCS and radiotherapy have equivalent survival to those treated with mastectomy, however the former is associated with slightly higher local recurrence rates [12]. The type of surgery undertaken may depend on several factors:

- Tumour characteristics, particularly size relative to breast size, multi-centricity and the presence of inflammatory change.
- Patient breast size and shape and the location of the tumour in the breast.
- Patient preference.

UK Clinical guidance also recommends that patients undergoing mastectomy should also be offered the choice of some form of reconstructive surgery [9, 13]. Some patients may be offered more complex conservation surgery options where breast reshaping is also performed to permit enhanced cosmesis whilst permitting larger volume resections (oncoplastic surgery/therapeutic mammoplasty techniques).

Surgery to the axilla

Surgery to the breast is usually accompanied by some form of axillary surgery. The axillary lymph nodes are usually the initial site of spread for breast cancer and contain metastatic deposits in around 40% of patients at diagnosis [14-16]. The presence and extent of axillary lymph node involvement is the most powerful predictor of recurrence and survival [17]; and decreases a patient's 5-year survival by approximately 28–40% [14, 18]. The secondary aim of axillary surgery is loco-regional control which has been shown to also improve survival [19-23].

If pre-operative imaging assessment confirms metastatic spread to the lymph nodes, the patient will be offered an axillary lymph node clearance at the same time as their initial breast surgery – this removes all the axillary contents, including all lymph nodes in this region. If there is no clinical or radiological evidence of lymph node involvement pre-operatively, the patient will undergo limited axillary sampling, usually via a sentinel lymph node biopsy technique, at time of initial surgery. This is less extensive surgery than full clearance and is associated with a reduced incidence of complications (for example, arm lymphoedema [24]). Axillary SLNB attempts to identify the sentinel lymph node – i.e. the first node to receive lymph from the area containing the primary tumour.

There are several methods that have been used to identify the sentinel node:

- Blue dye [25].
- Radioactive isotope injection with lymphoscintigraphy and intra-operative gamma-probe localisation [26-28].
- Iron oxide injection with an intra-operative magnetometer [29].
- A range of other localisation techniques are also available (iodine seeds [30], fluorescent dyes [31] etc)

If SLNB identifies metastatic deposits in the nodes, the patient will usually undergo axillary clearance as a second procedure; if negative, no further axillary surgery is required. This pathway has recently been called into question by the controversial but practice changing Z0011 trial which suggested that omission of clearance in low risk disease where the axilla will be irradiated as part of tangential RT fields is associated with equivalent survival and local control to standard care [32]. Protocols are currently undergoing review as further research is carried out to validate these findings.

1.1.3.2. Adjuvant therapies

Adjuvant therapies aim to reduce the risk of breast cancer recurrence in those patients with early breast cancer who undergo potentially curative surgery.

There are four main types:

- Radiotherapy;
- Chemotherapy;
- Endocrine Therapy;
- Biological Therapy.

Not every patient is suitable for or requires every type of adjuvant therapy and decisions are made on the basis of many factors, including:

- The type of surgery undertaken;
- The stage of the cancer;
- The biology of the cancer, for example the hormone receptor and HER-2 status;
- The calculated prognosis, for example, using the Nottingham Prognostic Index or more recently more sophisticated scoring algorithms such as PREDICT and Adjuvant OnLine;
- More complex biological prognostic scores may also be of value in borderline cases where chemotherapy benefit may be less certain. These include measuring the tumour

proliferation index (Ki67 score) or using a commercial multigene array such as Oncotype DX [33], MammaPrint [34], etc.

- The age, fitness and wishes of the patient.

Radiotherapy

Radiotherapy to the breast is necessary following breast-conservation surgery [9, 35] as it significantly reduces the rate of local disease recurrence [36], making it as effective as mastectomy [36].

Patients who undergo mastectomy may be offered adjuvant radiotherapy to the chest wall and regional lymph nodes if they are at high risk of loco-regional recurrence. Tumour characteristics with an increased risk of loco-regional recurrence include [9]:

- Large tumour size;
- Axillary lymph node involvement;
- Extensive lympho-vascular invasion;
- Positive resection margins.

Post-mastectomy radiotherapy reduces the risk of breast cancer recurrence by around two thirds and consequently reduces mortality [37-40]. The indications for post mastectomy radiotherapy may have slightly broadened recently since the publication of the latest overview from the EBCTCG which showed both overall survival, LR and DFS advantage in a wider range of scenarios [41].

Endocrine therapy

Some breast cancers express the oestrogen receptor (ER) on the surface of their nuclear membrane. These cancers are stimulated to proliferate in the presence of oestrogen. ER positivity increases with age [42, 43].

- A large American database of 50,828 patients with invasive breast cancer demonstrated 83% ER positivity in 55-64 year olds, compared to 91% positivity in those aged 85 years or older [44].
- A Canadian cohort of 1174 women found 70.4% ER positivity in women age 50-69 years and 79.4% in those aged 70 years or older [45].

- In the UK, of the 14,330 women diagnosed with breast cancer in 2006 with known ER status, patients younger than 50 years were ER positive in 77%, compared with 87% in those aged 50-70 years [46].

Endocrine therapies are used in patients with ER positive breast cancer and work to reduce the effect of oestrogen on breast cancer cells. The type of endocrine therapy used depends on the menopausal status of the patient [47], examples include:

- Tamoxifen, which is a selective oestrogen receptor modulator, prevents oestrogen from binding to the ER and can be used in both pre- and post-menopausal women. Tamoxifen has been shown to improve survival by 31% in women with ER positive breast cancer after 5 years treatment [48] and longer durations of therapy (up to 10 years) may have even greater benefit [49].
- Aromatase inhibitors (AIs), such as anastrozole, letrozole and exemestane, work by inhibiting the synthesis of oestrogen (via the enzyme aromatase) and are used in post-menopausal women. AIs have been shown to be more effective than tamoxifen at improving disease-free survival and time to recurrence in the adjuvant setting in post-menopausal women [50, 51].
- In pre-menopausal women, ovarian ablation (by surgery or irradiation) or ovarian suppression (e.g. using a luteinising-hormone-releasing-hormone inhibitor) has a similar effect as tamoxifen as the ovaries are the main source of oestrogen production in this group [48]. Adding ovarian suppression to tamoxifen has been shown to improve disease outcomes for premenopausal women who are at sufficient risk of recurrence to warrant chemotherapy [52].

Chemotherapy

Chemotherapy reduces the risk of recurrence and death in women with early stage breast cancer [48]. A meta-analysis of randomised controlled trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that the survival benefit is highly dependent on age at diagnosis [48] and a Cochrane review [53] demonstrated both overall and disease-free survival with the use of taxanes. NICE therefore recommends that a docetaxel chemotherapy regimen should be offered to patients with lymph-node positive breast cancer [9].

Due to the aggressive nature of chemotherapy treatment, with side-effects including lethargy, nausea and vomiting, alopecia and infertility (in premenopausal women), it is reserved for treating

women with significant risk of recurrence or among those with oestrogen receptor (ER) negative tumours.

Women over the age of 70 years have been under-represented in studies and clinical trials focusing on chemotherapy benefit; however there are data to suggest that fitter, less frail, older women should be offered the same treatment as younger women [54, 55].

Biological agents

Human Epidermal Growth Factor Receptor 2 (HER-2), also known as Neu, ErbB-2, CD340 or p185, is a cell-surface protein that is over-expressed in approximately 20% of breast cancers [56]. Over-expression, or amplification, of HER-2 is associated with increased recurrence and poorer prognosis [57].

Trastuzumab (Herceptin™) is a monoclonal antibody that is used to treat breast cancers that over-express the HER-2 receptor and has been shown to significantly reduce the risk of recurrence by up to 50% in these women [58]. The range of biologically targeted agents with evidence of benefit in breast cancer is rapidly evolving and well beyond the scope of this review but the most mechanistically interesting are agents such as TDM1 which is a HER-2 directed delivery mechanism (antibody) which permits precise targeting of the chemotherapy agent emtansine directly to HER-2 positive breast cancer cells [59]. Whether state funded health care systems will be able to afford these agents may be a major factor in limiting their use.

1.1.3.3. Neo-adjuvant therapies

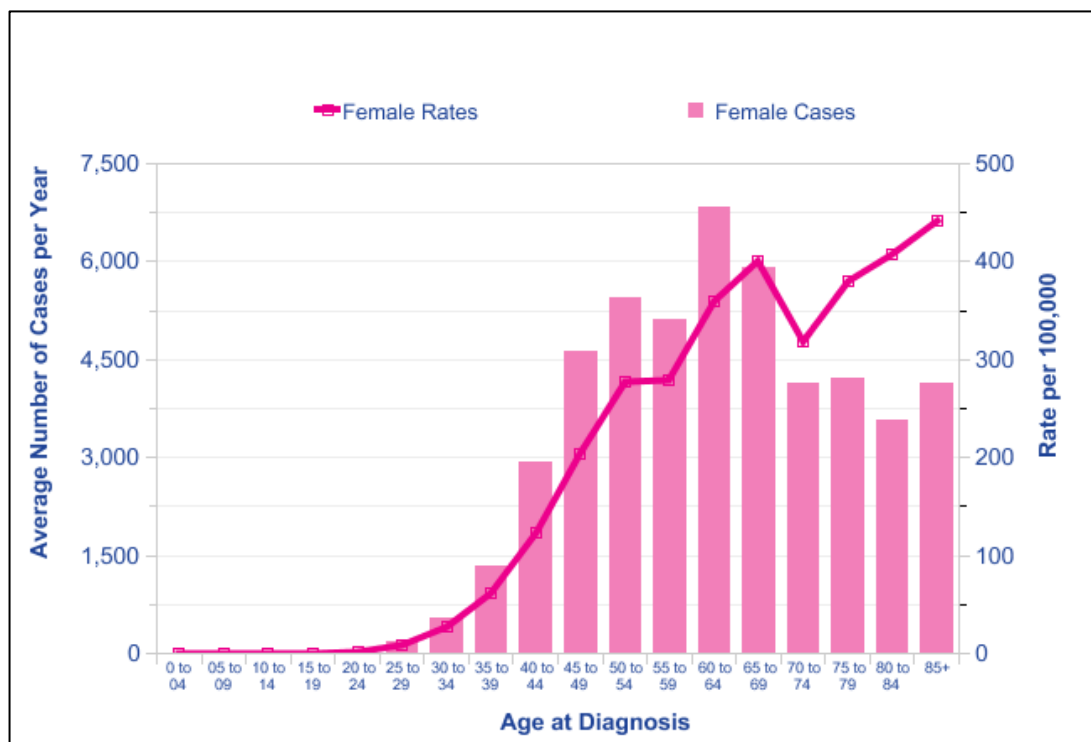
Neo-adjuvant therapy, also called primary or preoperative treatment, is used before surgery to down-stage large or locally-advanced tumours in order to allow surgical removal or enable breast conservation. Endocrine therapy, chemotherapy and trastuzumab are all used in the neo-adjuvant setting to shrink the primary tumour prior to definitive surgery [60].

1.2. Breast cancer in older women

This thesis focusses on the treatment variation in older women with operable breast cancer. Within the literature various age cut-offs are used to define “older” or “elderly” women, including those aged 65, 70 and 80 years or over. For the purposes of this thesis, “older women” will be used to describe those aged 70 years or over, unless otherwise stated, as this was the most consistently used age cut-off.

1.2.1. Rising incidence of breast cancer in older women

Age has been shown to be the strongest risk factor for the development of breast cancer after female sex [61] and as such, the incidence of breast cancer, like most cancers [62, 63], has a strong positive correlation with increasing age [64] (see figure 1.2, reproduced with data from the Cancer Research UK website [1]). Worldwide, around one third of breast cancers occur in those women over 65 years old, with this percentage increasing to over 40% in more developed countries [65, 66]. There has also been a rise in the number of older women attending breast screening, with a resultant increase in the diagnosis of small cancers in this group [67].



Figure

1.2: Number of breast cancer cases by age at diagnosis (reproduced with data from the Cancer Research UK website [1]).

There are three proposed mechanisms that are thought to increase the incidence of cancer in older patients [63]:

1. Older patients have an increased duration of exposure to carcinogenic factors.
2. Ageing cells and tissues are thought to be more susceptible to carcinogens than younger ones.
3. Ageing produces changes in the body environment that favour tumour development (such as chronic inflammation and reduced sensitivity to insulin).

1.2.2. Variability in the treatment of older women with breast cancer

In the UK, the use of PET to treat older women is common and non-surgical management increases with increasing age [68], with studies demonstrating that 40% of women over the age of 70 years [69, 70] and 55% of women over the age of 80 years [71] are treated in this way. Despite this, there is wide variation in practice in the UK, with some regions having up to 40% non-operative treatment rates for older women with breast cancer, compared to other areas where the rate is only 10% [72] – see figure 1.3. The result is that there may be some women in the low surgery rate regions who are inappropriately denied surgery, whereas in the high surgery areas women may undergo surgery for little or no benefit.

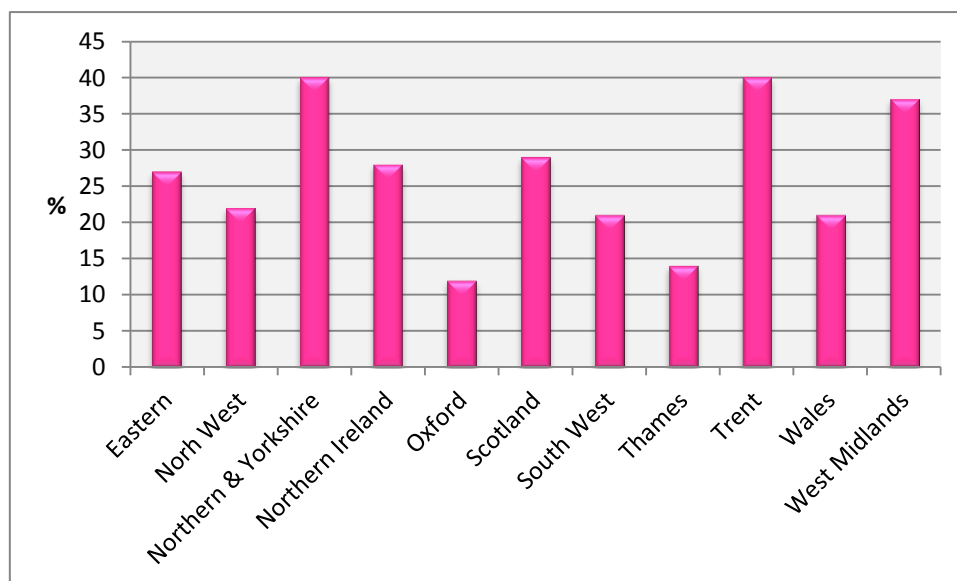


Figure 1.3: Percentage of women over 70 treated non-operatively by UK region (reproduced with data taken from the BCCOM Audit Year 3 [73]).

Outside of the UK, non-surgical treatment of older women with operable breast cancer is far less common:

- A study from Eire found 26% of women over 70 years were treated with PET [74].

- In France, Garbay and colleagues reported that only 9% of older women did not receive surgery [75].
- In Italy, the percentage of women who are treated non-surgically falls to 3% according to a study by Crivellari [76].
- Van Dalsen in the Netherlands showed that 16% of older women were treated without surgery [77].
- In Sweden, the Geneva Cancer registry recorded that 32% of women over the age of 80 years were treated with tamoxifen only [78].
- A large audit across Australia and New Zealand demonstrated that 97% of women were treated with some form of surgery [79].
- A large population study from the US found that 99.5% of women aged 75-84 and 99.3% of those over 85 were treated surgically [44].

1.2.3. Why variation in treatment of older breast cancer patients is an important issue

1.2.3.1. An ageing population

The developed countries of the world, including western Europe, the USA, Canada, Australia, New Zealand and Japan, have increased their populations' life expectancy by around 30 years during the 20th Century [80]. The greatest survival gains are in the older age groups, which represent the most rapidly increasing population groups in developed nations [81]. The result is an ageing population, and the overall health status of this group is also improving [80, 82]. Improved disease prevention with better control of chronic diseases, mean older people are living longer even in the presence of chronic health problems. Despite this, there is wide variation in the health status of this age group, with some 75 year olds who are fit, healthy and active, whilst others are frail, with multiple co-morbidities, necessitating assisted living.

1.2.3.2. Survival in older women with breast cancer

Breast cancer outcomes have been shown to be inferior in older women compared to those in younger women [83-86]. In fact, recent reports demonstrate that patients over the age of 70 are the only group of cancer patients where the mortality from cancer is not falling and may even be rising [83].

In addition, evidence suggests that cancer outcomes in those aged over 75 are poorer in the UK compared to other comparable countries [87] and this inequality is a major priority for the NHS [87].

Despite this, however, the clinical significance of breast cancer is proportionally less in older women as breast cancer specific mortality is overtaken by other-cause mortality; with breast cancer causing only approximately 23% of deaths in women with breast cancer in their mid-80s, compared to 73% of deaths in patients in their early 50s [44]. That being said, there is convincing evidence that women over the age of 80 have a higher risk of dying of their breast cancer than women in their 70s [84], a phenomenon that is thought may be due, in part, to sub-optimal treatment [88].

1.2.3.3. Evidence of “sub-optimal” treatment in older women with breast cancer

Several studies have demonstrated the deviation from standard treatment protocols in the older breast cancer population compared to their younger counterparts:

- In a UK population study that included 14048 patients, Ali and colleagues [89] showed that a lower percentage of older women (80+) received surgical treatment (42%), radiotherapy (26%) and chemotherapy (1%) than their younger counterparts (50-69 years old: 96%, 74% and 29% respectively).
- Another UK registry study showed that women aged 80 or above with operable (stage 1-3a) breast cancer were 43 times less likely to receive primary surgery than patients aged 65-69 years [68].
- Bastiaannet and colleagues [90] demonstrated similar findings in the Netherlands in their large population-based study including 127,805 patients. Surgical treatment was omitted significantly more in the older age groups (only 41.2% of 90+ year olds) than in the 65-69 year old cohort (98.8%). Their use of hormone monotherapy, or PET, increased with increasing age, with only 2.0% of 65-69 year olds treated this way, compared with 47.3% of 90+ year olds. The use of adjuvant systemic therapy also followed an age-related trend, with 70.7% of 65-69 year olds receiving some form of systemic adjuvant therapy, compared to 53.3% of 90+ year olds [90].
- A German cohort of 1922 patients again showed a discrepancy in treatment for older women; with less adherence to guidelines for radiotherapy and chemotherapy in the older age groups (omission of radiotherapy and chemotherapy respectively in the 80+ years: 60% and 98% vs. <70 years: 9% and 54%). The authors demonstrated a significant impact on both overall and disease-free survival as a consequence of under-treatment with radiotherapy [91].

- A Canadian study including 1174 patients showed that women 70+ were much less likely to receive definitive loco-regional treatment than those aged 50-69 years (48.7% vs. 83.5%, $p < 0.0001$) [45].
- These results were again confirmed by an analysis of patients with early stage breast cancer in the Netherlands [84], comparing those of 75 years or more with patients younger than 65 years. Patients in the older group were more likely not to receive any surgical treatment (21.5 vs. 0.5%; $p < 0.001$) or any axillary surgery (25.7 vs. 1.6%; $p < 0.001$), and were less likely to receive radiotherapy (25.1 vs. 67.8%; $p < 0.001$) or chemotherapy (49.0 vs. 0.4%; $p < 0.001$). In addition, they demonstrated that under-treatment had a significantly worse impact on 5-year survival. In the younger cohort, overall survival was significantly lower in those who received non-conventional guidelines (HR 1.68, 95% CI: 1.46-1.94, $p < 0.001$) and this was even more pronounced in the older group (HR 2.56, 2.31-2.84, $p < 0.001$).

Some of this treatment variation may be explained by levels of co-morbidity and frailty, where older women are deemed “unfit” to undergo the more intensive therapies. However, some studies have shown that increased age is the strongest predictor of lesser treatment [92].

1.2.3.4. A healthcare inequality

The *NHS Constitution* makes clear that a core duty of the NHS is to promote equality [93]:

“The NHS provides a comprehensive service, available to all irrespective of gender, race, disability, age, sexual orientation, religion or belief. It has a duty to each and every individual that it serves and must respect their human rights. At the same time, it has a wider social duty to promote equality through the services it provides and to pay particular attention to groups or sections of society where improvements in health and life expectancy are not keeping pace with the rest of the population.”

As such, the Department of Health has deemed the variation in outcomes and treatment of older cancer patients a “healthcare inequality” [94] and the National Cancer Equality Initiative (NCEI) and Cancer Reform Strategy were created with the aim of tackling the inequalities in cancer, including those due to age [94, 95].

The Cancer Reform Strategy states that the only acceptable criteria for not giving clinically appropriate treatment should be poor patient health or patients themselves choosing not to receive a particular treatment [95]. The Department of Health stresses that whilst it may be appropriate for some older patients to receive less intensive cancer treatments due to increasing comorbidity and frailty, chronological age itself should not be a determining factor [87].

1.2.4. Breast cancer biology in older breast cancer patients

The biology of breast cancer tends to differ in older women from that in young women, with older patients tending to develop tumours with more favourable biology [90]. Older patients tend to have tumours with higher rates of ER positivity [44, 96, 97], lower rates of HER-2 receptor expression [44, 96] and lower grades and proliferative indices [44, 96].

However, older women are more likely to be diagnosed with more advanced disease [88]; the size of the primary tumour is larger [44, 65, 70, 88, 98, 99] and there are higher rates of locally advanced [65, 86] and metastatic disease [69, 100]. Several factors may account for these negative features, including the discontinuation of routine breast screening, reduced breast cancer awareness [101, 102] and lower rates of regular self examination [103] amongst the older female population.

1.2.5. Physiological effects of ageing

Senescence is the term for the physiological changes that occur due to the ageing process. These changes are substantial and affect all bodily systems. This has a significant impact on the way older women tolerate treatments for breast cancer and may influence treatment choice. These physiological changes are summarised in table 1.2.

1.2.5.1. Association between co-morbidity and ageing

Increasing age is associated with higher rates of comorbidity [105], which potentially reduce the survival advantage of more aggressive breast cancer therapies [106] as other cause mortality increases [107]. Of particular importance are the diseases that may render anaesthesia hazardous, such as cardiac, respiratory and cerebrovascular disorders – all of which are more common in older patients [108, 109]. Breast-cancer patients with three or more significant co-morbidities have a 20-fold higher rate of non-breast cancer deaths [110] and so the presence of comorbidities in older women is associated with less extensive treatment and poorer prognosis [105].

Organ/System	Overall Changes	Pathophysiology	Clinical Impact
Cardiac	Reduced cardiac reserve	<ul style="list-style-type: none"> ↓Number of myocytes. ↓Number of pacemaker cells. ↓Arterial compliance. ↓Exercise levels. ↓Maximal heart rate. ↑Afterload. Stiffening of myocardium, reducing diastolic filling. 	<ul style="list-style-type: none"> ↓Tolerance to cardiac stress. ↓Tolerance to rhythm disturbance. ↑Risk of anaesthesia.
Respiratory	Reduced respiratory reserve	<ul style="list-style-type: none"> ↓Vital capacity. ↓Lung elasticity. ↓Strength/endurance of respiratory muscles. ↓Mucous production. ↓Ciliary function. ↓Oxygen diffusion capacity. 	<ul style="list-style-type: none"> ↓Respiratory reserve during exertion. ↑Risk chest infection. ↑Risk of anaesthesia.
Renal	Reduced renal reserve	<ul style="list-style-type: none"> ↓Number of nephrons by 50% by age 70. ↓Renal blood flow by 50%. ↓Creatinine clearance by 30%. ↓Ability to conserve water. ↓Sensitivity to thirst and therefore poor self-regulation. ↓Ability to conserve sodium and excrete hydrogen. 	<ul style="list-style-type: none"> ↓Ability to maintain fluid and electrolyte balance under stress. ↑Risk of dehydration and fluid overload. ↑Risk of anaesthesia.
Sensory-motor and CNS	Reduced cognitive and motor functions	<ul style="list-style-type: none"> 40% incidence significant cognitive impairment by age 90. Reduced balance and agility. Reduced muscle strength. 	<ul style="list-style-type: none"> Risk of poor convalescence from therapy, falls, worsening of global function caused by anaesthesia.

Table 1.2: Physiological effects of Ageing (reproduced from [104]).

Comprehensive Geriatric Assessment (CGA)

Several attempts have been made to quantify the impact of co-morbidities and frailty on expected life expectancy. These Comprehensive Geriatric Assessments [111-113] are detailed but time-consuming assessments that require the clinician to undergo specialist training to administer. There is no standard method for CGA but it should include measures of functional status, comorbidity, nutritional status, drug therapy, socioeconomic issues and the presence of geriatric syndromes.

Other less complex tools exist that may be used to assess patient in terms of their co-morbidity burden, functional status or levels of frailty:

- There are number of scoring systems for comorbidity in existence, with the Charlson Index (CCI) being one of the most commonly used and widely validated [114-117]. Others include the Kaplan-Feinstein Index (KFI) [118] and the Adult Comorbidity Evaluation-27 (ACE-27) [119, 120].
- The Activities of Daily Living Score (ADL) [121] and Instrumental Activities of Daily Living Score (IADL) [122] are measures of functional status.
- The Groningen Frailty Index (GFI) is an example of a specific measure of frailty, although other tools, such as the Timed Up and Go Test [123] are often used as surrogate markers for frailty.

In addition, Adjuvant! On-Line is a web-based tool that is used to predict the prognosis of individual patients and how this is may be altered by different adjuvant therapies [124]. The Adjuvant! Software accounts for the impact of co-morbidity but the categories are broad and vague, and is only of use in patients who have already undergone their primary surgery [125]. However it is not age specific.

1.3. Primary endocrine therapy (PET) as a treatment option for older women with operable breast cancer

Primary Endocrine Therapy (PET) is the use of “anti-oestrogens” as the sole therapy for early stage, operable breast cancer. It is an alternative to the standard treatment of operative intervention combined with adjuvant therapy, and was first proposed as an alternative to surgery in older patients in the 1980s [126].

Current guidelines from the National Institute for Health and Care Excellence (NICE) state that PET should only be used where there are “significant comorbidities that precludes surgery” [9] and recommendations from the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) suggest that PET should only be offered to patients with a “short estimated life expectancy (<2-3 years), who are considered unfit for surgery... or who refuse surgery” [127]. However, neither specify which comorbidities may preclude surgery or what constitutes being unfit for surgery. As such it is left to the treating clinician to decide which breast cancer treatments a patient should be offered. This may be a causative factor in the considerable variability in treatment practice of older women with breast cancer across the UK, where rates of non-surgical management range from 12-40% depending on region [73]. Indeed, a questionnaire survey found that whilst the majority of UK surgeons use PET to treat older women who are unfit for surgery, the percentage of older patients they treat in this way still varies considerably (<10-70%) [128].

1.3.1. Biology of PET in breast cancer

1.3.1.1. Oestrogens

Oestrogens are steroid hormones and are the primary female sex hormones. There are three main, naturally occurring oestrogens:

- Oestrone (E1).
- Oestradiol (E2).
- Oestriol (E3).

Oestrogens are responsible for the development of secondary sexual characteristics, such as breast development and maturation, and regulation of the menstrual cycle. During adulthood, oestrogen is also responsible for cyclical epithelial proliferation within the breast, as well as epithelial growth and proliferation during pregnancy.

Oestrogen production

In pre-menopausal women, oestrogen production is mainly by the ovaries, following stimulation by Follicular Stimulating Hormone (FSH). However, oestrogens are produced in smaller amounts by the liver, adrenal glands, breasts and adipose tissue, mainly by a process of aromatisation of androstenedione [129-132].

Oestrogen receptors (ER)

The actions of oestrogens are mediated by oestrogen receptors (ER). These are a group of intracellular proteins that are activated by oestradiol [133], and form part of the nuclear hormone receptor family. Oestrogen, as a steroid hormone, is lipophilic and so passes through the cellular and nuclear membranes by a process of diffusion [134]. Inside the nuclei, oestrogen binds with ERs with high affinity and high specificity [134].

Once activated, ERs are able to bind to DNA, forming the oestrogen receptor response element (ERE), which regulates gene activity in a process called gene transcription (see figure 1.4). The resulting protein products act as growth factors, their receptors and signalling molecules which promote cellular proliferation [135, 136].

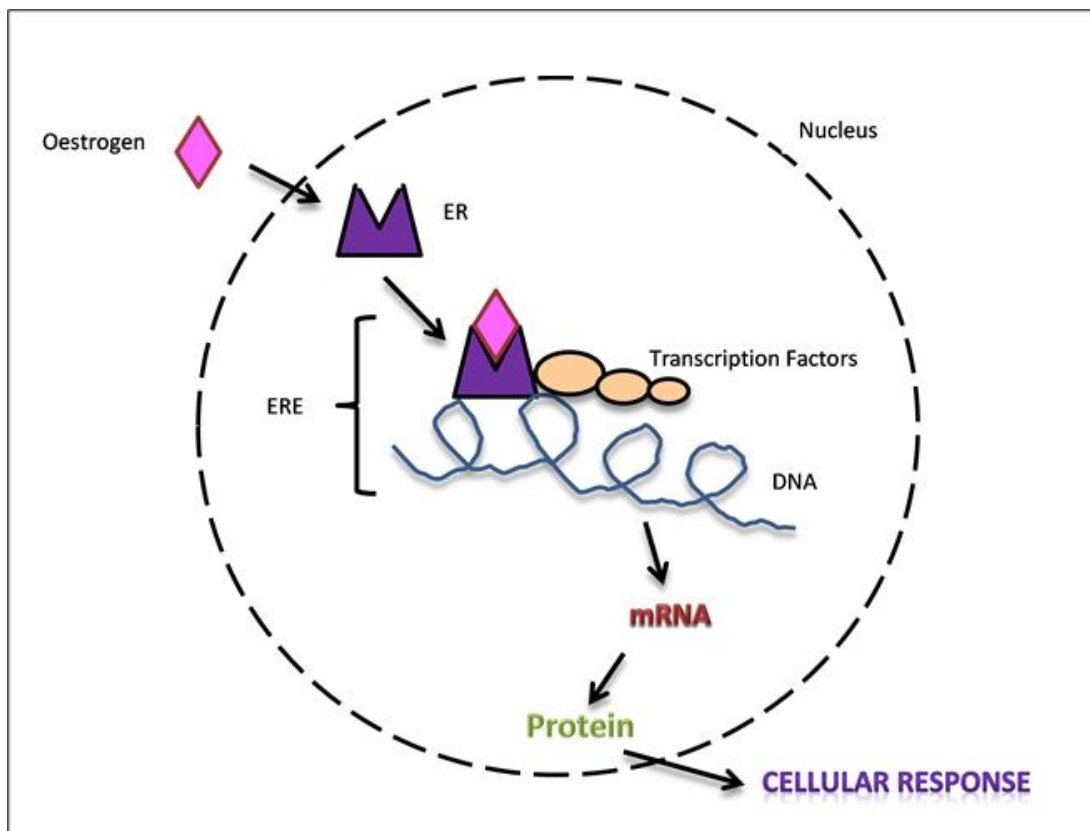


Figure 1.4: Intracellular Oestrogen Pathway (modified from [137]).

There is also evidence to suggest that ERs located at the cell membrane may provide another mechanism for the growth-promoting effects of oestrogen, by activating other growth factor receptors, such as epidermal growth factor receptor (EGFR) family, for example HER-2 [138, 139].

Oestrogen function in breast cancer

ER expression by breast cancer cells is variable, but expression increases with age [42, 43]. Women aged less than 40, have ER positive tumours in approximately 60% of cases [140], compared to women aged 85 years or older where the percentage of ER positivity increases to around 90% [44].

Tumours that express the ER are stimulated to grow under the influence of oestrogen [141]. The mechanism behind this action has been examined in laboratory settings in terms of the cell; in ER positive cancers, oestrogens increase the number of G_0/G_1 cells entering into the cell cycle, hence promoting mitosis and, therefore, proliferation [142, 143].

Antagonism of the ER inhibits cell proliferation and may cause cell death [144], by blocking them in the Gap phase (G_0/G_1) of the cell cycle. This forms the basis for the mechanism of action of primary endocrine therapy (PET).

1.3.2. History of PET

Endocrine therapies have been used as a treatment for breast cancer for over a century, with the first bilateral oophorectomies being performed in 1872 [145, 146]. However it wasn't until ten years later that the relationship between breast cancer and ovarian function was first recognised, when Thomas Nunn reported a case of breast cancer that regressed at the commencement of menopause [147]. Seven years later, surgical oophorectomy was proposed as a treatment for breast cancer [148]. It was on June 15th 1895 when a Glaswegian surgeon, George Beatson, first performed a bilateral oophorectomy to treat a woman with breast cancer, successfully resulting in a complete remission, with the patient surviving for 4 years after surgery [149, 150].

The exact benefits of ovarian ablation remained unclear until several randomised controlled trials were performed in the 1960s and 70s and the Early Breast Cancer Trialists Collaborative Group (EBCTCG) published their meta-analysis demonstrating improved disease-free and overall survival in pre-menopausal women treated in this way [151, 152].

Further developments in the field of endocrine therapy for breast cancer included adrenalectomy, hypophysectomy [153] and the introduction of anti-oestrogens, most notably tamoxifen and the

Aromatase Inhibitors. These drugs are still widely used today for the treatment of breast cancer in the adjuvant, neo-adjuvant and primary settings.

1.3.3. Anti-oestrogen Therapies

1.3.3.1. Tamoxifen

Mechanisms of action of tamoxifen

Tamoxifen is a selective oestrogen receptor modulator (SERM). It has a “mixed organ” effect, meaning that in some sites in the body, such as the breast epithelium, it acts as an oestrogen receptor antagonist, but in others (e.g. bone and endometrium) it acts as an agonist. Some of these effects are beneficial, such as its anti-breast cancer and anti-osteoporotic effects; however some are detrimental, leading to increased risks of endometrial cancer [154] and thromboembolism [155].

Tamoxifen is metabolised in the liver into its active metabolites, including 4-hydroxytamoxifen, which have a high affinity for binding with the ER. In the breast, 4-hydroxytamoxifen binds competitively to the ER and alters, or modulates, its formation – preventing the cellular events which occur as a result of the ERE complex. The resulting effect is inhibition of cellular proliferation (see figure 1.5), as the cell cycle is blocked in the early to mid G1 phase [156].

Discovery of tamoxifen

Tamoxifen was discovered in the early 1960s by scientists searching for a new contraceptive at ICI Pharmaceuticals Division in the UK [157] and the academic community worked to develop the drug as a new targeted breast cancer treatment during the 1970s [158].

Clinical evidence for tamoxifen

The first UK clinical study took place in 1971, with promising results in patients with advanced breast cancer [159]. A second clinical study led to further interest in the drug following a more definitive response [160].

The first trial to demonstrate any survival advantage for tamoxifen was published in 1983 [161], and this looked at patients with early breast cancer who were given tamoxifen in addition to chemotherapy. The problem with most of the early tamoxifen trials was that they didn’t select patients according to ER status and as such, didn’t show such a large or consistent benefit [162]. It wasn’t until the late 1990s, when the Early Breast Cancer Trialists’ Collaborative Group finally demonstrated that tamoxifen resulted in a definite increase in survival with their large meta-analysis [163].

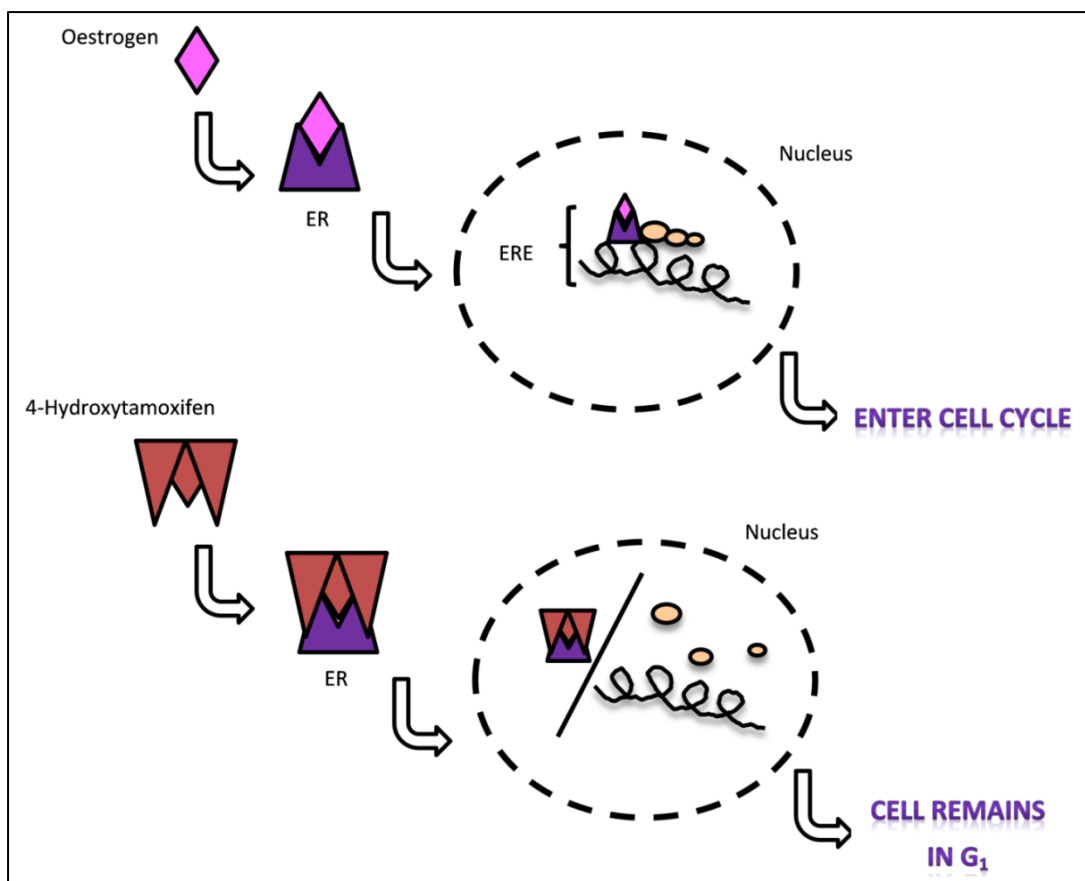


Figure 1.5: Mechanism of action of tamoxifen.

1.3.3.2. Aromatase Inhibitors (AIs)

Mechanism of action of AIs

In post-menopausal women, because of cessation of ovarian function, the main source of oestrogens is synthesis from adrenal androgens via the process of aromatisation in the skin, fat and muscle [153]. This process is catalysed by the enzyme aromatase which is the target molecule for aromatase inhibitors (AIs) – see figure 1.6. The result is suppression of oestrogen synthesis and as such, these drugs have none of the agonist activities of tamoxifen.

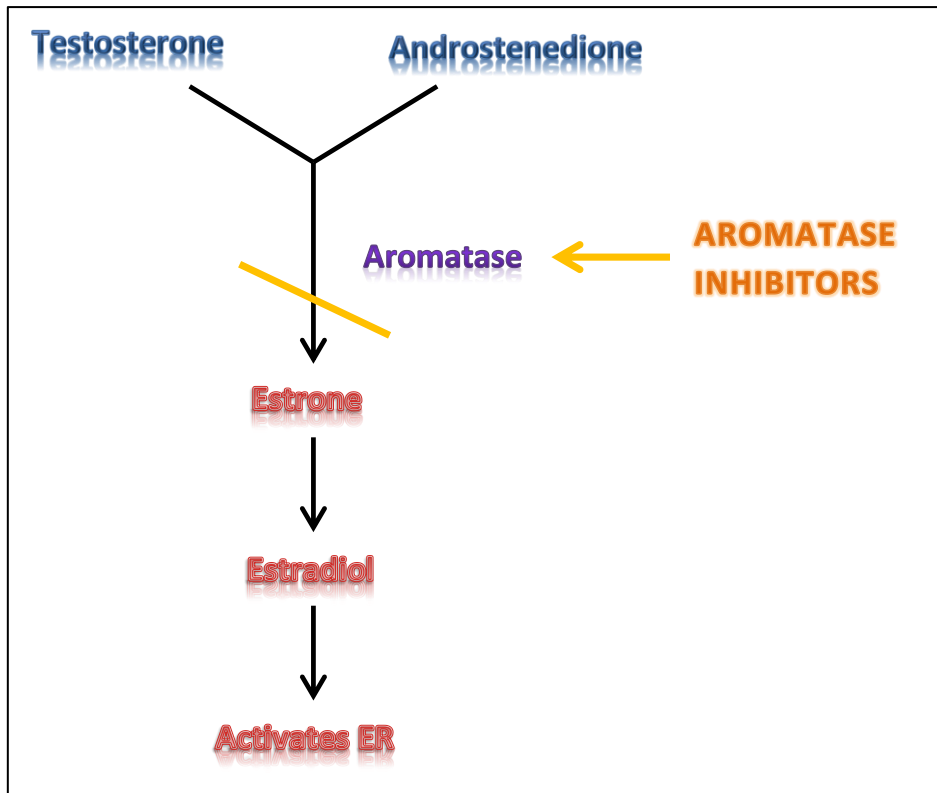


Figure 1.6: Mechanism of Action of Aromatase Inhibitors.

Type I AIs

Type I AIs are also known as aromatase inactivators – they have a steroidal structure and work by forming an irreversible bond with aromatase, thus permanently deactivating it [164]. Formestane and exemestane are both examples of type I AIs.

Type II AIs

Type II AIs are non-steroidal inhibitors and bind reversibly to a haem group in the activation site of the aromatase enzyme [153]. Anastrozole is an example of a type II AI.

Discovery of Aromatase

The isolation of both androgens and oestrogens in the 1930s allowed identification of the similarities between their biochemical structure and subsequent speculation that androgens might be converted into oestrogens [165-167]. However, the purification of aromatase did not occur until the 1980s [168-170].

Aminoglutethamide

Aminoglutethamine belongs to a group of drugs called adrenal steroid inhibitors and is also known as the first generation, non-selective aromatase inhibitor. It inhibits the conversion of cholesterol to 20- α -hydroxycholesterol and blocks the synthesis of steroid hormones, including cortisol, aldosterone and oestrogens [171]. Aminoglutethamide was used as an alternative to surgical adrenalectomy for the treatment of breast cancer in post-menopausal women [172]. During the 1970s, scientists began investigating the use of aminoglutethamide as a breast cancer treatment in clinical trials [173, 174]. Aminoglutethamine has since been used as a treatment for breast cancer among women who relapse following tamoxifen treatment [175]. Due to common side-effects, including inhibition of cortisol synthesis, drowsiness and skin rashes [176], this treatment is no longer commonly used and it has been replaced by newer generation AIs.

Formestane

Formestane is a second-generation, type I AI that was discovered in the 1970s and was shown to reduce oestrogen levels in rats [177]. The first clinical trial of Formestane for the treatment of women with breast cancer was undertaken during the 1980s [178]. Again, Formestane is no longer in clinical use as it has been replaced by newer generation AIs.

Third generation AIs

The third generation AIs were developed in the early 1990s and block oestrogen production without exerting effects on other steroid pathways. The three AIs commonly used today include:

- Anastrozole (Arimidex), a selective type II AI.
- Letrozole (Femara), also a selective type II AI.
- Exemestane (Aromasin), a selective type I AI.

1.3.4. Relative efficacy of anti-oestrogens

1.3.4.1. Metastatic setting

Several trials have evaluated the efficacy of the third generation AIs compared to tamoxifen for the treatment of metastatic breast cancer [179-185]. The European TARGET study showed no significant difference between overall response rate (ORR) and time to progression (TTP) [184]. However the American TARGET study did show a significantly improved clinical benefit rate and longer TTP using anastrozole [183]. Anastrozole was subsequently approved as the first-line therapy for metastatic

breast cancer [179]. The International Letrozole Breast Cancer Group demonstrated superior efficacy with letrozole over tamoxifen with respect to several outcomes including: TTP, time to treatment failure, ORR, clinical benefit and overall survival (OS) rates [180]. Additionally, the European Organization for Research and Treatment of Cancer compared exemestane with tamoxifen for metastatic breast cancer and favoured exemestane for ORR and progression-free survival (PFS) [181].

1.3.4.2. Adjuvant setting

Specific to the adjuvant setting, the third generation AIs have also been shown to be superior to tamoxifen. The first of these trials, the ATAC trial, comparing anastrozole, tamoxifen alone or in combination and that presented preliminary results at the San Antonio Breast Cancer Symposium in 2001, demonstrated superior activity of anastrozole over tamoxifen in terms of disease free survival but little significant benefit in terms of overall survival [186]. These results were confirmed in the 5 and 10-year follow-up reports [51, 187] and by others since including the Italian Tamoxifen and Anastrozole Trial [188] and the Austrian Breast Cancer Study Group and Arimidex-Nolvadex Trials (Pooled Analysis) [189], both of which compared anastrozole to tamoxifen; the Breast International Group 1-98 Trial assessed letrozole versus tamoxifen monotherapy and also sequenced treatment [190]; and the Intergroup Exemestane Study compared tamoxifen alone for five years versus switching to exemestane after 2-3 years on tamoxifen [191]. All showed DFS advantage to the AI containing regimes over tamoxifen alone.

There is also now good quality evidence that 10 years of adjuvant tamoxifen has superior efficacy to 5 years of therapy [49].

1.3.4.3. Neo-adjuvant setting

Studies investigating the use of third-generation AIs in the neo-adjuvant setting have, again shown them to be clinically effective, which is most relevant in terms of considering therapies for PET [192-195]. Similarly, all three have been compared with tamoxifen within this setting:

- Anastrozole, when compared to tamoxifen, has been shown to be equal in terms of objective tumour response rates in the neo-adjuvant setting, and superior in terms of breast conservation rates [196, 197]. However, both trials only used three months of neo-adjuvant therapy, which is not considered an adequate length of time to see a full response.

- Neo-adjuvant letrozole compared to tamoxifen for four months demonstrated significantly better tumour response rates and breast-conservation surgery rates in another randomised controlled trial [198].
- A randomised trial comparing exemestane with tamoxifen in this setting also demonstrated better results with the AI [199].
- Ellis and colleagues compared all three third-generation AIs in the neo-adjuvant setting for a period of up to 18 weeks in an randomised trial and found that treatment with letrozole resulted in the best clinical response rates [200].
- There is therefore compelling high level evidence in all treatment settings (adjuvant, palliative and neoadjuvant) that AIs are superior to tamoxifen in the treatment of ER positive breast cancer. In the PET setting (most analogous to neo-adjuvant) there is no RCT evidence but numerous cohort studies have reported on both treatments suggesting that AIs may be the superior treatment. These studies are reviewed formally in Chapter 3.

1.4. Surgery as a treatment for older women with operable breast cancer

As discussed above (Section 1.1.3), surgery to fully excise the primary and any nodal disease is the mainstay of treatment for women of any age with early breast cancer [9]. Despite this, older patients are less likely to undergo surgery of any type and for those that do have surgery to the primary tumour, they are less likely to have axillary surgery compared to younger women [68, 84, 90]. There is also good evidence that they are also less likely to receive other standard therapies such as post-operative adjuvant radiotherapy [68, 84, 89-91, 201] or chemotherapy [84, 89, 91].

There are good theoretical reasons why omission of what may otherwise be standard treatment may be adequate for older women. Breast cancer may be an indolent disease and be controlled well by antioestrogens for many years; this time span may exceed the naturally predicted life expectancy of the women if she is frail or unfit and so be unnecessary.

Older patients are likely to have increased levels of co-morbidity, decreased functional capacity and reduced physiological reserve seen in the older population [109, 202], making general anaesthesia more hazardous and reducing tolerance to the toxicity of adjuvant therapies. In addition, older patients' cognitive and functional ability may worsen following general anaesthesia [203] and some post-operative complications are more common in older patients [204-207]. Having said this, surgery for breast cancer is generally well-tolerated in older women, with both low morbidity and very low mortality rates [65, 208, 209]. There are also several anaesthetic techniques which may permit surgery without general anaesthetic, including:

- High thoracic epidural [210].
- Paravertebral block [211].
- Intercostal nerve block (not axillary surgery) [212].
- Local anaesthetic (limited axillary surgery only and challenging in women with larger breasts requiring mastectomy) [213].

1.5. Comparison of PET vs surgery

1.5.1. Advantages and disadvantages of PET and surgery

1.5.1.1. Advantages of PET

There are several clear advantages of PET as a treatment for older women with breast cancer. Some of these are discussed below.

Efficacy

Clinical benefit rates for PET in older women with ER positive breast cancers are generally high; a Cochrane review of seven randomised controlled trials reported that overall the cancer shrinks or fails to progress in 75% of cases [214, 215]. However, six out of the seven of these RCTs recruited patients without knowledge of the ER status of their cancer. A good clinical response can be expected in 79-90% of women with moderately or strongly ER positive tumours [216] compared to up to 100% progression rate in patients with ER negative tumours [217-221].

The overall survival with PET has also been shown to be equivalent to that of surgery on meta-analysis of the available historic randomised controlled trials [214, 215]. However it must be noted that the trials are flawed in several ways which may have biased their outcomes. These flaws include the fact that all of the women were fit for surgery under GA and the median age was relatively young compared to the more standard age for consideration of PET in current UK practice and most of the studies did not test for the ER status of the cancer so over 10% of the cases in the PET arms will have been effectively receiving no active treatment.

Tolerability

PET is well tolerated by older women [222-224] and has low toxicity [225].

Studies have demonstrated the older women express a high degree of satisfaction with this treatment [226].

Reassurance

In addition to finding the treatment acceptable, some women report being reassured by the clinical response to PET, and have confidence that the treatment is working because they can feel the lump regressing [226].

Avoidance of surgery

For older women with a short life expectancy, either due to co-morbidity or extremes of age, PET may allow the avoidance of surgery altogether [225]. This is a particular advantage for those women who either refuse surgery, or are unfit to undergo a surgical procedure due to significant co-morbid conditions or extreme frailty.

By avoiding surgery, patients also avoid the associated physical and psychological morbidity of an operation [216]. For more detail on these risks, see section 1.5.1.4.

Avoidance of anaesthesia

By not having surgery, these patients also remove the need for an anaesthetic, with all the associated risks (see section 1.5.1.4.). One of the main reasons patients do not wish to have an operation is due to their fear of anaesthesia [226], and this is negated by using PET.

Avoidance of hospitalisation

Older patients who are treated with PET do not need to be admitted to hospital for their treatment, allowing them to maintain their independence and providing minimal disruption to their daily life – these have all been shown to be important issues to this cohort of patients when choosing a treatment for operable breast cancer [226].

1.5.1.2. Disadvantages of PET

Palpable lump

Whilst the majority of patients with ER positive tumours will exhibit some regression of their clinical disease, a small but significant proportion will experience “static disease” – this is where, although the tumour is not progressing, there is no regression or shrinking of the palpable lump. This may be a source of anxiety in some women although in most studies, the reverse was reported, patients being reassured by the fact that they could feel the lump and it did not seem to be getting any bigger [226].

Relapse and progression

The major drawback of PET is the relatively short and variable duration of response [216]. Up to half of all patients will suffer a relapse [227] on longer term follow-up with recurrence or progression of their disease after a mean duration of 18-24 months [216]. The duration of response is generally shorter in women who have only exhibited a partial or static response to PET, compared to those with a complete response [217, 220]. Looking at long-term data, one study showed that at 12 years, 81% of older women treated with primary tamoxifen had developed progressive disease – this was compared with 38% after mastectomy alone [227]. The implication being that these women may require a change of management – either in the form of second-line hormone therapy, or with surgery or radiotherapy. It is probably worth noting that this study must have recruited a very fit cohort of women for this type of treatment considering that a significant number were still alive at 12 years of follow up and most current clinical practice would not consider a woman with a 12 year predicted life expectancy to be suitable for this type of treatment.

However, another study [219] found that 37% of women treated with PET had disease control for more than 5 years, and 16% had control for up to 10 years.

Delay in surgical management

Women who require an operation following progression on PET have the additional risks associated with being older at the time of surgery compared to when they were first diagnosed and Bergman and colleagues [228] found that up to 59% of women who needed a change in management were unfit for an operation at the time of progression.

Several studies have reported that some clinicians feel that PET only “delays” the definitive surgical management [227] and that patients may not be fit for surgery or the tumour may be inoperable at that time of progression [229]. However, if case selection is appropriately limited to women with a substantially reduced life expectancy, surgery may be avoided altogether in many women.

Disease-free survival

A Cochrane review of the available randomised controlled trials found that PET was associated with a lower disease-free survival when compared to surgery [214, 215]. This is understandable, considering the high rate of progression associated with PET [227].

Side effects of PET

General effects

Reported side-effects of tamoxifen include: hot flushes, nausea and sickness, fatigue and tiredness, mood disturbances, musculoskeletal disorders, vaginal bleeding and discharge, endometrial cancer, ischaemic cardiovascular events, ischaemic cerebrovascular events and venous thromboembolic events [230].

Reported side-effects of Aromatase Inhibitors are similar to those reported with tamoxifen but with a few key differences [230]. The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial compared the frequency of complications in groups and the results are shown below table 1.3.

	Anastrozole (n=3092)		Tamoxifen (n=3092)		p-value
	n	%	n	%	
Hot flushes	1082	35.0	1246	40.3	0.001
Nausea and vomiting	346	11.2	339	11.0	0.777
Fatigue and tiredness	512	16.6	491	15.9	0.469
Mood disturbances	519	16.8	508	16.4	0.707
Musculoskeletal disorders	936	30.3	732	23.7	<0.001
Vaginal bleeding	147	4.8	270	8.7	<0.001
Vaginal discharge	94	3.0	378	12.2	<0.001
Endometrial malignancies	3	0.1	15	0.7	0.007
Fractures	219	7.1	137	4.4	<0.001
Ischaemic cardiovascular disease	86	2.8	67	2.2	0.121
Ischaemic cerebrovascular events	68	2.2	116	3.8	<0.001
Venous thromboembolic events	68	2.2	116	3.8	<0.001

Table 1.3: Incidences of side-effects of anti-oestrogen therapy [230].

Endometrial cancer

There is a documented higher incidence of endometrial carcinoma in patients treated with adjuvant tamoxifen [230, 231], however this has been shown to have little effect on survival [232].

Bone health

Aromatase inhibitors are associated with an increased incidence of osteoporosis [233]. Oestrogen inhibits bone resorption by affecting osteoclastogenesis and osteoclast function through its effects on local cytokines and growth factors [234]. The pathogenesis of osteoporosis in patients treated

with AIs results from a deficiency in oestrogen and subsequent increase in bone resorption, coupled with a decrease in the deposition of new bone in weight-bearing bones. In contrast, treatment with tamoxifen is protective against osteoporosis by acting as an oestrogen receptor agonist, thereby inhibiting osteoclast activity [235, 236].

In practice as most women in the over 70 age group have some degree of osteoporosis or osteopenia, steps should be taken when using these agents to monitor bone density and use prophylactic medication to offset this risk. UK guidelines recommend that use of AIs in this age group be accompanied by bone protection therapies [237]. This may add to the cost of AI use relative to tamoxifen where such measures are not necessary.

Follow-up

In view of the high rate of disease progression on PET [227] and the variability in the length of time taken to progress [219], patients treated with PET alone require close follow-up in order to detect recurrence at an early stage, necessitating more frequent hospital visits which may be associated with disruption to their daily lives, anxiety and stress.

1.5.1.3. Advantages of surgery

Local control

The Early Breast Cancer Trialists' Collaborative Group have emphasised the importance of adequate local control [238] and in a Cochrane review comparing surgery with PET, local control in the surgical group was superior to that of the PET group [214, 215].

Better survival?

Despite a Cochrane review reporting that there was no difference in overall survival when comparing PET to surgery [214, 215] – several of these trials were flawed by modern standards, particularly with regards to the treatment given; four out of the seven trials used a comparison of surgery *only* – when nowadays, all patients undergoing operative intervention would be treated with adjuvant endocrine therapy were appropriate. This is without taking into account modern surgical techniques, with adequate margins and the routine addition of radiotherapy to patients who undergo wide-local excision.

Additionally, there have been several studies demonstrating that survival is in fact superior in those older women who undergo surgical treatment:

- Of the RCTs, a long-term report, with follow-up of 12 years, demonstrated a significantly higher overall and breast cancer-specific mortality in the group of women treated with tamoxifen only, when compared to those who underwent surgical intervention with adjuvant tamoxifen (HR = 1.3; 95%CI = 1.05-1.61 and HR = 1.75; 95%CI = 1.18-2.59 respectively) [239]. However the comments above about poor selection criteria for PET such that any of these women would survive to have 12 year survival, make it almost inevitable that PET would fail.
- Bouchardy and colleagues [78] reviewed the outcomes of 407 breast cancer patients aged 80 years or over, treated between 1989 and 1999 in a retrospective cohort study. They found that adjusting for age, 5-years breast cancer-specific survival was low among women who were treated with tamoxifen only (51%) when compared to those women treated with breast-conserving surgery and adjuvant treatment (90%) [78].
- More recently, Ali and colleagues [89] reviewed the outcomes of 14048 women with breast cancer, who aged 50 years or older and treated in the East of England between 1999 and 2007. They found that taking account of age, tumour stage, grade, deprivation level and type of hospital, surgery was associated with the greatest increase in relative survival on multivariate analysis [89].

Well tolerated

Surgery for breast cancer is generally well-tolerated, even in older women and evidence suggests that even mastectomy with axillary clearance in older women has both low morbidity and mortality rates [65, 208]. A study looking at older women's views about treatment found that surgery was well tolerated in this group and patients reported being satisfied with how little their lives changed as a result of surgery [226]. However little is known about the long term impact and quality of life has never been formally assessed between these 2 groups. One study has used the General Health Questionnaire (GHQ; 28 items) to assess anxiety and depression in a randomised controlled setting comparing PET and surgery and found no long term difference in outcomes [240].

1.5.1.4. Disadvantages of surgery

Mortality

Mortality rates from breast cancer surgery are very low, even in very elderly, frail women [104, 241].

Mortality rates for women over 65 years who undergo mastectomy under general anaesthesia was reported to be 1% in studies published over 30 years ago [208, 209]. A more recent study that analysed the outcomes of patients over 70 who had undergone wide local excision, either under local or general anaesthesia, reported a mortality rate of only 0.3% (two deaths in 658 patients) [69].

Other surgical complications

Mortality is not the only potential complication of surgery and morbidity may be substantial.

Complications may be physical or psychological [242].

Physical complication after breast surgery include: bleeding (including haematoma and the need for blood transfusion), infection, scarring, acute and chronic wound pain, seroma formation and skin necrosis after mastectomy (see table 1.4).

	Incidence	Affected by age	Reference
Seroma	Variable, 10-30% depending on procedure.	Women >70 years have 2.4 times higher risk than those <70.	[204-207]
Haematoma and wound infection	8-10%	No difference with age	[69]
Skin flap necrosis	1-6%	No difference with age	[245-247]
Axillary paraesthesia	5-13%	Decreased incidence in older women	[207, 248]
Lymphoedema	Variable, up to 38%, depending on procedure	Decrease incidence in older women	[207, 249]
Arm symptoms (pain, stiffness, numbness, weakness) after axillary surgery	Variable, up to 73%, depending on procedure	Decreased in the older women.	[250, 251]
Ability to self-care after axillary lymph node dissection	25-35%	Older women more likely to have difficulty with household chores.	[248]

Table 1.4: Incidence of surgical complications and their association with increasing age.

Physical complications after axillary surgery include: bleeding (including haematoma and need for blood transfusion), seroma formation, paraesthesia, shoulder stiffness, damage to the long thoracic nerve (leading to “winging” of the scapula), chronic neuropathic pain, lymphoedema and breast oedema [243, 244].

The overall the morbidity rate is approximately 19%, with the incidence of serious complications, such as chest infection, cardiac arrhythmia and myocardial infarction being quoted as 11% in one study [209].

It is also important to consider the psychological effects of breast surgery, in terms of a woman’s body image, sexuality and relationships and both breast-conserving surgery and mastectomy are associated with psychological morbidity [252, 253]. A randomised controlled trial looking at psychological distress in older women treated with either surgery or PET showed short-term impairment in psychological wellbeing at 3 months in the surgical group, however this difference had disappeared by 2 years [240].

Risks of anaesthesia

General anaesthetic carries a small, but significant risk. Older patients in general have increased levels of co-morbidity, decreased functional capacity and reduced physiological reserve [109, 202], making general anaesthetic more hazardous.

Reduction in quality of life

There is evidence that surgery results in a reduction in quality of life for all patients [242, 254].

However in a comparison between surgery and PET, one study used the General Health Questionnaire (GHQ) to assess quality of life and showed that despite the initial reduction in scores with surgery, the long-term quality of life is equivalent between these two treatment types [240]. Quality of life using a robust, validated tool has not been assessed in patients treated with PET.

Despite this, loss of independence and hospitalisation are among the reasons older women have stated for wishing to avoid surgical treatment [226, 255].

Body image perception

Surgery, in particular mastectomy, results in obvious deformity and consequent psychological morbidity. Husain and colleagues [226] found that some older women feel “less of a woman”

because of loss of their breast and expressed that this was the worst part of the experience of undergoing breast cancer surgery.

Lack of benefit

A significant proportion of older breast cancer patients will die from co-morbid conditions, hence reducing the relative survival advantages associated with surgical treatment [106].

1.6. The impact of clinician preference on the treatment of older women with breast cancer

1.6.1. A trend towards shared decision-making

Recent times have seen a change within the UK National Health Service, with a shift in the clinician-patient relationship away from the paternalistic approach towards consultations [256] (with clinicians as primary decision makers and patients as passive recipients) toward a more shared decision-making (SDM) approach, which involves more active participation of patients in medical decision-making [257-265]. The SDM model was developed in the 1980s and is characterised by equal participation of both the patient and clinician in all components of decision-making with a mutual exchange of information [256]. The role of the clinician in SDM involves eliciting the patients' desires [266] and providing an appraisal of the current best evidence to allow the patient to make an informed choice [267].

The General Medical Council, the UK's regulatory body for doctors, states that clinicians should elicit a patient's individual needs and priorities when discussing treatment options and should provide patients with adequate information regarding the risks and benefits of each treatment [268]. The Royal College of Surgeons also support this ethos, stating that clinicians should allow sufficient time to explain the pros and cons of a potential treatment, including available alternatives, and they should ascertain and respect the patients' wishes [269].

SDM is particularly promoted in preference-sensitive decisions where there is more than one feasible treatment option and the optimal choice can only be determined by an individual patient's characteristics, values and preferences [270-273]. SDM is associated with an increase in patient satisfaction with both the decision and the process of making it [274-276].

1.6.2. Variation in shared decision-making preferences in older women

In order for patients to express a preference for a particular treatment, they must first be informed of the different treatment options as advocated in SDM [277], which means that for some older women it may be appropriate to offer PET as an alternative to 'standard' surgical treatment and allow the patient to decide what is best for them. In addition, not all older patients want to engage in SDM, with many preferring a more passive role [88, 278-280] which may account for as many as 50% of older patients [281-283]. Several studies have shown that older patients tend to prefer a more clinician-directed style of decision-making [281, 284-292], suggesting that older patients prefer to be informed, but not involved in the decision-making [283, 293], and that some may even

perceive decision-making to be a burden [294]. Indeed, encouraging an active role in DM when patients prefer a more passive role may increase anxiety and cause distress [295, 296]. Unfortunately, clinicians are poor at judging a patient's preferred level of decision-making control [281, 287, 297, 298].

A preference for a more passive decision-making style may result from patients being unfamiliar with SDM within medical decision-making [289, 299], or feeling that they do not have sufficient understanding, information or support to make informed decisions [299, 300]. Decision-making stress may be especially compounded by fear of a cancer diagnosis, connotations of dying and worry about choosing the "right" treatment [301, 302], particularly older patients who may face more complex decisions and greater risks from treatments [303].

1.6.3. The impact of clinician preference on treatment

Despite the trend towards SDM in today's clinical practice, clinicians vary in their decision-making styles. For example some clinicians believe it is not necessary to present all treatment options to a patient [304-307], and the opportunity for patients to participate in decision-making may be dependent on their clinician's consultation style [308]. Even those clinicians who do participate in SDM, may have a personal preference for one or the other treatment option, which they may impart to the patient, either intentionally or unintentionally.

Clinician recommendation is the most influential factor affecting older women's breast cancer treatment decisions [88]. Indeed, patients rank a clinician's recommendation higher than their own preference, implying that many patients are not willing to contradict their clinician's recommendation even in pure preference-sensitive decisions [309].

1.7. The gap in knowledge

It is clear that the treatment of older women with operable breast cancer may be considered a preference-sensitive decision, that there is variation in practice across the UK and that clinician preference may influence patient choice in SDM. However it is not known whether clinician preference is one of the causes of the observed variation in treatment of older women with operable breast cancer across the UK.

This thesis aims to address this gap by identifying the extent of treatment variation in older women with operable breast cancer, how much of this variation can be accounted for by case-mix and how variability in clinician preference may contribute to the unexplained treatment variation:

- Chapter 1 outlines the background to the study, underpinning why it is important to investigate this problem.
- Chapter 2 presents the research question with the aims and objectives of this thesis before going on to describe the methodological and philosophical approaches used to address these.
- Chapter 3 examines the current use of PET and surgery in the treatment of older women with operable breast cancer by means of a systematic review of the literature and meta-analysis.
- Chapter 4 reports on the variation in treatment practice and whether this can be accounted for by case mix.
- Chapter 5 explores the factors that HCPs consider important in the treatment decision-making process and identifies areas of variability in HCP opinions relating to the treatment of older breast cancer patients.
- Chapter 6 uses the themes identified in Chapter 5 to investigate the important factors and variability in opinion regarding treatment of older breast cancer patients on the wider UK breast HCP population.
- Chapter 7 assesses how the factors identified as important to HCPs affect treatment decision-making in experimental conditions to identify whether they account for variation.
- Chapter 8 summarises the main findings from the study in relation to the aims and objectives.
- Chapter 9 discusses study findings in the wider context of the problem being addressed.
- Chapter 10 concludes the thesis by summation of the work presented and the conclusions that can be drawn.

Chapter 2: Study Overview

2.1. Research question

“Is clinician preference a variable in the management of older women with operable breast cancer?”

2.2. Study aim

To examine the variability in the treatment of older women with operable breast cancer, after controlling for case mix, in relation to the views of specialist healthcare professionals (HCPs).

2.3. Study objectives

- To determine the level of variance in the treatment of older women with operable breast cancer.
- To explore the views of specialist healthcare professionals towards the management of older women (>70yrs) with operable breast cancer, particularly in terms of PET versus surgery.
- To identify the factors underlying treatment decision-making by HCPs relating to older women with breast cancer.
- To quantitatively assess the above factors on a wide group of HCPs to determine whether they account for variation in treatment.

2.4. Study components

This is a mixed methods study, comprising of both qualitative (QUAL) and quantitative (QUAN) methods, including:

- Systematic review and meta-analysis: QUAN (Chapter 3)
- Retrospective registry data analysis, using case-mix adjustment: QUAN (Chapter 4)
- Semi-structured qualitative interviews: QUAL (Chapter 5)
- HCP questionnaire survey: QUAN (Chapter 6)
- Discrete choice experiment: QUAN (DCE; Chapter 7).

The first two strands (systematic review, meta-analysis and registry data analysis; Chapters 3 & 4) examine the current use of PET and surgery for older women with operable breast cancer in the UK and whether the observed variation can be accounted for by case mix. The third strand (qualitative interviews; Chapter 5) explores which factors HCPs consider important in the treatment decision-making process and the variability in HCP opinions relating to this. The fourth strand (questionnaire survey; Chapter 6) investigates these factors and the variability in opinion on the wider population of UK breast HCPs. The fifth strand (DCE; Chapter 7) assesses the factors identified in earlier strands on HCP decision-making in experimental conditions to identify whether they account for the observed variation.

Figure 2.1 shows how the individual study components of the project fit together and are presented within this thesis.

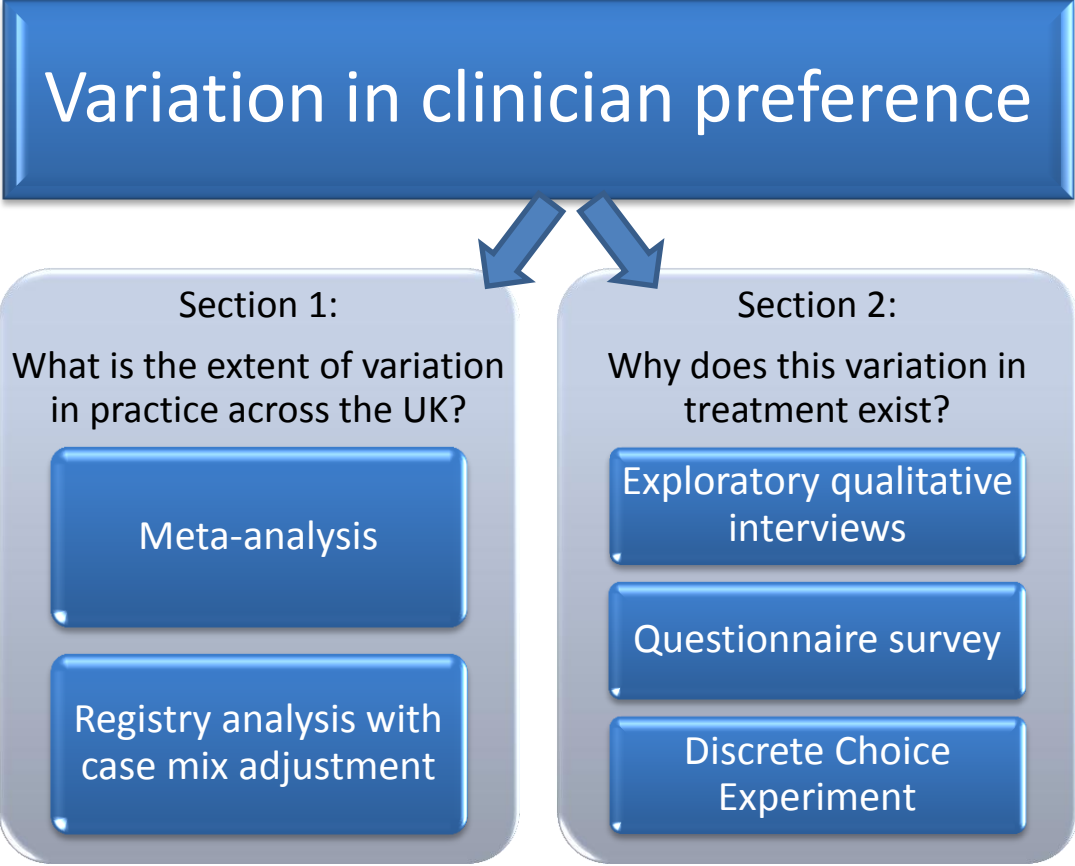


Figure 2.1: Schema of PhD.

2.5. Methodological approach

2.5.1. Philosophical underpinning of the study

The philosophical world view point, or research paradigm, of a researcher has an important influence on the way research will be undertaken: Burrell and Morgan argue that scientific research involves either a subjective or objective approach. These approaches have their own research paradigms; positivism and constructivism respectively (see table 2.1). In terms of methodology, positivism is commonly associated with quantitative (QUAN) approaches and constructivism with qualitative (QUAL) approaches [310]. Objectivism and subjectivism can be described as two polar ends of a spectrum or continuum with varying philosophical positions aligned between them. These two opposing philosophical approaches are delineated by several core assumptions concerning ontology, epistemology and methodology – each of these assumptions consequently affecting each other [311]. Knowledge of these assumptions is important in order to identify them within a project, and since mixed methods (MM) projects, combining both QUAN and QUAL methodologies do not fit neatly into either paradigm, it has been suggested that all MM researchers clearly articulate their philosophical assumptions in their research [310]. Table 2.1 describes the basic characteristics of four world viewpoints that are commonly used in research.

For the purposes of this study, a pragmatic world viewpoint is adopted. Pragmatism is often considered as occupying a “middle ground” between the polar extremes of positivism and constructivism and is one of the commonly embraced paradigms for researchers conducting MM projects [312]. This pragmatic perspective allows the researcher to occupy different positions on the paradigm continuum [310], employing a “what works” approach, thereby giving primacy to the importance of the research question and valuing both objective and subjective knowledge [313]. This is in contrast to critical realism, which focusses only on the ability to point out the limitations of the polar opposite paradigms, and as such offering a platform for the use of a variety of methods to overcome these in a process of triangulation [314, 315].

As a surgical trainee with an interest in breast cancer treatment, I have worked alongside a variety of HCPs in different units who have differing standpoints and ways of working. As such I am used to trying out different clinical methods and adopting those that work within my own practice, for example practical techniques within the operating theatre, as well as investigating diagnostic problems using a combination of different techniques. Hence, on a personal level it seemed appropriate for me as a researcher to use the combination of methods in order to meet the overall aims and objectives of the study.

	Positivism	Constructivism	Pragmatism	Critical Realism
Ontology: The philosophy of existence, concerned with explaining the fundamental nature of being – what exists?	There is a real world (or a single reality) which can be seen, understood and directly observed.	All we know is interpreted through human senses and so there are multiple constructed realities which are products of human intellects. We therefore cannot know the real world.	There is a real world independent of our thinking but that single reality cannot be determined. Concerned not with an account of how things are, but only solutions to problems and applications.	There is a real world independent of our thinking and science can study this single reality but only imperfectly and not with certainty.
Epistemology: The philosophy of knowledge, concerned with explaining how we come to know the world – what is the relationship between the knower and the known?	Cause probably determines effect, the results of which can be objectively perceived by the researcher. Being objective is paramount. Use checks to eliminate bias.	Results are subjective and based on the individuals studied as they develop differing meanings of their experience, and it is these views which are studied. Subjectivity results in bias which is openly reviewed and results are interpreted in light of these biases.	There is a continuum of objectivity-subjectivity and the researcher will be at differing points on this continuum in different stages in the research process. Inclusion of both unbiased and biased perspectives.	Scientists are inherently biased by their culture experience and world views. All observation and measurement is fallible and possess error (or bias) and that all theory is revisable. Use triangulation to reduce error.
Methodology: The actual ways, or methods, used to try and understand the world – the process of research.	Deductive methods (theory-driven) – quantitative in nature.	Inductive methods (theories are built from the views of the participants) – qualitative in nature.	Uses whichever methodology works in the context of the problem and may combine both quantitative and qualitative methods to gain the best answers.	Emphasises the importance of multiple measures and observations, each of which may possess different types of error and the need to use triangulation.

Table 2.1: Summary of characteristics of four research paradigms (adapted from [310]).

As such, at different points within the study, as a researcher I am occupying different points on the research paradigm continuum:

- Subjectively utilising my “insider’s perspective” to more fully understand the research problem.

- Ensuring different views and voices are integrated into the study, giving the maximum diversity of viewpoints.
- Being sensitive to the process of reflexivity and the influence that my personal experiences and position may exert on the research.
- Viewing the overall problem of variation from an objective stance by statistically analysing data using a case-mix adjustment.
- Objectively testing generated theory with experimental methods.

In summary, a MM approach from a pragmatist's perspective was viewed as being an effective methodological approach in order to develop a more comprehensive understanding of this research project, whilst at the same time being consistent with my pragmatic stance within my career and generally within my personal viewpoint.

2.5.2. Quantitative, Qualitative and Mixed Methods approaches

At its very simplest, quantitative and qualitative research methods can be described as gathering and analysing numbers and stories, respectively. Both have advantages and disadvantages [310, 316, 317], as are summarised in table 2.2.

Mixed methods research uses and integrate both QUAN and QUAL research methodologies together. MM has the advantages of drawing on the positive aspects from both QUAN and QUAL methodologies (see table 2.3) and these types of studies may access knowledge or insights unavailable to either QUAN or QUAL studies undertaken independently [318].

QUAN methods may be the best way to answer questions that ask "what is there?" [320] whilst QUAL methods are the best way to answer questions that ask "why is this the case?" [321]. In this study, there is a need to identify "what is the treatment variation" within the population with QUAN methods, investigate reasons as to "why this variation occurs" using QUAL methods and apply these theories back to the wider population with QUAN methods, thus justifying a mixed methods study design.

	Advantages	Disadvantages
QUAN	<p>Large sample so conclusions can be generalised to target population</p> <p>Statistical validity</p> <p>Efficient data analysis</p> <p>Demonstrate relationships</p> <p>Examine probable cause and effect (confirmatory)</p> <p>Bias controlled or limited</p> <p>People like numbers</p>	<p>Impersonal, dry</p> <p>Do not hear the words of the participants</p> <p>Limited understanding of context of participants</p> <p>Largely researcher driven</p> <p>Superficial understanding of participants' thoughts and feelings</p> <p>Biases of the researcher in interpretation of results are seldom discussed</p>
QUAL	<p>Detailed perspectives of a few people: rich, in-depth data</p> <p>Can hear voices of participants</p> <p>Understand participants' experiences and behaviours within context</p> <p>Built from views of participants, not researcher</p> <p>People like stories</p>	<p>Small sample so limited generalizability to target population</p> <p>Soft data, not as hard as numbers</p> <p>Few people studied</p> <p>Highly interpretive, subjective – not conclusive</p> <p>Reliance on participant minimizes researcher's expertise</p> <p>Bias can be introduced by researcher in the execution and analysis</p>

Table 2.2: Summary of the advantages and disadvantages of quantitative (QUAN) and qualitative (QUAL) research.

QUAN	MM	QUAL
Pre-determined instrument	Pre-determined and emerging methods	Emerging methods
Instrument-based questions	Both open and closed ended questions	Open-ended questions
Performance, attitude, observation, census data	Multiple forms of data drawing on all possibilities	Interview, observation, document and audio-visual data
Statistical analysis	Stats and text analysis	Text and image analysis
Statistical interpretation	Across database interpretation	Themes, patterns interpretation

Table 2.3: Comparison of QUAN, MM and QUAL methods (adapted from [319]).

2.5.3. Why use MM research?

Undertaking a MM research study has the advantages of overcoming the limitations of a single design study, providing strengths that help counterbalance the weaknesses of either QUAN or QUAL studies undertaken alone [310]. Specific reasons may include the following [310, 322-327]:

- **Triangulation:** looking for convergence or corroboration by using different methods,
- **Complementary:** one method elaborates, enhances or clarifies results from the other method.
- **Offsetting:** using a combination of methods with different strengths that offset the weaknesses of each method.
- **Development:** uses results from one method to develop or inform the other method.
- **Expansion:** using different methods extends the breadth and range of inquiry.
- **Comprehensiveness:** using both methods allow an issue to be addressed more fully.
- **Salvaging:** a second method is used after one has failed.
- **Sampling:** where a combination of methods also different sampling methods of a population.

In the context of this thesis, a MM approach was chosen for a combination of these reasons, including triangulation, complementary, development and expansion/comprehensiveness. More specifically, for example, results from the semi-structured interviews were used to develop a bespoke questionnaire. Results from each of the strands were also compared and contrasted,

searching for explanations and to corroborate the findings. Figure 2.2 shows the relationship between the strands in more detail.

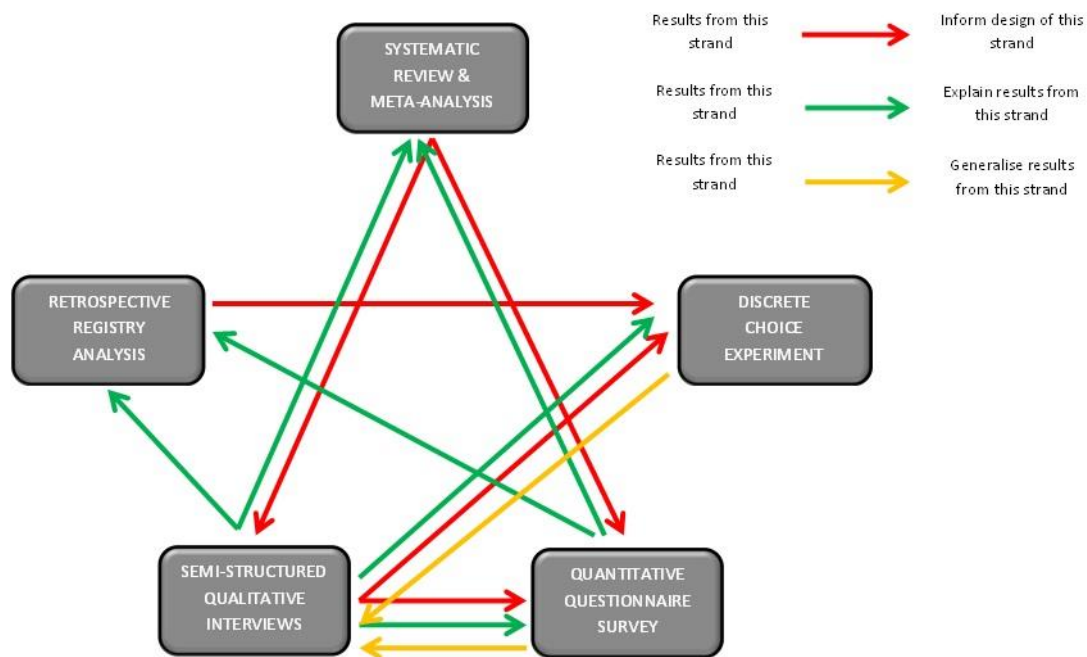


Figure 2.2: Interconnecting relationships between research strands.

2.5.4. Development of a mixed methods research project

When conducting MM projects there are several factors to consider in the design development [310]:

- Determining the level of interaction between the QUAN and QUAL strands.

The level of interaction between strands may be considered **independent** (where the data collection and analysis of each strand is kept separate and mixing occurs when drawing conclusions during the overall interpretation at the end of the study) or **interactive** (where the results from one strand may inform the development of the next strand).

- Determining the priority of the QUAN and QUAL strands.

The study may be weighted, so that greater emphasis is placed on either the QUAN (**quantitative priority**) or QUAL (**qualitative priority**) strands, or there may be **equal priority**, where both play an equally important role in addressing the research question.

- Determining the timing of the QUAN and QUAL strands.

The timing of the MM design can be considered as **concurrent** (where both QUAN and QUAL phases are implemented together in a single phase of the study), **sequential** (where the data collection and analysis of one strand occurs following that of the other), or **multiphase combination** (where multiple phases including sequential and/or concurrent timing are implemented over a program of study).

- Determining where and how to mix the QUAN and QUAL strands.

Mixing of the two approaches may occur at several points during the research process – during **interpretation**, during **data analysis**, during **data collection**, or at the **level of design**

There have been several typologies of MM designs created in order to help the researcher address these factors [310, 322], however these tend to be theoretical, and are not necessarily based on the actual conduct of MM research [323]. Figure 2.3 demonstrates some of the most common MM study designs.

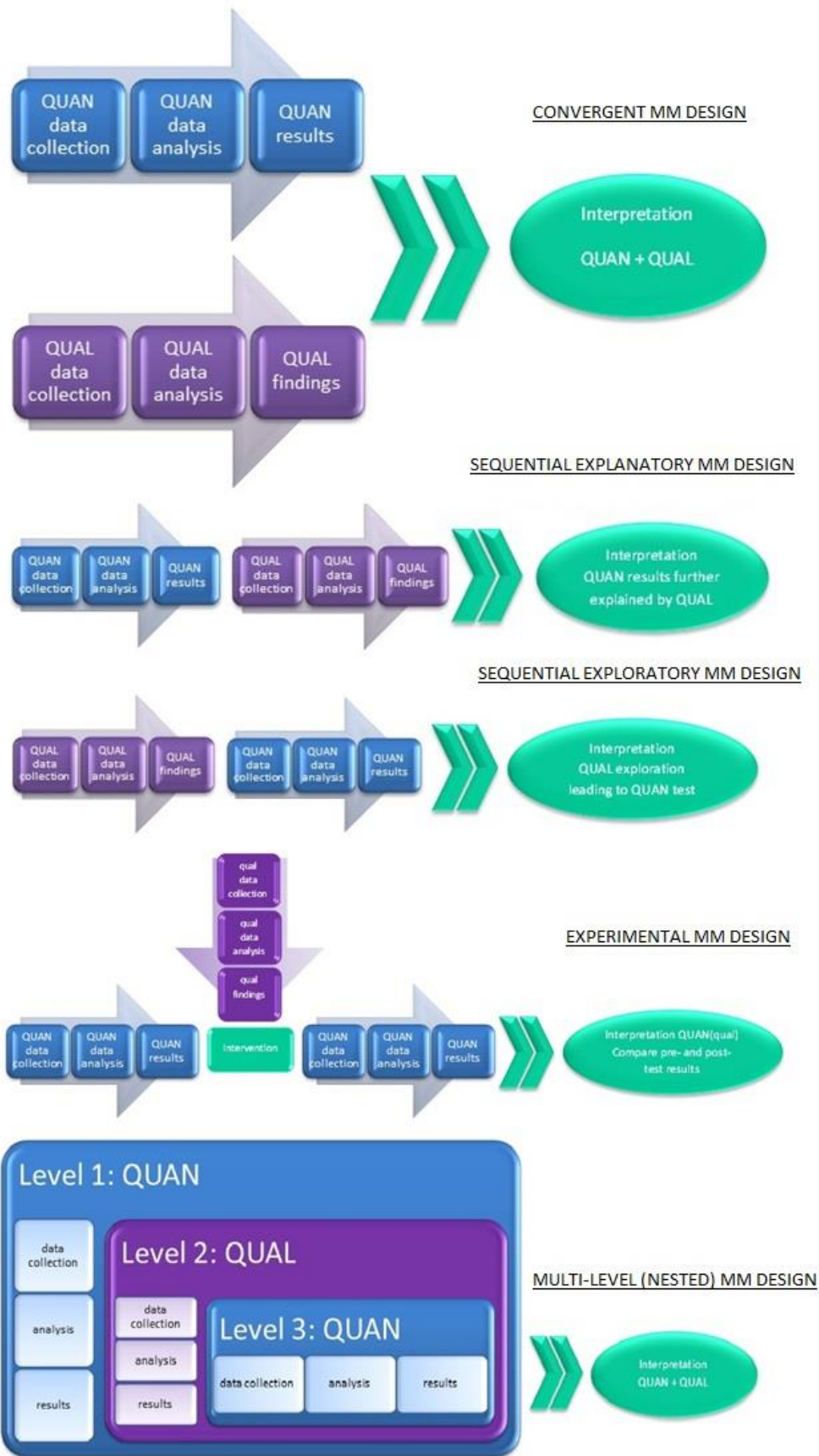


Figure 2.3: Examples of some common MM designs.

In order to answer the study research question and to address the aims and objectives of the study, a multi-level approach containing a nested sequential exploratory design has been adopted. The development of the questionnaire using the exploratory interview findings can be seen as a nested sequential exploratory design within the wider multi-level project where all the QUAN+QUAL findings are reviewed and interpreted together at the end. Figure 2.4 shows how the individual strands inform one another.

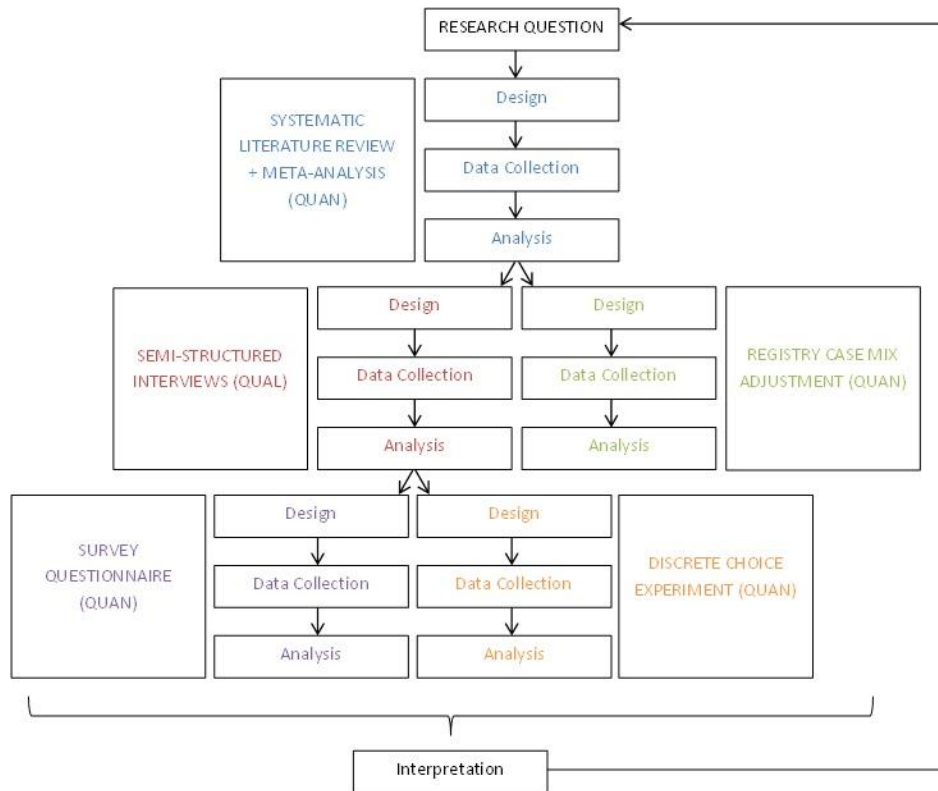


Figure 2.4: Schematic overview of the interaction between each strand within the study.

2.6. Project development

This thesis forms part of a NIHR funded programme grant (RP-PG-1209-10071) 'Bridging the Age Gap in Breast Cancer' focusing on addressing the variation in treatment practice for older women with operable breast cancer. Further details can be found in Appendices 1&2.

The current project was developed by Lynda Wyld, Karen Collins, Malcolm Reed and Jenna Morgan with input from individuals on the Bridging the Age Gap in Breast Cancer Trial Management Team and others in developing specific components of the study:

- Meta-analysis: Breast Cancer Cochrane Group
- Registry component: Paul Richards, Sue Ward, Matthew Francis, Gill Lawrence, Catherine Lagord, Sarah Lawton, Thompson Robinson.
- Interview component: Karen Collins, Maria Burton.
- Questionnaire survey component: Thompson Robinson, Kwok-Leung Cheung, Riccardo Audisio.
- DCE component: Thompson Robinson, Stephen Walters.

2.7. Ethics and research governance

All components of the study were conducted with appropriate ethics and research governance approvals, details of which can be found under each study component chapter and in Appendices 2, 5, 6 and 7.

2.8. Funding

This thesis presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-1209-10071 (See Appendix 3). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Section I: What is the extent of variation in practice across the UK?

Chapter 3: Systematic Review and Meta-analysis

3.1. Abstract

3.1.1. Introduction:

Since primary endocrine therapy (PET) was introduced and proven to be effective in the early 1980s, it has become a popular management strategy as an alternative to surgery for the treatment of operable breast cancer in older women. However, with continuing advances in the field, it is unclear how much of the published evidence remains relevant to the treatment of older women with operable breast cancer.

3.1.2. Methods:

A systematic review of the literature pertaining to the use of PET was performed between the dates of January 1980 to July 2014. Meta-analysis of relevant studies was also performed.

3.1.3. Results:

Six randomised controlled trials (RCTs), 31 non-randomised studies and 37 population studies were identified. Available data demonstrate an advantage for surgery over PET in terms of disease control and a likely survival benefit in patients with a predicted life expectancy of five years or more.

Patients treated with aromatase inhibitors (AIs) for their primary endocrine therapy had superior rates of disease control when compared to those treated with tamoxifen.

3.1.4. Conclusion:

Primary endocrine therapy should be reserved for patients with reduced predicted life expectancy (e.g. less than five years). Unless there are contra-indications, AIs should be the preferred agent for PET as its efficacy is superior to tamoxifen.

3.2. Introduction

As discussed in Chapter 1, the standard treatment for operable breast cancer in women of all ages was surgery until the early 1980s when primary endocrine therapy (PET) was first described as an alternative to standard therapy in older women [328, 329]. Primary endocrine therapy rapidly gained popularity in the UK as a management strategy for older women, leading to a number of randomised controlled trials (RCTs) being conducted internationally. These aimed at comparing the efficacy of tamoxifen PET against surgery in older patients [219, 225, 227, 231, 330-332]. In 2006, a Cochrane review of these 6 RCTs demonstrated superior local control with surgery but no difference in survival between the two treatments [214, 215].

Since the introduction of PET more than 30 years ago, there have been significant advances in the treatment of operable breast cancer. Tamoxifen has largely been replaced in post-menopausal women by the introduction of third generation aromatase inhibitors (AIs) as first line treatment for both PET and adjuvant endocrine therapy [9]. The testing of oestrogen receptor (ER) status, rarely performed when these RCTs were conducted, has now become routine practice in all patients with a new diagnosis of breast cancer [9]. Additionally, improvements in anaesthetic and surgical techniques, including the recent trend towards less invasive techniques, such as sentinel lymph node biopsy, mean that breast surgery today, even in the older, frailer patient has a very low morbidity and mortality [333]. These changes in the field serve to limit the applicability of the RCT data to modern clinical practice.

More recently, there continue to be new data published from non-randomised studies assessing the use of PET in a more up-to-date clinical setting. Given the potential flaws with the published RCT data to date, these non-randomised studies provide another source of data on the use of PET in modern clinical practice. The aim of this systematic review was to analyse the data pertaining to PET that has been published in the literature since it was introduced as a treatment for operable breast cancer.

3.3. Methodology

3.3.1. The use of RCTs as evidence in this clinical setting

Randomised controlled trials, although considered to be high-quality in terms of study design when compared to other non-randomised methodologies, may not always be the most appropriate study method to answer a clinical question.

In the case of PET vs surgery, the main limitation of the RCTs was that the women recruited to the trials had to be fit for surgery under general anaesthesia. The fact that the RCT study groups were able to go back and reanalyse data at 20 years and even 28 years, with long-term survivors at these stages, suggests that they recruited a very fit group of older women [67, 335]. In current UK practice, PET tends to be reserved for the less fit, older age groups and in practice, these two groups of women would not be comparable in terms of co-morbidity or frailty. None of the RCTs stratified for or even recorded co-morbidities which may have had a significant impact on survival, and even those older women who are fit for surgery often die of co-morbid diseases, thereby reducing the survival advantage of any breast cancer therapies [106].

The average age of the women recruited to these RCTs was relatively young, being in the early to mid-70s; women in this age group can be expected to have a median life-expectancy of 17 years [336] – considerably longer than the duration of benefit that can be expected with PET [224, 337-341].

In addition, a recent attempt at recruiting to a multi-centre RCT comparing PET and surgery, using more currently acceptable eligibility criteria, known ER+ cancers and the optimal anti-oestrogen (aromatase inhibitor rather than tamoxifen) was unsuccessful due to lack of equipoise amongst both patients and clinicians so few women were offered or accepted randomisation [342].

3.3.2. Cochrane review meta-analysis.

Meta-analysis of high quality RCTs are generally regarded to be the highest level of evidence in evidence-based medicine [343], with Cochrane reviews being considered to have greater methodological rigor compared with other types of systematic reviews and meta-analyses [344]. This is because they base their findings only on RCTs which meet certain quality criteria [345]. However, this places limitations on the evidence that can be included and may result in large quantities of potentially relevant data being discarded, with the results becoming less generalizable

as a consequence. Meta-analyses in general are also limited to the outcomes assessed and reported by the included trials and these must be comparable in order to draw any meaningful conclusions.

In the case of the PET versus surgery meta-analysis, the results of the Cochrane study were limited by the inclusion of only a few small studies, discarding data from several non-randomised studies that also sought to address the same question.

3.3.3. The use of non-randomised cohort studies in this clinical setting

The non-randomised data in the literature provides a unique opportunity to compare the different types of PET in the “real-life” setting, and to explore the survival difference between studies that treated all women, regardless of ER status, fitness for anaesthesia and comorbidities, in this manner versus those who only used PET to treat ER positive women. In effect what would normally be regarded as a source of bias can be used to get a better understanding of real world outcomes in clinical practice.

Additionally, there are tools available that allow assessment of the methodological rigour of these types of studies, in a manner similar to that performed on RCTs in a Cochrane review [346-348]. Ten distinct areas are rated on a 4-point scale (very poor to good), including: title and abstract; introduction and aims; methods; sampling; data; analysis; ethics and bias; results; transferability or generalizability; implications and usefulness. Each paper is then given an overall score between 10 and 40, indicating its methodological rigour.

3.4. Methods

3.4.1. Search methods.

Relevant studies were identified by searching the following electronic databases:

- MEDLINE*^
- EMBASE*^
- CINHAL^
- PsychINFO^
- CENTRAL*
- The Cochrane Breast Cancer Group Specialised Register*
- WHO International Clinical Trials Registry Platform (ICTRP)*
- ClinicalTrials.gov*

*denotes searches were undertaken by the Breast Cancer Cochrane Group.

^denotes searches were undertaken by JM.

Hand searching of references was also performed in an attempt to identify all relevant studies.

In view of the fact that breast cancer mainly affects women and the use of PET was first described in the early 1980s, several limits were placed on the search:

- Date: 1980-present day.
- Participants: Humans, Females.
- Language: Articles in English.

Several searches were performed, using a combination of the following search terms:

- Breast cancer, breast neoplasm, breast tumour, mammary cancer, mammary neoplasm, mammary tumour.
- Primary endocrine therapy, endocrine, tamoxifen, anastrozole, letrozole, exemestane, femara, arimidex, aromasin.
- Primary, sole, versus, neo-adjuvant, only.
- Cohort study, population study, longitudinal study, randomised controlled trial, randomized controlled trial, RCT.
- Elderly women, older women, over 70 years, over 65 years, over 80 year.

For the full search strategies, please see Appendix 4.

3.4.2. Results of the search

A total of 6,634 results were generated by these initial searches. Abstracts and titles were reviewed for relevance and compared to the inclusion criteria and full text articles were obtained. Where it was unclear from the title/abstract whether the studies met the inclusion criteria, full text articles were also obtained and a decision made based on the entire paper.

Figure 3.1 shows the review process in diagrammatic form.

After excluding ineligible and duplicate abstracts, 271 papers were deemed potentially eligible and the full papers were retrieved.

References of relevant papers were hand searched to identify additional studies missed by the primary search.

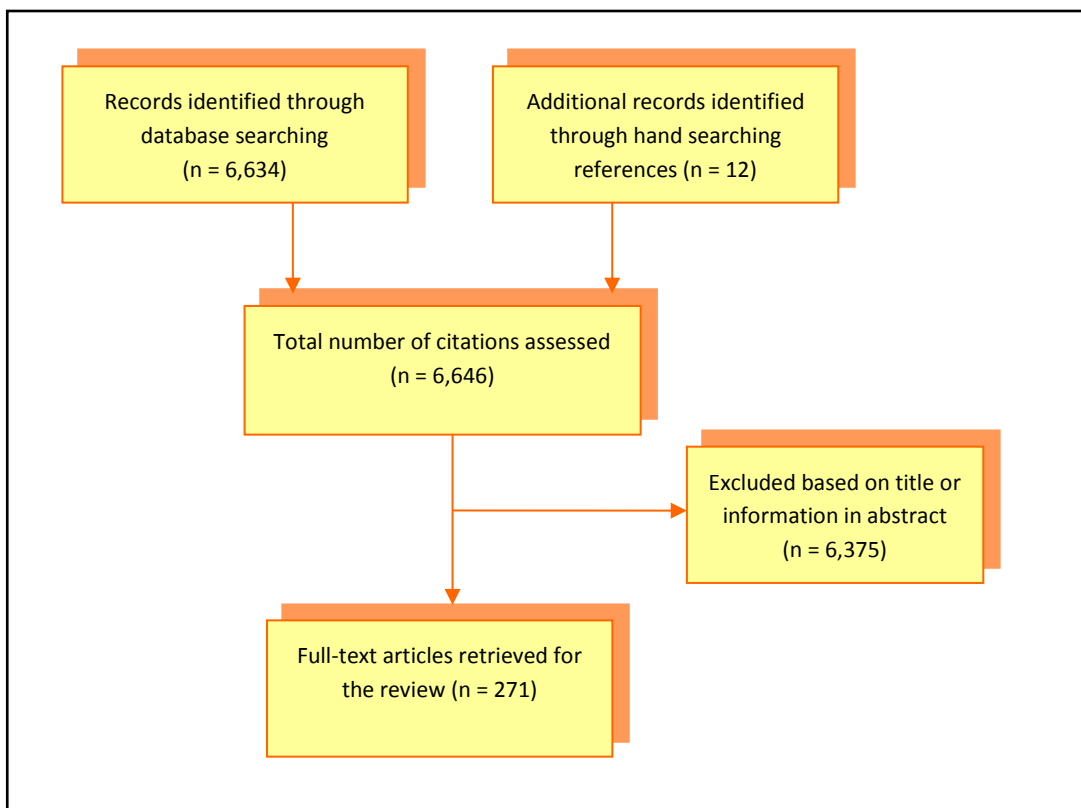


Figure 3.1: Flow diagram showing review process.

3.4.2.1. Assessment of eligible papers

Inclusion criteria for RCTs

Articles describing randomised controlled trials (RCTs) were deemed to meet the inclusion criteria if they included older women with potentially operable primary breast cancer (i.e. stages I-IIIa) that were randomised to PET vs. some form of surgical treatment.

Inclusion criteria for case-series and cohort studies

Non-randomised studies were deemed to meet the inclusion criteria if:

- They included patients with potentially operable primary breast cancer (i.e. stages I-IIIa).
- They pertained to the management of older or frail women.
- They included patients treated with primary endocrine therapy (PET).
- They included patients treated with neo-adjuvant endocrine therapy for at least 6 months prior to surgery.
 - They reported response to neo-adjuvant endocrine therapy prior to surgery being performed.

Exclusion criteria

Articles were excluded from the overall analysis if:

- More than 30% of the patients had non-operable disease (stage IIIb – where the tumour has spread to the skin of the breast or the chest wall – or metastatic disease).
- Neo-adjuvant therapy was given for less than 6 months.

3.4.3. Data extraction

3.4.3.1. Data extraction for RCTs

Data was extracted pertaining to the number of patients, type of anti-oestrogen used, ER status, complete response rate (CR), partial response rate (PR), static disease (SD), progressive disease (PD), clinical benefit rate (CR + PR + SD), disease progression, breast cancer-specific survival (BCSS) and overall survival (OS). Data analysis was performed using SPSS® software version 20 (IBM®) and Review Manager version 5.2. Associations were identified using Chi² analysis.

3.5. Results

3.5.1. Results of the search

Of the 271 papers that were examined, 74 were deemed relevant for inclusion in the reviews, these included articles pertaining to:

- Seven RCTs comparing PET vs. surgery in older women [219, 225, 227, 229, 231, 330-332, 335, 349, 350].
- Thirty case-series looking at cohorts of women treated with PET [74, 218, 220, 222, 228, 328, 329, 337-341, 351-369].
 - Seven of these were also cohort studies that compared women treated with PET against a surgically-treated control group [355, 357, 361, 364, 365, 367, 369].
- Thirty-seven large population studies looking at the overall treatment of older women, including the non-surgical management, but without data on PET efficacy, were also deemed relevant [44, 45, 68, 69, 75, 77, 78, 83-85, 88-92, 201, 370-394].

3.5.1.1. Characteristics of included studies

Characteristics of included RCTs

To date, there have been seven RCTs that have compared primary tamoxifen with surgery for the treatment of operable breast cancer in older women. The characteristics of these studies are shown in table 3.1.

Characteristics of included case series

To date there have been 30 published case series that have examined women treated with PET. These studies have been divided into those using tamoxifen only, those using an AI only and those studies including patients treated with both tamoxifen and AIs or where it was unclear from the paper which type of PET had been used. The characteristics of these studies are shown in tables 3.2-3.4.

Study	n	PET*	Surgery	Adjuvant anti-oestrogen	Average Age	ER Status	Stage	Follow-up
Nottingham I, UK [67, 227, 229, 349]	66	TAM	Wedge Mx, limited axillary surgery	No	>70	Not assessed	I-II	Up to 21-27 years
Nottingham II, UK [219]	94	TAM	Wedge Mx, limited axillary surgery	Yes (TAM)	78	All mod/strong +ve H score >100	I-II	Over 10 years
Naples, Italy [330]	37	TAM	Mx or WLE	Yes (TAM)	>70	Not assessed	T1-3, N0-1	Over 10 years
GRETA, Italy [331]	235	TAM	Mx or WLE with DTx	Yes (TAM)	77	Not assessed	T1-3, N0-1	80 months
St Georges, UK [225, 395]	100	TAM	Mx or WLE without DTx	No	75.5	Not assessed	T1-4	Up to 28 years
EORTC 10851, UK [332]	82	TAM	Mx, full ANC	No	76.3	Not assessed	Upto T3,N1	Up to 14 years
CRC, UK [231, 396]	230	TAM	Mx or WLE without DTx	Yes (TAM)	76 (70-90)	Not assessed	I-III	Up to 16 years
TAM = tamoxifen; Mx = mastectomy; WLE = wide local excision; ANC = axillary node clearance; DTx = radiotherapy								

Table 3.1: Characteristics of RCTs comparing PET with surgery.

Study	n	PET type*	Comparison	Average Age	ER status	Stage	Follow-up (m)
Gävle, Sweden [352]	27	TAM	None	80	Not stated	I-II	6-40
Dundee I, UK [329]	67	TAM	None	78	Not stated	I-III	36
Mayday I, UK [357]	161	TAM	Surgery/ radio-therapy/ medical	77 (70-98)	Unselected	I-III	60
Newcastle, UK [355]	61	TAM	Surgery	77	Unselected	70% stage I	14
Royal Marsden I, UK [356]	42	TAM	None	62 (29-84)	Not stated	I-III	19 (6-42)
Mayday II, UK [328, 357]	51	TAM	None	78 (70-91)	Not stated	I-III	36
Southampton I, UK [337]	58	TAM	None	78 (59-94)	Not stated	I-II	19
Edinburgh I, UK [223, 224]	100	TAM	None	>70	Unselected	I-IV	59
Florence, Italy [338]	62	TAM	None	78 (70-91)	Not stated	I-III	48
Southampton II, UK [358]	56	TAM	None	70-93	Not stated	I-III	60
Dundee II, UK [353]	113	TAM	None	82 (68-93)	Unselected	I-II	29 (1-103)
Radboud, Netherlands [339]	40	TAM	None	>70	Unselected	I-III	24
Edinburgh II, UK [218]	59	TAM	None	>70	ER+	I-II	>6
NKI/DdHK, Netherlands [228]	84	TAM	None	83 (69-93)	Unselected	I-III	60
Royal Marsden II, UK [359]	54	TAM	None	elderly	Unselected	I-IV	23 (14-55)
Nottingham II, UK [354]	47	TAM	None	>70	Unselected	Not stated	Not stated
Ireland [74]	68	TAM	None	>70	Unselected	I-IV	Not stated
Leicester, UK [397]	70	TAM	None	79 (70-93)	ER+	Not stated	70 (9-119)
Tilberg, Netherlands [361]	113	TAM	Surgery	84	Unselected	Not stated	49

Table 3.2: Characteristics of Case Series using tamoxifen (TAM) only.

Study	n	PET type*	Comparison	Average Age	ER status	Stage	Follow-up (m)
Luton, UK [362]	104	LET	None	83 (58-98)	ER+	Not stated	56 (4-106)
Hanover, Germany [340]	56	AI	None	74 (52-102)	ER+	I-IV	51 (19-78)
Hull II, UK [341, 351]	45	LET	None	87 (70-101)	ER+	I-III	60
Valencia, Spain [363]	56	LET	None	79 (66-91)	ER+	I-III	12

*ANZ = Anastrozole, LET = Letrozole

Table 3.3: Characteristics of Case Series using Aromatase Inhibitors only (AI).

Study	n	PET type*	Comparison	Average Age	ER status	Stage	Follow-up (m)
Nottingham I, UK [220]	50	NS	None	75-96	Unselected	I-IIIa	28 (3-97)
Hull I, UK [365]	62	TAM /AI	Surgery	82	ER+	Not stated	20 (2-150)
Nottingham III, UK [366]	84/64	TAM /ANZ	None	81 (62-93)	ER+	Not stated	24 (6-72)
Sunderland, UK [367]	99	TAM /LET	Surgery	80	ER+	Not stated	76
Wales [368]	82	TAM /AI	None	81 (62-93)	ER+	Not stated	24 (6-72)
Nottingham IV, UK [364]	616	TAM /AI	Surgery	81 (70-99)	ER+	I-III	41 (1-202)
Queen Mary's, UK [222]	91	TAM /AI	None	80 (50-96)	ER+	I-IV	18 (2-70)
Eindhoven, Netherlands [369]	184	TAM /AI	Surgery	84 (75-89)	Unselected	I-III	31 (1-102)

*TAM = tamoxifen, ANZ = Anastrozole, LET = Letrozole, NS = Not Specified

Table 3.4: Characteristics of Case Series using a combination of TAM/AI or Not Specified (NS).

Characteristics of large cohort/populations studies

To date there have been 37 cohort studies published, investigating the differences in the treatment of older women, although not all of them examined the effect of non-surgical management in these larger cohorts. The characteristics of these studies can be seen in tables 3.5 and 3.6.

Study	Source	Date range	n	Average Age	Non-surgical n treatment %
Canada [45]	Quebec tumour registry or Quebec hospital	1988-1994	1174	417/1174 aged 70+	Not stated
US I [44]	San Antonio breast cancer database; SEER registry	1973-1995	50828; 256287	23053/50828 aged 65+	126/35154 (<1%)
US II [377]	Mount Sinai Medical Centre	1978-1998	1126 (206 aged 70+)	70+ cohort: mean 77 years (71-92)	8/206 (3.9%)
UK I [69]	North Trent Cancer Network	March-August 2002	378 (167 aged 70+)	70+ cohort: median 78.9 (70-98)	70/167 (40.3%)
UK II [378]	Glenfield Hospital, Leicester	1997-2000	2209	Not stated	534/2209 (24.2%)
US V [201]	Four US regions	1997-1999	689	269 aged 75+	None
Germany I [91]	University of Ulm	1992-2005	1922	563 aged 70+	Not stated
Australia [380]	Australian National Breast Cancer Audit	1998-2006	57100 (6100 aged 70+)	70+ cohort: mean +/- SD 78.0 +/- 5.3 years	213/57100 (3.5%)
UK VI [85]	Eastern Cancer Registry Information Centre	1999-2003	9051 (2945 aged 70+)	2945/9051 aged 70+	789/2945 (26.8%)
Netherlands II [83, 90]	National Cancer Registry	1995-2005	127805	38.6% aged 65+	Shown as % for each age range per year
UK VII [89]	Eastern Cancer Registry Information Centre	1999-2007	14048	~40% aged 70+	4840/14048 (34.5%)
Netherlands IV [84]	National Cancer Registry	2005-2008	31520 (6561 aged 75+)	75+ cohort: median 82.5 years	1411/31520 (4.5%)
Germany II [381]	Breast Unit Heidelberg	2003-2010	3338 (810 aged 65+)	Median age 57.	45/3338 (1.3%)
Switzerland II [372]	University Women's Hospital Basel, Switzerland	1990-2005	523 (151 aged 80+)	80+ cohort: mean 84.3 years (80-95)	18/151 (11.9%)

Table 3.5: Characteristics of Cohort Studies of Older Women with a Younger Cohort for Comparison.

Study	Source	Date range	n	Average Age	Non-surgical n (%)
Italy [382]	North-East Clinical Cooperative Group in Italy	-	72	All 70+	2/72 (2.8%)
Netherlands I [77]	Sophia Hospital	1980-1992	210	All 70+	34/210 (16.2%) treated with PET
France I [75]	Rene-Huguenin Centre	1978-1992	1143	All 70+	131/1143 (11.5%)
Switzerland I [78]	Geneva cancer registry	1989-1999	407	All 80+	132/407 (32.4%) treated with PET.
US III [92]	Memorial Sloan-Kettering Hospital	1997-2000	96	All 75+	None
France II [394]	Institut Curie, Paris	1981-1995	1755	Median 75 (70-94)	None
US IV [379, 383, 384]	Six US healthcare systems	1990-1994	1837	All over 65	22/1859 (1.2%)
UK III [68]	North Western Cancer Registry	1999	480	>64 years	67/480 (14.0%)
UK IV [398]	Breast units Greater Manchester	2002-2003	76	All >64	12/76 (15.8%)
UK V [385]	Royal Marsden Hospital	1980-2000	950	All over 70	366/950 (38.5%)
US VI [386]	Four US geographic regions	1997-2006	660	All 65+	17/660 (2.6%)
Spain I [387]	Lluís Alcanyis Hospital	2005-2006	91	76 (70-92)	None
US VI [88]	SEER	1992-2003	49 616	All 67+	1.7%
France III [388]	Institut Curie, Paris	1995-1999	538	All 70+	29/538 (6.4%)
Netherlands III [389]	Comprehensive Cancer Centre East registry	2001-2006	2336	All 60+	112/2336 (4.8%)
Spain II [371]	Hospital Universitari Vall d'Hebron	1990-2009	259	Median 84	84/259 (32.4%)
US VIII [390]	MD Anderson Center, Texas	1989-2004	212	Median 83.5 (80-97)	7.1% treated with PET
Wales [391]	Nevill Hall Hospital	2003-2006	57	All 75+	29/57 (50.1%)
UK VIII [392]	Royal Bolton Hospital	2008	43	All 70+	8/43 (18.6%)
UK IX [393]	Nottingham Hospital	1973-2010	1758	Median 77 (70-99)	855/1758 (48.6%)
UK X [374]	Northern & Yorkshire and West Midlands registries	1997-2005	2303 8	All over 65 years	14.3% of stage I-III.
Netherlands V [373]	National cancer registry; 5 regional hospitals	1995-2005; 1990-2005	1086 51	Median 85.9 (75.0-97.7)	187/108651 (<1%)
UK XI [375]	22 English breast cancer units	2010-2013	800	All >69	136/800 (17%)

Table 3.6: Characteristics of large cohort/populations studies looking solely at older women.

3.5.2. Differences in the treatment of older women with operable breast cancer.

The population studies confirmed that older patients are more likely to have higher stage disease at diagnosis with larger, more strongly ER+ tumours [44, 45, 69, 84, 88-91, 377, 380, 388, 389, 399].

The main finding of the large population studies was that older women are less likely to receive standard treatment, including surgery, for their operable breast cancer when compared to younger women [68, 78, 83, 84, 88-91, 374, 375, 377, 378, 385, 388, 389, 391, 398, 399]. This is constant across all countries studied but varies by the degree to which this is seen. Table 3.7 shows the rates of non-surgical treatment by country.

Country	Rates of non-surgical treatment
Netherlands [77, 83, 84, 90, 373, 389]	1-16%
Sweden [78, 399]	12-32%
Spain [371, 387]	0-32%
France [75, 388, 394]	0-11%
Ireland [74]	26%
Italy [382]	2.8%
Germany [91]	1.3%
United States of America [44, 88, 201, 377, 379, 383, 386, 390]	0-7.1%
Australia [380]	3.5%

Table 3.7: Rates of non-surgical treatment by country.

They also demonstrated that breast cancer was a relatively less important cause of death in older compared to younger patients [44, 88-90], with Bastiaannet and colleagues [90] demonstrating that almost 100% of patients aged 15-65 years who died, died of their breast cancer, compared to only 20% in the 90+ group. Diab and colleagues [44] showed similar findings, with breast cancer responsible for 73% of all deaths in the 50-54 year olds with breast cancer vs. 29% of deaths for patients aged 85+, as did Ali and colleagues [89], with the proportion of patients dying of breast cancer relative to other causes declining from 70% in the 50-69 year olds to only 39% in the over 80s.

Rates of non-surgical management in older patients were found to vary according to region [374] and between hospitals [85], with patients in district general hospitals less likely to receive surgery than at a university hospital [68].

3.5.3. Reasons for the use of PET in older patients.

Several reasons were stated for the use of non-surgical treatment in these older cohorts, including old age, co-morbidity, lack of fitness, overall health status, patient choice and frailty [222, 362, 369, 373, 378].

Increasing levels of co-morbidity and a reduction in functional status are more common with increasing age [45, 201] and were associated with a reduction in rates of surgery in older patients [374, 375, 398]. However Hamaker and colleagues found that co-morbidity accounted for only 6% of decisions to omit surgery and overall health status for only 5% [373]. Rai and colleagues found that the reasons for not treating older patients with early surgery was due to either extreme age or being unfit for surgery in 60% [378] and in the study by Balakrishnan and colleagues, 29% of patients were treated with PET due to co-morbidities and 46% due to frailty [362]. Additionally, Ayantunde and colleagues found that 32% of patients treated with PET were treated thus due to them being unfit for surgery [222] and in 35% of the patients treated with PET in the study by Wink and colleagues this was due to the treating physician declaring the presence of co-morbidities as the reason [369].

Patient request was also found to be a commonly stated reason for the omission of surgery, including in 32% of patients in the study by Hamaker and colleagues [373], in 16% according to Balakrishnan and colleagues [362] and in 18% of patients in the study by Ayantunde and colleagues [222]. This is in contrast with the findings of Rai and colleagues [378] who found only 4% of patients treated without early surgery were due to patient choice, although this study related to a specialist elderly breast clinic run in combination with a geriatrician where the patients receive extensive counselling and comorbidity and frailty assessments, so may not be reflective of normal UK practice. Lavelle and colleagues [375] found that lower rates of surgery were unlikely due to patients actively opting out of surgery. Interestingly, Rao and colleagues [365] found that clinician choice in the absence of co-morbidities was the most common reason for patients receiving PET.

3.5.4. The evidence for the use of PET as a treatment for older women with breast cancer

3.5.4.1. Efficacy of PET

The efficacy of PET is measured according to tumour response using the RECIST Response Criteria [400]:

Using the sum of the longest diameter of the palpable lesion:

- Complete Response (CR): Complete disappearance of disease.
- Partial Response (PR): At least a 30% decrease in the size of the lesion relative to baseline.
- Progressive Disease (PD): At least a 20% increase in the size of the lesion relative to the smallest measurement since start of treatment or an increase in the total number of palpable lesions.
- Static Disease (SD): Neither sufficient shrinkage for PR nor sufficient increase for PD.

Patients with complete, partial or static responses are said to experience clinical benefit (CB). Patients may experience a period of clinical benefit prior to subsequently relapsing – these patients, together with the initial progressive disease patients are often combined to give a failure rate.

Efficacy reported in RCTs

The CR, PR, SD, PD and failure rates are summarised in table 3.8 below for the RCTs published to date.

Study	n	PET	ER Status	Clinical Benefit Rate	PD Rate	Failure Rate
Nottingham I, UK [67, 227, 229, 349]	66	TAM	Not assessed	74% (CR 50%; PR 17%; SD 8%)	26%	62%
Nottingham II, UK [219]	94	TAM	All mod/ strong +ve H score >100	97% (CR 30%; PR 44%; SD 24%)	3%	32%
Naples, Italy [330]	37	TAM	Not assessed	73% (CR 14%; PR 22%; SD 38%)	27%	35%
GRETA, Italy [331]	235	TAM	Not assessed	99% (CR 9%; PR 32%; SD 55%)	1%	45%
St Georges, UK [225, 395]	100	TAM	Not assessed	Not stated	Not stated	25%
EORTC 10851, UK [332]	82	TAM	Not assessed	Not stated	Not stated	68%
CRC, UK [231]	230	TAM	Not assessed	Not stated	Not stated	53%

Table 3.8: Response to PET as reported in Published Randomised Controlled Trials.

Efficacy reported in case series and cohort studies

The CR, PR, SD, PD and failure rates are summarised in tables 3.9-3.11 below for the non-randomised studies published to date. The studies are separated according to treatment type.

Study	n	PET used*	ER Status	Clinical Benefit Rate	PD	Failure rate
Gävle, Sweden [352]	27	TAM	Not stated	93% (CR 56%; PR 22%; SD 7%)	7%	19%
Dundee I, UK [329]	67	TAM	Not stated	73% (CR 27%; PR 21%; SD 25%)	27%	31%
Mayday I, UK [328]	161	TAM	Unselected	86% (CR 27%; PR 34%; SD 24%)	14%	60%
Newcastle, UK [355]	61	TAM	Unselected	77% (CR 18%; PR 39%; SD 20%)	23%	38%
Royal Marsden I, UK [356]	42	TAM	Not stated	95% (CR 2%; PR 55%; SD 38%)	5%	31%
Mayday II, UK [357]	51	TAM	Not stated	54% (CR 18%; PR 24%; SD 12%)	20%	Not stated
Southampton I, UK [337]	58	TAM	Not stated	69% (CR 17%; PR 17%; SD 35%)	31%	66%
Edinburgh I, UK [223]	100	TAM	Unselected	90% (CR 40%; PR 28%; SD 22%)	10%	Not stated
Florence, Italy [338]	62	TAM	Not stated	96% (CR 11%; PR 40%; SD 45%)	3%	31%
Southampton II, UK [358]	56	TAM	Not stated	59% (CR 21%; PR 29%; SD 9%)	29%	34%
Dundee II, UK [353]	113	TAM	Unselected	79% (CR 34%; PR 15%; SD 30%)	21%	62%
Radboud, Netherlands [339]	40	TAM	Unselected	82% (SD 40%)	18%	Not stated
Edinburgh II, UK [218]	59	TAM	ER+	54% (CR 24%; PR 22%; SD 8%)	34%	46%
NKI/DdHK, Netherlands [228]	84	TAM	Unselected	85% (CR 14%; PR 24%; SD 46%)	15%	44%
Royal Marsden II, UK [359]	54	TAM	Unselected	94% (CR 7%; PR 50%; SD 37%)	6%	24%
Nottingham II, UK [354]	47	TAM	Unselected	83% (CR 4%; PR 30%; SD 49%)	17%	Not stated
Ireland [74]	68	TAM	Unselected	57% (SD 28%)	31%	Not stated
Nottingham III, UK [366]	84	TAM	ER+	100% (CR 8%; PR 18%; SD 74%)	0%	Not stated
Leicester, UK [397]	70	TAM	ER+	77%	Not stated	84%
Tilberg, Netherlands [361]	113	TAM	Unselected	62%	2%	Not stated

Table 3.9: Response to PET as Reported in Published Case Series/Cohort Studies using tamoxifen (TAM) only.

Study	n	PET used*	ER Status	Clinical Benefit Rate	PD	Failure rate
Nottingham III, UK [366]	64	ANZ	ER+	97% (CR 9%; PR 30%; SD 58%)	3%	Not stated
Luton, UK [362]	104	LET	ER+	82% (CR 23%; PR 40%; SD 18%)	18%	37%
Hanover, Germany [340]	56	AI	ER+	100% (CR 11%; PR 77%; SD 13%)	0%	20%
Hull II, UK [341, 351]	45	LET	ER+	60%	4%	Not stated
Valencia, Spain [363]	56	LET	ER+	100% (CR 25%; PR 52%; SD 23%)	0%	Not stated

Table 3.10: Response to PET as Reported in Published Case Series/Cohort Studies using Aromatase Inhibitors (AI) only. *ANZ = Anastrozole, LET = Letrozole

Study	n	PET used*	ER Status	Clinical Benefit Rate	PD	Failure rate
Nottingham I, UK [220]	50	Not stated	Unselected	98% (CR 52%; PR 34%; SD 12%)	2%	12%
Hull I, UK [365]	62	TAM /AI	ER+	Not stated	Not stated	55%
Sunderland, UK [367]	99	TAM / LET	ER+	Not stated	Not stated	37%
Wales [368]	82	TAM /AI	ER+	Not stated	Not stated	15%
Nottingham, UK [364]	616	TAM /AI	ER+	84% (CR 26%; PR 30%; SD 29%)	16%	45%
Queen Mary's, UK [222]	91	TAM /AI	ER+	78% (CR 17%; PR 45%; SD 16%)	16%	Not stated
Eindhoven, Netherlands [369]	184	TAM /AI	Unselected	58% (SD 11%)	13%	35%

Table 3.11: Response to PET as Reported in Published Case Series/Cohort Studies using a combination of TAM/AIs or not stated.

Effect of ER status on women treated with PET

Twelve of the thirty non-randomised studies [218, 222, 341, 351, 362-368, 397, 401], including 1,417 patients, treated only women with only ER positive tumours. Eleven non-randomised studies [74,

220, 223, 228, 328, 339, 353-355, 359, 361, 369] treated women regardless of ER status, and seven [329, 337, 338, 352, 356-358] didn't assess for ER status, giving a total of 1,348 patients in the studies that included both ER positive and negative patients.

Comparing the clinical benefit rate (CR+PR+SD) according to ER status demonstrates a significantly higher clinical benefit rate for studies who included only ER positive patients (86% vs. 75%, $p < 0.001$), as would be biologically expected however the rate of disease progression was the same in both groups (41% vs. 41%). Unfortunately analysis of time taken to progress, the more clinically relevant aspect, was not possible due to the variation in length of follow-up between studies.

Effect of PET type on clinical benefit

Nineteen of the thirty non-randomised studies [74, 218, 223, 228, 328, 329, 337-339, 352-359, 361, 366, 397], including 1,256 patients used tamoxifen only and five studies [340, 341, 362, 363, 366] used AIs only (three used letrozole, one anastrozole and one did not specify) with 325 patients. Six studies [222, 364, 365, 367-369] used both tamoxifen and AIs and one study [220] didn't specify the type of PET used.

Clinical benefit (CR+PR+SD) was significantly higher in patients treated with AIs compared to patients treated with tamoxifen (88% vs. 77%; $p < 0.001$) and the rate of disease progression was lower in patients treated with AIs compared to tamoxifen (31% vs. 46%; $p < 0.001$).

3.5.5. Surgery vs. PET.

A Cochrane meta-analysis has been performed on the data from the RCTs looking at survival advantages [214, 215]. Since this review was published, the St George's group have released their long-term results at 28-years follow-up [395] and the Cochrane review has been updated as part of this PhD [402]. The results are reviewed here.

It was also possible to meta-analyse some of the results from the cohort studies in a similar manner [403]. This analysis is limited by the outcomes reported, with only seven studies reporting a surgical comparison cohort alongside their PET cohorts [355, 357, 361, 364, 365, 367, 369]. Six reported on overall survival (OS) and six reported on breast cancer-specific survival (BCSS). Below is an overview of the RCT meta-analyses, followed by the cohort data meta-analyses.

3.5.5.1. Overall survival (OS)

OS in RCTs

There were no significant differences between the two treatment arms, however the results favoured the surgical group in the surgery plus adjuvant endocrine therapy versus PET analysis.

- Surgery only vs. PET (EORTC 10851, Nottingham I, St Georges): HR 0.98, 95% CI 0.74-1.30, $p=0.9$ (see figure 3.2).
- Surgery plus adjuvant endocrine therapy versus PET (Nottingham II, CRC, GRETA): HR 0.86, 95% CI 0.73-1.00, $p=0.06$ (see figure 3.3).

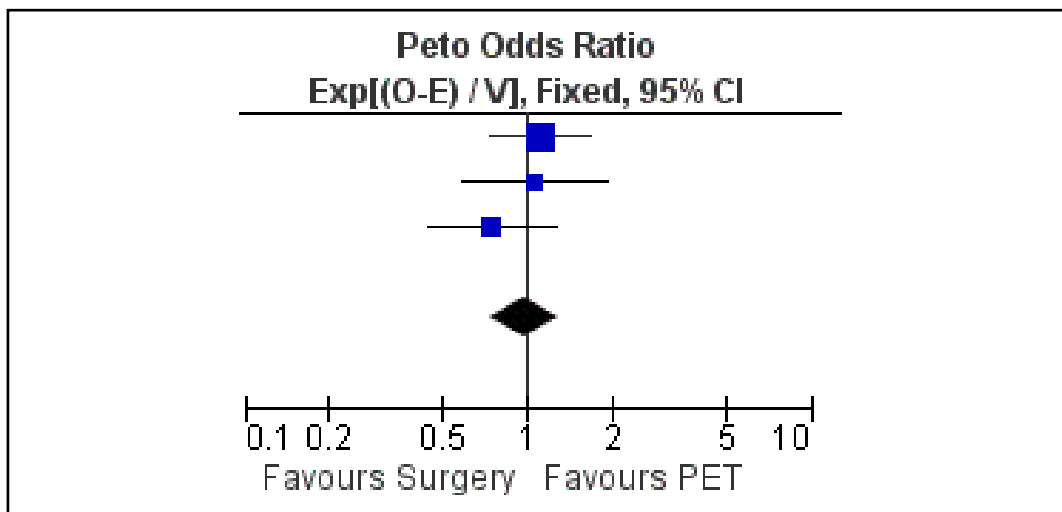


Figure 3.2: Forrest Plot 1 – Overall survival (Surgery alone vs. PET), reproduced from [402].

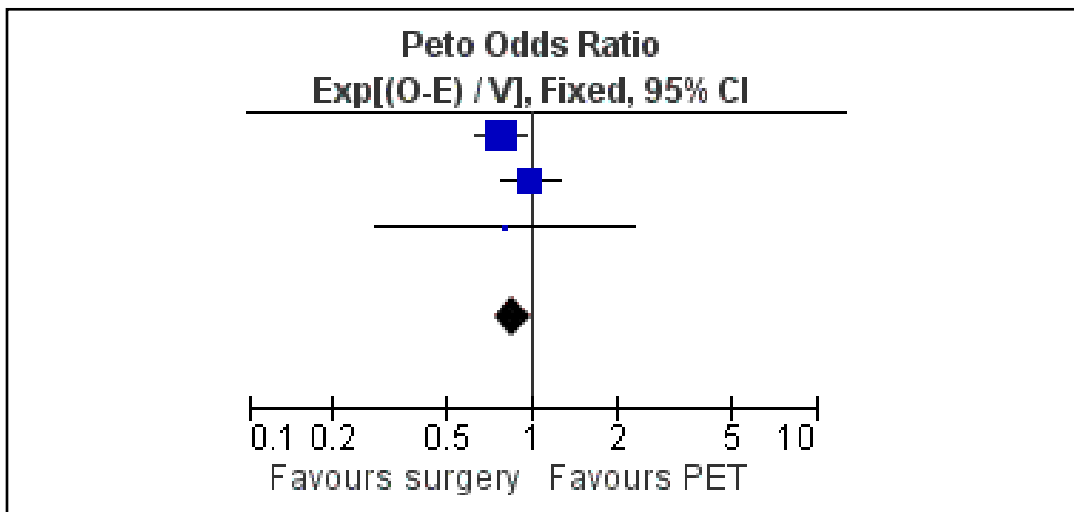


Figure 3.3: Forrest Plot 2 – Overall survival (Surgery + ET vs. PET), reproduced from [402].

Overall survival in cohort studies

Six cohort studies compared OS in their PET groups compared to a surgically-treated comparison group [355, 357, 361, 365, 367, 369]. Combining this data and using the Chi² test to assess significance, there was a significantly higher OS rate in patients treated with surgery when compared to those treated with PET (67% v 49%, p<0.001).

Overall survival in population studies

Lack of surgical management was also found by some of the larger population studies to result in poorer overall survival when compared to those patients surgically treated [78, 85, 371] but not all [84].

3.5.5.2. Breast cancer-specific survival (BCSS)

BCSS in RCTs

Mustacchi and colleagues published a meta-analysis of individual patient data from the CRC and GRETA studies [404]. Their results favoured surgery plus adjuvant endocrine therapy: HR 0.7, 95% CI 0.51-0.95.

Gazet and colleagues [335] published long-term follow-up data that included BCSS after 28 years of follow-up, by which time all recruited patients had died. They reported 43/100 of the surgical arm compared with 40/100 in the PET arm died from breast cancer, demonstrating no significant difference between the two interventions for this outcome.

These 2 studies differed in that Gazet did not use adjuvant endocrine therapy in the surgery group which may explain in part the lack of relative benefit of surgery compared to the CRC and GRETA trials which did use adjuvant endocrine therapy in the surgical arm.

BCSS in cohort studies

Six of the cohort studies examined BCSS between their PET cohort and a “control” cohort of women treated with surgery [355, 357, 361, 364, 365, 367]. Combining this data and using the Chi² test to assess significance, the surgically treated arm was associated with a higher BCSS than PET (90% vs. 85%, p<0.001).

BCSS in population studies

Breast cancer-specific survival in the population studies was found to be worse in older patients treated without surgery compared to those treated with surgery [78, 88, 371].

3.5.5.3. Disease-free survival

Disease-free survival in RCTs

Dividing the RCTs into those who assessed surgery only against PET and those that looked at surgery plus adjuvant endocrine therapy (ET) against PET, only one trial in each category provided data, both favouring the surgical arm over PET in this outcome:

- Surgery only vs. PET (EORTC 10851): HR 0.55, 95% CI 0.39-0.77, p=0.0006.
- Surgery plus ET vs. PET (GRETA): HR 0.65, 95% CI 0.53-0.81, p=0.0001 (see figure 3.4).

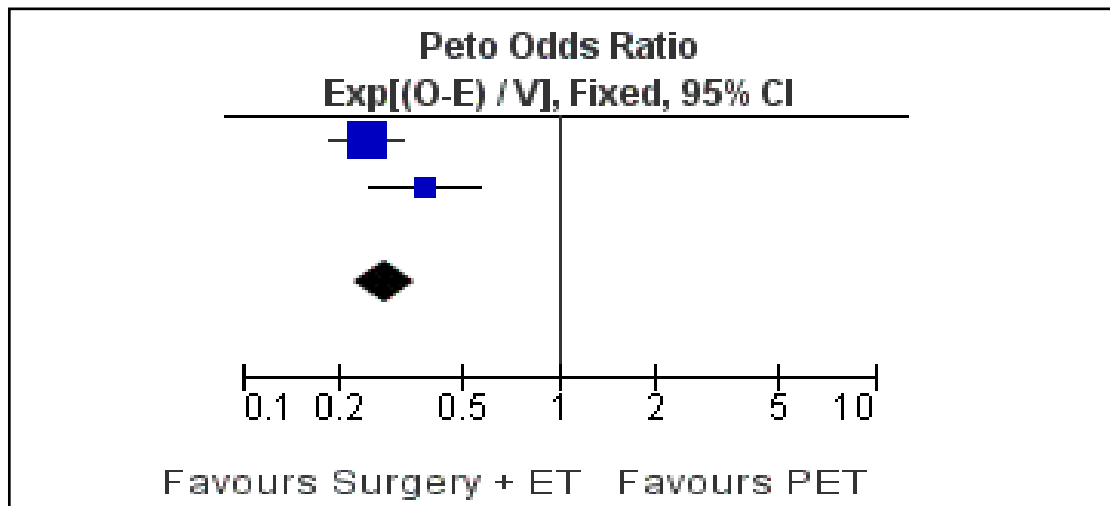


Figure 3.4: Forrest Plot 3 – Local Control (Surgery + ET vs. PET), reproduced from [402].

3.5.5.4. Quality of life

Only the CRC trial collected information on quality of life [396] using a socio-demographic questionnaire and the General Health Questionnaire (GHQ; 28 items). They found no difference between the two groups in their ability to manage household tasks and no significant difference in the psychosocial morbidity between the two groups [396]. However the GHQ is not a true measure of quality of life but is a screening tool for psychiatric disorders, such as anxiety and depression [405]. Quality of life has never been rigorously assessed in this population using a validated quality of life instrument.

3.5.6. Quality of the evidence

3.5.6.1. Quality assessment of the RCTs

The results of the Cochrane meta-analysis of RCTs are limited by the inclusion of only a few small studies. Meta-analyses in general are also limited to the outcomes assessed and reported by the included trials and these must be comparable in order to draw any meaningful conclusions. The Cochrane Collaboration provides a method for assessing the quality of RCTs [345] and each of the studies were assessed according to these criteria, including generation of allocation sequence, comparability between groups at baseline, and inclusion of all randomised patients in the analysis. Other quality issues are also examined here.

Generation of allocation sequence

Three trials stated adequate generation of their allocation sequence [67, 227, 229, 231, 331, 349]; CRC used computer-generated random numbers, GRETA used random numbers and Nottingham I used random card allocation.

The remaining four trials [219, 225, 330, 332, 395] didn't state their method, although both EORTC 10851 and St George's stated their allocation sequence was "randomised". No evidence of bias could be identified in the published reports, however an inadequate randomisation process can lead to inequality between groups at baseline, introducing bias.

Comparability of groups at baseline

Five of the studies reported that their groups were "well-balanced", "comparable" or "similar" which was considered adequate [219, 227, 231, 331, 332, 349, 350]. St George's [225, 395] reported that there were more T4 tumours in the PET group (14/100 vs. 7/100) however due to small numbers, this may have had limited significance. Naples did not report data on this [330].

Inclusion of all randomised participants in the analysis

Five studies analysed on an intention-to-treat basis [67, 219, 227, 231, 331, 332, 349]. St George's did not report any exclusions [225, 395] and Naples did not report adequate data to comment on this [330].

Lack of ER status assessment

Perhaps the most important flaw in the RCTs was the lack of ER status assessment, resulting in the treatment of women with ER negative tumours with endocrine therapy. Only the Nottingham II trial recruited only ER positive patients [219]. Those women with ER negative disease and treated in the PET arms of these trials can be considered a control group treated with placebo at best.

Lack of adjuvant endocrine treatment

Another significant difference in the methodology compared with modern practice, was the absence of any adjuvant endocrine treatment in the surgical arms of the Nottingham I, EORTC 10851 and St George's trials [67, 225, 227, 332, 349, 395]. In today's clinical practice all ER positive women treated with primary surgery would also receive adjuvant endocrine therapy unless contraindicated as it has been proven to improve survival and reduce recurrence rates [48, 163]. By not doing this, these three trials were effectively under-treating the surgical group.

Tamoxifen versus AIs

All seven RCTs used tamoxifen as PET and the three trials using adjuvant endocrine therapy also used tamoxifen in this setting [67, 219, 225, 227, 231, 330-332, 349, 395, 404, 406]. Since these trials were conducted, AIs have largely replaced tamoxifen, both in the PET and adjuvant settings in post-menopausal women as they have superior efficacy [187]. The beneficial effect of AI across both groups may have balanced and therefore not affected the differential outcome however.

Additionally, though all seven trials used tamoxifen, they did not use the same treatment regimes, with Nottingham I and CRC trials using 40mg daily [67, 227, 231, 349] and the remaining five trials using 20mg daily [219, 225, 330-332, 395, 406].

Variation in surgical treatment

There was large variation between the RCTs in terms of their surgical treatment. Both Nottingham I and II [219] used "wedge" mastectomy as their surgical intervention to the breast, a procedure usually only performed in modern practice in very frail patients where a quick and simple operation is needed as it leaves residual breast tissue on the chest wall. It is quicker to perform than a standard mastectomy which may be an advantage in frail patients where a short anaesthetic is desirable.

EORTC 10851, Nottingham I and Nottingham II all used only mastectomy as their breast surgery control [219, 332, 350], whereas St Georges, CRC, GRETA and Naples all used either mastectomy or wide local excision [225, 231, 330, 331, 395]. In addition, it is unclear whether adequate surgical margins were achieved as this was not commented on by the papers.

Of the trials using wide local excision, St Georges and CRC did not report the use of adjuvant radiotherapy in combination with this treatment [225, 231, 395]. Both GRETA and the Naples trials however did give breast radiation following wide local excision [330, 331] – a practice that is routine following this procedure in modern treatment strategies and one that has been shown to reduce local recurrence by two thirds [36, 41].

In addition, the St George's group used breast conservation surgery to treat women with large T3 and T4 tumours [225, 395] which may be associated with a high recurrence risk unless combined with either neo-adjuvant therapy and/or post-operative radiotherapy.

RCTs versus clinical setting.

These randomised-controlled trials recruited women who were fit for surgery into both of their treatment arms. By modern standards these are not the women who are routinely offered PET who tend to be frailer women where the risks of general anaesthesia would be higher. None of the RCTs stratified for co-morbidities which may have a significant impact on survival in this age group of women. [106].

3.5.6.2. Quality assessment of the case series and cohort studies

In an attempt to assess the methodological quality of these types of non-randomised studies, ranking scales have been designed to score these types of “lower ranking” studies [346-348]. The studies were rated on the following areas: title and abstract; introduction and aims; methods; sampling; data; analysis; ethics and bias; results; transferability or generalizability; implications and usefulness. Each paper was then given an overall score between 10 (poor) and 40 (excellent), indicating its methodological rigour.

The scores for methodological quality ranged from 17 [352] to 33 [364] out of a possible score of 40. The median score was 24, suggesting that the majority of cohort studies were of moderate quality.

This group of studies were heterogeneous in their methodology, analysis and interpretation. Some of these issues are considered here, together with some additional quality factors.

Variability in disease stage

There was considerable variation between studies with regards to the included patients. One study declared they included a large number (47%) of T₄ tumours and performed “limited” staging, resulting in the inclusion of patients with distant metastases (9%) [223]. Four other studies included stage I-IV disease (in all of these metastatic patients represented <30% of the overall cohort) [74, 222, 223, 340, 359]. In comparison, four studies included only patients with stage I or II disease [218, 337, 352, 353] and one stated that 70% of their patients had stage I disease. Nine studies did not state the stage of disease they included in their analysis [341, 354, 361, 362, 366, 368, 397].

Disease stage has a significant impact on overall survival [407], and possibly the clinical effect, with patient who have a high disease load potentially responding more slowly, or with PR, rather than CR. In addition if the percentage of patients in one arm or other of those with stage 4 disease was higher, as may be the case with PET then this would strongly bias the results in favour of surgery. This is the reason for excluding studies with a significant proportion of Stage IIIb or IV patients.

ER status

Not all studies measured ER status for all their patients (see tables 3.2-3.4), with only 12 of the included studies including only ER positive women in their analysis [218, 222, 340, 341, 362-368, 397]. This has obvious implications for the efficacy of PET as well as how transferable the results are to modern day clinical practice, where only women with moderately or strongly ER positive tumours would be treated in this way.

Co-morbidity assessment

The co-morbid status and ages of the patients varied greatly between included studies. Mansi and colleagues [356] included a 29 year old patient in their study which, in terms of modern day practice, would be considered a wholly inappropriate indication for PET. The majority of studies took 70 years as a cut off for “older” or “elderly” and the majority did not comment on the level or type of co-morbidities.

- Allan and colleagues [224] commented that 38% of their study population had significant co-morbid conditions, meaning that 62% did not and were assigned to treatment based purely on their age.

- Okunade and colleagues [366] stated that all included patients were deemed unfit for surgery or refused, but did not explore the reasons patients were considered “unfit”.
- Ayantunde and colleagues [222] reported that 32% of included patients were “unfit for surgery” and 18% declined surgery but 27% were assigned to treatment with PET based solely on advanced age. It is interesting that despite the high proportion of “unfit” and “advance aged” patients, this study had a 93% 5-year survival rate.
- Balakrishnan and colleagues [362] stated frailty as a reason for treatment choice in 46%, co-morbidity in 29%, patient preference in 16% and old age in 9%.
- Bergman and colleagues [228] found that patients had been treated with PET for multiple documented reasons, including physical or mental condition in 38%, age in 36% and patient choice in 35%.
- Co-morbidities were a reason for treatment with PET in 35% in Foudraine and colleagues’ study [339]. Other reasons included patient refusal (38%) and age (15%).
- Hille and colleagues [340] stated that of the 56 patients in their study, 25% were considered “ineligible for surgery”; in 20% the decision was made based on old age and 57% of patients refused.
- Hooper and colleagues [74] reported that 61% of their group had significant co-morbidity. Age was a factor in 14% and patient preference was a contributing factor in 11%.
- Rao and colleagues [365] commented that the decision to treat patients with PET was down to consultant decision in 47%, patient decision in 18% and due to co-morbidity in 27%.
- In the study by Wink and colleagues [369], treatment with PET was due to patient choice in 41%, age in 15% and co-morbidity in 35%.
- Osborn and colleagues [368] in their study were the only authors to use a formal assessment of co-morbidity. They used the Charlson Index and reported that only 34% of their patients had greater than a 2% chance of surviving 10 years, with only 6 patients having a greater than 50% chance of surviving 10 years. The majority of these six patients also had some form of dementia. Fourteen (17%) of the patients in this cohort eventually needed to undergo surgical treatment due to disease progression, and this was performed under local anaesthetic.

Co-morbidities have a significant impact on survival, and even those older women who are fit for surgery in this age group are quite likely to die of co-morbid diseases, thereby potentially reducing the survival advantage of any breast cancer therapies [106].

Allocation bias

With respect to the cohort studies that compared non-randomised groups of women treated with either surgery or PET, it is important to examine the differences in the characteristics of the two groups – particularly with regards to co-morbidity levels which will impact on all-cause overall survival rates. One might expect that, in view of the reasons quoted by authors for choosing PET as a treatment – many of which include factors that impact on mortality, such as co-morbidity or extremes of age – that the women in the PET arms were more likely to have reduced survival for reasons other than treatment allocation.

Of the seven cohort studies, only two compared any characteristics between the two groups:

- Dordea and colleagues [367] compared outcomes between patients treated with surgery and PET and reported a significant difference in ASA grades between the two groups.
- Syed and colleagues [364] also compared surgical and PET cohorts but didn't report rates of co-morbidity but they did state that the patients in the PET arm were relatively older than those in the surgical group. This is likely to be of significance as the incidence of co-morbidities increases with age [408] and life expectancy is decreased. It therefore represents a significant but expected bias in all-cause mortality.

Treatment

Another significant source of heterogeneity is the drug used as PET. The early studies had all used tamoxifen, with later studies tending to use AIs (see table 3.2 and 3.3). Some studies included patients treated with both, with patients recruited earlier into the cohort using mainly tamoxifen and those recruited later in the study being treated with an AI (see table 3.4).

As seen in the sub-group analysis performed looking at the type of drug used as PET, patients treated with AIs seem to have a better clinical benefit rate and lower rate of progression compared with those treated with tamoxifen.

Follow-up length

There was also huge variation in the length of follow-up between studies, which will have an impact on the number of patients who went on to develop progressive disease. Syed and colleagues [364] had both the shortest and longest follow-up with a range between one and 202 months.

Assessment of response

One study required patients to have repeat mammograms every three months to assess response [338] and another repeated mammographic surveillance at 1, 2, 4, 6, 9, 12 and every 6 months thereafter [352]. One study also required patients to undergo three biopsies to assess biomarker response [359]. In terms of intensity of follow-up, these protocols would seem inappropriate for this frail older population. Response assessment methods were variable between studies and largely based on clinical assessment which is less reliable than imaging assessment.

Cross-over

Many of the studies commented on further treatment required by patients who subsequently relapsed following initial successful results – several studies went on to treat these patients surgically [74, 223, 228, 337, 340, 353, 355, 358, 362, 368, 406]. This suggests that at least some of the included women were fit to have surgery from the outset and therefore may have been more appropriately treated in this way, although it is accepted that many older women chose PET when given a choice due to borderline fitness.

3.5.6.3. Quality assessment of population Studies

There are several other issues pertaining to the quality of the data from the population-based studies which is inherent to all registry-based data, including selection bias due to unrecorded factors (for example if there are differences in assignment of patients to treatment [409], missing data that results from the coding process, as well as being non-randomised. Up to 50% of patients had missing ER status [373] and this figure increased with increasing age [88]. Lavelle and colleagues [374, 375] showed that rates of surgery fell with increasing co-morbidity and worsening functional status but most studies didn't account for this when assessing overall survival.

3.6. Discussion

3.6.1. Use of PET

In the UK, the use of PET to treat older women is common, with studies demonstrating that 40% of women over the age of 70 years [69, 70] and 55% of women over the age of 80 years [71] are treated solely with hormone therapy. This is mirrored in the published population studies documenting between 14 and 50% of older breast cancer patients treated without surgery [68, 69, 85, 89, 92, 374, 375, 378, 385, 391-393, 398]. Studies published in the rest of Europe show lower rates but demonstrate that non-surgical treatment still forms a significant part of the management of these patients, with rates of up to 30% [74, 75, 77, 78, 83, 84, 90, 91, 371, 373, 382, 387, 388, 394, 399]. However in the United States of America and Australia [44, 88, 201, 377, 379, 380, 383, 386, 390], rates of non-surgical management are much lower, although in the USA drivers of medical practice are often dominated by medico-legal and financial considerations which may make PET less attractive to clinicians.

3.6.2. Efficacy of PET is generally high

When examining the efficacy of PET, clinical benefit rates in older women with ER positive breast cancers are generally high and overall the cancer reduces in size or fails to progress in 75% of cases [402]. However, most of the original published RCTs recruited patients regardless of their ER status. Patients with moderate to strongly ER positive breast cancer can expect a good response in around 79-90%, this is in comparison to up to a 100% progression rate in patients with ER negative tumours [217, 218, 220, 221, 331]. This can be seen from the non-randomised data where there is a significantly higher response rate for those trials that included only ER positive patients.

Efficacy of PET also appears higher for patients treated with AIs rather than tamoxifen, which is consistent with the findings from studies in other settings for this population, including the adjuvant, neo-adjuvant and metastatic settings, where AIs are well-established as the superior option [180, 187, 191, 200].

3.6.3. Is PET or surgery associated with a survival benefit?

3.6.3.1. Meta-analysis of RCTs shows no overall survival benefit

In terms of overall survival benefit, there is no clear advantage to either treatment shown by the meta-analysis of the RCTs published to date. However, many of these trials were flawed by modern

standards, particularly with regards the treatment given; three out of the seven trials used a comparison of surgery *only* – when in current clinical practice, all patients undergoing operative intervention would be treated with adjuvant endocrine therapy where appropriate. This is without taking into account modern surgical techniques, with adequate margins and the routine addition of radiotherapy to patients who undergo wide-local excision.

Three of the RCTs have published data pertaining to BCSS and meta-analysis of two of these studies favoured surgery plus adjuvant endocrine therapy over PET [404], although the third study reported no significant difference between the two therapies [335]. However, this study did not use adjuvant therapy in their surgery group which may in part explain the lack of relative benefit of surgery.

As discussed above, it is worth bearing in mind the limitations of the RCT data and that they may not be representative of current UK practice. The main limitation is that all of the women recruited to the RCTs were fit for surgery under general anaesthesia and the average age of the groups was in the early to mid-70s

3.6.3.2. Meta-analysis of case series shows survival benefit in favour of surgery

Looking at the non-randomised case series, the combined data showed an advantage in terms of both overall and breast-cancer specific survival in favour of surgery. However, it must be noted that due to the selection criteria for these two groups of patients, particularly in terms of fitness for surgery and co-morbidities, the overall health status of the two populations are likely to be inherently different which will result in confounding when looking at OS as it includes all-cause mortality, something that would be expected to be higher in a less fit cohort.

Breast cancer specific survival should be less subject to bias associated with baseline fitness levels between groups than overall survival and as this also favours surgery, this is of potential clinical significance. It suggests that in studies of what may be regarded as ‘normal clinical practice’ (as opposed to the artificial conditions imposed by RCTs) there is still some advantage to surgery except in women with a very high burden of comorbidity or frailty who die of non-breast cancer related diseases within a few years of diagnosis. However there is another potential source of bias to consider: that of death certification. If a woman has had surgery and has no evidence of local recurrence and dies of unrelated illness, breast cancer may not be mentioned on the death certificate. If she is on PET and still has a palpable or visible breast cancer, she may be more likely to have the breast cancer listed as a contributing cause, even when this was not the case. This

phenomenon is increasingly recognised as a potential bias in observational studies using death certification to assess cause of death [410-414].

The non-randomised case-series data has provided a unique opportunity to compare the different types of PET in the “real-life” setting, and to explore the survival difference between studies that treated all women, regardless of ER status, fitness for anaesthesia and comorbidities, in this manner versus those who only used PET to treat ER positive women. In effect what would normally be regarded as a source of bias can be used to get a better understanding of real outcomes in clinical practice.

3.6.3.3. Population data suggests under treatment is associated with poorer survival

Several of the population studies demonstrated a survival advantage for both overall and breast cancer-specific survival for patients treated with “guideline therapy” – that is surgery and appropriate adjuvant therapy, compared to those receiving non-standard therapy [78, 85, 88, 89, 201, 371, 390], although this was not true for all [84]. Due to the size of these studies, non-standard therapy may include patients who refused any kind of treatment and only two population studies compared cohorts of surgically treated patients with PET specifically, both of which found worse BCSS in the PET groups [78, 371]. This may be due to a genuine difference in matched cases but may also reflect subtle case selection bias (stage may have been higher in those offered PET and therefore surgery more complex and less likely to be tolerated, and in some cases patients with metastatic disease at presentation will have been included in this group as registry staging accuracy is often imperfect).

Again, death certification is a potential source of error and bias in these studies, as with the case series [410-414] and this is further compounded by problems with missing data. Again, as with all observational studies, allocation bias is an inherent flaw with this type of study and will affect survival outcomes.

3.6.3.4. Quality of life

There are currently very little data on quality of life outcome measures comparing surgery and PET. What there is demonstrates no long term difference in psychosocial morbidity between the two treatments [240, 396]. However each treatment may carry different risks that may affect quality of life and complications of surgery in particular may limit functional independence in the short term post-operatively by necessitating admission, affecting arm mobility [230, 250] and worsening cognitive and functional ability following general anaesthesia [203].

There is evidence to suggest older women are more interested in understanding the impact of treatment on their functional independence and quality of life [127, 226, 286], that older patients may prioritise quality of life over quantity [415] and patient choice is commonly stated as a reason for treating patients with PET [128, 369].

3.7. Summary

Based on the current evidence in the literature, there are currently no definite answers about the treatment of older women with operable primary breast cancer. It is clear that this is a heterogeneous group of patients, and older women presenting with a new diagnosis of breast cancer should be treated on an individual basis.

Whilst RCT data suggests little or no survival advantage for surgery over PET, these trials were flawed. Cohort study data, which is also subject to innate bias, does appear to suggest a survival advantage favouring surgery and hence fit and healthy older women should probably be treated according to standard practice, using the same strategies as are used in younger women, i.e. a choice of surgical treatment with the appropriate adjuvant therapies.

Very frail women at the extremes of age, or those with multiple significant co-morbidities, so that their predicted life-expectancy is significantly reduced, may benefit from treatment with PET.

Only those women with strongly ER positive cancers should be considered for treatment with PET. For those women in whom PET is considered appropriate on the basis of reduced life expectancy, an AI should be used in preference to tamoxifen where it is not contra-indicated, and letrozole appears to be the most effective of these in the literature to date.

All women who are treated in this manner should have regular clinical follow-up to assess the response of the primary tumour. If there are signs of disease progression then surgery if they are fit for it or second-line hormone therapy should be considered.

This review highlights the need for further research to define criteria for selection of PET in terms of age/comorbidity and frailty cut offs as a safe and effective treatment option.

Chapter 4: Retrospective Analysis of Eight Years' UK Cancer Registry Data

4.1. Abstract

4.1.1. Introduction:

Wide variation in the rates of non-operative management of breast cancer in older women exists across the UK. Some of this may be explained by variation in socio-economic status which may impact on levels of co-morbidity, education, screening uptake and stage at presentation, all factors that may contribute to treatment decision. It is therefore important to correct treatment variance for differences between populations by adjusting for patient and tumour characteristics to understand whether these explain variation in treatment.

4.1.2. Methods:

Data from two UK cancer registries between 2002 and 2010 were analysed to identify whether variation in treatment observed at hospital and clinician level persisted following adjustment for case mix. Expected case-mix adjusted surgery rates were derived by logistic regression using the variables age, proxy Charlson Co-morbidity Score, deprivation quintile, method of cancer detection, tumour size, stage, grade and nodal status.

4.1.3. Results:

Data on 17154 women over 70 with ER+ operable breast cancer were analysed. There was considerable variation in rates of surgery at both hospital and clinician level. Despite adjusting for case mix, this variation persisted at hospital level, although not at clinician level.

4.1.4. Conclusion:

This study demonstrates variation in selection criteria for older women for operative treatment for early breast cancer, meaning that some older women may be under or over treated and may partly explain the inferior disease outcomes associated with this age group. It emphasises the urgent need for evidence based guidelines for selection criteria in older women with breast cancer.

4.2. Introduction

As discussed earlier, there is considerable variation in the management of older women with breast cancer across the UK, with regional rates of non-operative treatment of patients over 70 years varying between 12 and 40% [73]. There is a 37-fold difference between the highest (37 per 10 000) and lowest (1 per 10 000) rates of surgery in the over 65s depending on where they live [416]. This variation in surgical treatment rates of cancer patients has been deemed a healthcare inequality [94].

Several factors may contribute to varying treatment rates in the older breast cancer population, including clinical factors such as tumour stage and patient health status which will impact HCP decision-making, as well as patient preference and local social and economic factors. There is evidence that more deprived populations are less likely to receive surgery to treat cancer [417] as variation in socio-economic status may impact on levels of co-morbidity, education, screening uptake and stage at presentation which are all factors that may contribute to the treatment decision. To date, studies that have examined the variation in surgical treatment rates for older breast cancer patients have failed to take account of these factors, which may in part explain some of the variation observed.

Several studies have used registry data to identify factors affecting the receipt of surgery in the older breast cancer patients, but none have examined the variation in treatment assignment according to individual hospital and clinician [85, 89, 374]. This component of the study aimed to analyse UK practice relating to older women with operable, ER-positive breast cancer to establish whether the variation observed at hospital and clinician level persists following adjustment for the patient and tumour characteristics.

4.3. Methodology

4.3.1. Choice of cancer registration data analysis

In the UK, all diagnoses of cancer are registered by one of the UK's eleven cancer registries, now part of Public Health England, an executive agency of the Department of Health. Cancer registration data therefore allows analysis of large cohorts of patients treated in everyday, normal clinical practice. In terms of breast cancer, data collected include information on patient characteristics, including age and postcode, and tumour characteristics including stage, and treatment received.

At the time of data collection, the West Midlands Cancer Intelligence Unit (WMCIU) was the National Cancer Intelligence Network (NCIN) lead registry for breast cancer, providing data on 4,000 cases per year for the West Midlands region (population 5.3 million) and undertaking annual collation of all UK registry data on breast cancer through the NHS Breast Screening Programme & the Breast Cancer Clinical Outcomes Measures Project (BCCOM Audit) [73, 418]. The Northern and Yorkshire Cancer Intelligence Unit region serves a population of 6.6 million and combined the two registry regions collect data on diagnoses representing a quarter of all breast cancer cases in the UK. The populations covered by these registries are demographically representative of the UK as a whole.

The WMCIU breast dataset has data from the 1980s and includes date of birth, ethnic origin, cancer stage (NPI), grade of tumour, laterality, ER status (from 2002), HER2 status (from 2004) method of diagnosis, treatment type (surgery, radiotherapy, chemotherapy, hormone therapy, other), date of diagnosis, recurrence rates and mortality including date and cause of death. The data from the Northern and Yorkshire region is less complete (see table 4.1).

The routine nature of data collection through hospital coding teams makes this type of observational data less prone to selection bias. However, this method is hampered by missing data and potential coding inaccuracies which is a limitation that needed to be addressed as, in order to adjust for case mix, it is important to account for the fact that some of the variables in the adjustment are not completely observed. Table 4.1 shows the data quality for the items collected.

Data item	% complete	
	West Midlands	Northern and Yorkshire
ER status	85.5%	8.3%
Grade	82.1%	79.7%
Nodal status	54.6%	48.0%
Tumour size	60.6%	73.7%

Table 4.1: Data completeness for each registry region.

4.3.1.1. Linkage of patient data to Hospital Episode Statistics (HES) and Proxy Charlson Index

Individual patient data can be linked, by means of linking individual NHS numbers to the Hospital Episode Statistics (HES) database, which is a record-based system that collects data on all admissions, outpatient appointments, A&E attendances and diagnostic codes [419] at NHS hospitals in England. HES data can act as a surrogate indicator of co-morbidity levels [114, 117, 420, 421], permitting derivation of a proxy Charlson Index [422] based on the International Classification of Diseases (ICD) codes for each individual's admissions to hospital. A large number of instruments have been developed to identify comorbidity in patient populations using administrative data, mainly from US data [423-427] and most are adaptations of the validated Charlson co-morbidity index developed in 1987 [115] that uses ICD codes [428]. However these Charlson-based instruments have also been validated using HES data in England [117].

The Charlson co-morbidity index allows prediction of ten-year mortality based on a patient's comorbid conditions [115, 116]. The index includes a total of 22 conditions which are scored as in table 4.2. The scores may then be summed to provide a total score which can be used with age to predict mortality (see table 4.3).

4.3.1.2. Calculation of deprivation

The 2010 Index of Multiple Deprivation (IMD) is a composite measure of deprivation made up of seven Lower layer Super Output Area (LSOA) level measures reflecting the broad range of deprivation that people can experience [429]. The seven domains are weighted and relate to: income deprivation, employment deprivation, health deprivation and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation and crime [429]. The IMD is determined at the LSOA level, census zones with socio-economically homogenous populations with a minimum population size of 1000 individuals.

For this analysis, a geographical measure of deprivation was recorded as quintiles of the income domain of the English Indices of Multiple Deprivation 2010 [429, 430], derived from the patient's postcode of residence at diagnosis, using the same methods as other English registry analyses [431-435].

Comorbid condition	Score assigned
Myocardial infarction	1
Congestive heart failure	
Peripheral vascular disease	
Dementia	
Cerebrovascular disease	
Chronic lung disease	
Connective tissue disease	
Ulcer	
Chronic liver disease	
Diabetes	
Hemiplegia	
Moderate or severe kidney disease	
Diabetes with end organ damage	
Malignant tumour	
Leukaemia	
Lymphoma	
Moderate or severe liver disease	3
Metastatic malignant tumour	6
AIDS	

Table 4.2: Weighting of comorbid conditions in the Charlson Index [115].

Comorbidity-age combined score	Predicted 10-year survival (%)
0	99
1	96
2	90
3	77
4	53
>5	21
Each co-morbidity rank is equivalent to one decade of age, with 40 years taken as the zero-rank for age (e.g. a patient who was 50 who had a co-morbidity index of 2 would have a score of 3, a patient who was 70 who had a co-morbidity index of 2 would have a score of 5).	

Table 4.3: Predicted 10-year mortality from combined comorbidity and age [115].

4.3.2. The multiple imputation by chained equations (MICE) approach to missing data

4.3.2.1. Options for dealing with missing data

There are several potential ways of handling missing data in statistical analysis, those most commonly used in registry data analysis include: Complete Case Analysis and imputation of the missing values [436].

Complete Case Analysis involves deleting all cases that have missing data from the analysis. This may cause obvious problems in analyses where a large proportion of cases have missing data as the dataset become substantially reduced and Complete Case Analysis is usually only recommended where less than 5% of data are missing. More importantly in this case, the probability of a case having complete data is related to the outcome measure (having surgery or not) as patients who do not have surgery do not have histological assessment of a surgical specimen which is the main source of data for cancer registries and as such this would not be a valid method of dealing with cancer registration missing data as the complete sample would no longer be representative.

Multiple imputation by chained equations (MICE) is a more complex method of dealing with missing data that has emerged as a principle method of addressing missing data in large datasets such as these [437-439]. Multiple imputation involves filling in the missing values multiple times, creating multiple “complete” datasets. Because multiple imputation involves creating multiple predictions for each missing value, the analyses of multiply imputed data takes into account the uncertainty in the imputations. It is therefore less prone to bias than other methods [437]. This technique can be used with datasets that contain different type of variables, e.g. continuous, categorical, etc.

4.3.2.2. The method of MICE:

The multiple imputation for this analysis was performed by another researcher from the Bridging the Age Gap study team, PR.

The procedure for MICE can be broken down into several steps:

1. A simple imputation (or “best guess”), such as imputing the mean is performed for every missing value in the data set.
2. The “best guess” values for one variable are set back to missing and a regression model* is used to predict the values based on all the other covariates.

*The type of regression model used will depend on the covariate – i.e. continuous, categorical, etc.

3. These predictions replace the “best guess” values for that variable.
4. The model continues performing step 2 and 3 for each of the covariates that have missing data. At the end of this “cycle” all the missing values for each covariate have been replaced by imputed values.
5. The model will run several “cycles” setting back the imputed values of each covariate to missing and re-running the regression model until the regression models do not demonstrate any upward or downward trend – i.e. they converge to a range of values.
6. Using the converged model you can produce several completed data sets to work with – each of these will have different predicted values replacing the missing one – i.e. they will have variability within the missing data. These data sets should be checked to ensure that the distribution of the missing values appear consistent with the observed values, and that there are no invalid values (for example, negative tumour diameter).
7. Statistical analyses are performed on each of the data sets and the results combined to take into account the variability within the imputed data [440].

4.4. Methods

4.4.1. Research governance

4.4.1.1. Ethics approval

Research Ethics Committee (REC) approval was granted for this component of the study as part of the wider Bridging the Age Gap Project (NREC approval: 12/LO/1808). Details of these approvals can be found in Appendices 1&2.

4.4.1.2. National Information governance board (NIGB) approval

This component of the study was also approved by the NIGB to process patient identifiable information without consent (NIGB approval: ECC 8-04 (g)/2013). This permission was needed to permit the linkage of the cancer registry and HES datasets which was performed independently by registry staff so no identifiable patient data was actually released to the research team. Full details can be found in Appendix 5.

4.4.1.3. Confidentiality

The received database contained no patient identifiable information except for date of death. All other patient identifiers, including patient name, date of birth, postcode and NHS number was not retained for analysis and did not form part of the obtained dataset. Clinician and hospitals were pseudo-anonymised by West Midlands Cancer Registry prior to data transfer.

Data obtained were password protected and stored on a secure, password protected university computer drive in accordance with the Data Protection Act 1998.

4.4.2. Sample and setting

Records on new invasive breast cancer diagnoses in women aged 70 years and over between the years of 2002 and 2010 were acquired from two UK cancer registry regions (West Midlands, Northern and Yorkshire). This time period was chosen as data quality prior to 2002 was not as high, for example ER status was not routinely collected by any registry region until this date, however the BCCOM audit data collection started in 2002, massively improving data quality nation-wide [73, 418].

Data on patient and tumour characteristics and deprivation were included (see table 4.4).

Deprivation was recorded as quintiles of the English Indices of Multiple Deprivation 2010 [430],

derived from the patient’s postcode. Data were also obtained from a linked, matched Hospital Episode Statistics (HES) dataset and a proxy Charlson Comorbidity Index [115] was calculated for each patient using the diagnostic codes recorded for any hospital admission in the year before diagnosis of their breast cancer. The cancer component of the Charlson Comorbidity Index was taken from the registry data and added to scores obtained from HES, in a method consistent with other similar registry data analyses [374, 421]. Higher scores indicate higher levels of comorbidity.

Characteristics included in analysis	
Patient Characteristics	Age
	Deprivation
	Co-morbidity
Tumour Characteristics	ER status
	Tumour size
	Nodal status
	Tumour Grade
	TNM stage
	Method of tumour detection
Treatment	Surgery
	Endocrine therapy

Table 4.4: Characteristics obtained for analysis.

4.4.2.1. Data cleaning

The raw data sets were combined by WMCIU and password encrypted before transfer. Data were cleaned, coded and missing data imputed by another researcher (PR) using the method of MICE (as described above), resulting in 25 unique complete datasets for analysis by the primary researcher (JM).

Missing data handling

Missing data on disease characteristics and co-morbidity was handled using the method of multiple imputation by chained equations (MICE)[441] to produce 25 imputed data sets and combining the results [440]. It was judged that 25 imputed datasets would be enough to account for the variability within the imputations. Covariates with over 50% missing data, such as HER2 status, were not included in the regression models.

4.4.2.2. Inclusion/exclusion criteria

Analyses were restricted to patients with operable, oestrogen receptor positive (ER+) disease at diagnosis. Patients with oestrogen receptor negative (ER-) disease, metastatic disease at diagnosis

or pre-invasive disease (ductal carcinoma in situ or pure Paget's disease of the nipple) were excluded. Patients who died within 91 days of diagnosis were also excluded from the analysis as they were likely to have had advanced disease or other terminal illness which would have influenced treatment decision-making. Figure 4.1 shows how the final study populations were derived.

Assumptions made regarding ER positivity

Oestrogen receptor status was only recorded for 43.5% (n=10 429) of the population, due in part to this information not being routinely collected in the Northern & Yorkshire registry until 2009. However the completeness of data regarding receipt of hormone therapy is more comprehensive and reliably documented (70.0%) [73]. As such, it was assumed that patients with unknown ER status who received hormone therapy were ER+ (as hormone therapy is only used in these patients). Patients with unknown ER status who did not receive hormone therapy were assumed to be ER- and were excluded.

4.4.3. Statistical analyses

4.4.3.1. Dependent variable

Primary treatment was dichotomised as surgery or no surgery according to whether or not the patient had an episode of breast surgery recorded within 6 months of diagnosis (OPCS4 codes: B27.1-6, B27.8-9, B28.1-9, B34.1-4, B35.2-3, B37.4, B40.1, B40.8-9, B32.3, B32.8, B37.8). The proportion of patients undergoing surgery was calculated for each clinician and hospital. Only hospitals and clinicians that treated 10 or more patients were included in the analysis (excluding 2.9% of hospitals and 3.1% of clinicians) as statistically, assessing variability in units with small numbers proves problematic – for example the average rate for surgery overall may be 58% but in a unit only treating 2 patients, it is highly feasible that both may be treated with surgery by chance but including this unit in the analysis will contribute a rate of 100% due to small numbers which would be misleading. A cut off of 10 patients was chosen pragmatically by JM and PR to include as many units as possible whilst maintaining statistical validity.

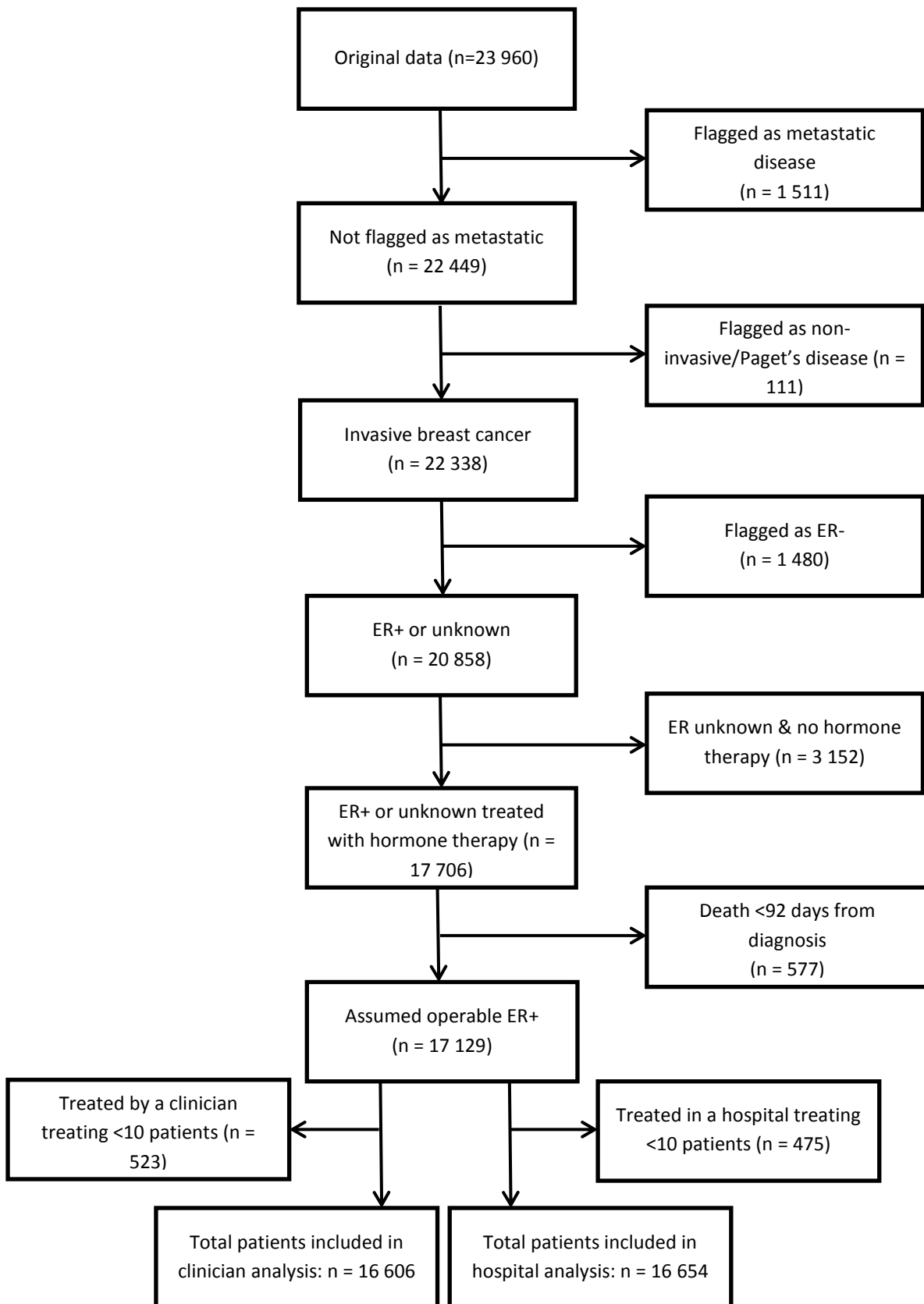


Figure 4.1: Determining the study population.

4.4.3.2. Logistic regression

Multivariable logistic regression was used to estimate the probability of a woman undergoing surgical treatment based on patient level factors, including her age, proxy Charlson co-morbidity score, level of socioeconomic deprivation, tumour detection method (screened versus non screened), size, Bloom and Richardson grade, TNM stage and nodal status, all of which may have an impact on treatment decision-making.

4.4.3.3. Case mix adjustment

Expected rates of surgical treatment were calculated for each clinician and hospital by summing the individual patient probabilities estimated from the logistic regression model. Risk adjusted rates of surgery were produced by dividing the observed rate by the expected rate for each clinician and hospital and multiplying this by the national rate [442].

4.4.3.4. Funnel plots

Both unadjusted and adjusted rates of surgery at clinician and hospital levels were displayed graphically as funnel plots to allow examination of the variability at each level and identification of outlying practice. Funnel plots contain two limits; under the hypothesis that treatment choice is randomly determined and independent of clinician or hospital, 95% of units would lie within the inner limits (2 standard deviations from the mean) and 99% within the outer limits (3 standard deviations from the mean).

4.4.3.5. Subgroup analysis

A subgroup analysis of patients with dementia was also performed to identify the impact of a diagnosis of dementia on treatment. Patients with dementia were identified using matched records from the linked HES dataset. Patients were classed as having dementia if one or more of the ICD10 diagnostic codes for dementia (F000-F039, F051, G300-G311) were recorded for any in-patient or day-case hospital admission in the 18 months prior to their breast cancer diagnosis. Patients for whom a matched HES record was not identified were excluded from the subgroup analyses as no comorbidity data was available for these patients, however baseline characteristics for this cohort are presented for comparison in order to assess the potential for bias due to missing data.

The proportion of patients undergoing surgery was calculated for patients with and without dementia. The chi-squared test was used to test whether or not there was a difference in the

proportion of surgically treated patients by dementia status. The joint effect of dementia and age on the odds of surgical treatment was assessed using multivariable logistic regression.

4.4.3.6. Data handling

Logistic regressions and Chi^2 tests were performed in IBM SPSS Statistics version 21 and multiple imputations were performed using the open source statistical programming language R (version 3.0.1), with the remaining data handling and analysis performed in Microsoft Excel for Windows 7.

4.5. Results

4.5.1. The study population

The registries provided records on 23 960 patients over the age of 70 years diagnosed with invasive breast cancer between the years 2002 and 2010. After applying the exclusion criteria (as described above) 17 129 records remained for analysis (see figure 1). On the basis of the assumptions made to define ER status, it was estimated that 77% of women with non-metastatic disease had ER+ tumours. This is lower than observed in previous cohort studies; for example Diab and colleagues [44] reported 90% of women over 75 diagnosed with breast cancer in the US had ER+ disease, although this percentage varies in published studies according to the precise method of ER analysis and the cut off used. Most UK breast units score ER status using either the H score or the Allred score and published data using these techniques would suggest that in this age cohort, 81% is reasonable and compares favourably with the 77% identified in this study [393].

The median age of the included population was 79 years (range 70-103 years). Of the 17 129 women, 9 955 were treated with surgery, giving an overall rate of 58.1%. Once again this is in keeping with other published data from the UK [73]. Patient and disease characteristics are shown in table 4.5. The proportion of older women being treated with surgery varied with patient and disease characteristics, with a woman being more likely to undergo surgery if she was younger, living in a less deprived area, having fewer or no co-morbidities, presenting through screening and having a smaller, node negative, Stage I or grade III cancer.

4.5.2. Treatment according to age

Rates of surgical treatment decreased with increasing age, with the proportion receiving surgery declining from 91.1% at age 70 to 38.5% at age 85 and less than 3% at age 95 and over, consistent with other published studies [78, 90, 398]. This is unsurprising as rates of comorbidity increase with age and life-expectancy becomes shorter, thereby decreasing the benefit of more aggressive treatments for breast cancer, such as surgery [106].

Patient and tumour characteristics	Prevalence (%)	Number who underwent surgery	Rate of surgical treatment
	17129	9955	58.1%
Age at diagnosis (years)			
70-79	9158 (53)	7307	79.8%
80-89	6605 (39)	2538	38.4%
90+	1366 (8)	110	8.1%
Mean	79.6 years	76.6 years	
Deprivation Quintile			
1 (least deprived)	2785 (16)	1800	64.6%
2	3540 (21)	2178	61.5%
3	3390 (20)	2012	59.4%
4	3636 (21)	1977	54.4%
5 (most deprived)	3779 (22)	1989	52.6%
Comorbidity (HES proxy Charlson)			
0	12160 (71)	8719	71.7%
1	1253 (7)	588	46.9%
2	629 (4)	279	44.4%
>2	337 (2)	77	22.9%
Missing	2750 (16)	292	10.6%
Method of detection			
Symptomatic	16014 (93)	8888	55.5%
Screening	1115 (7)	1067	95.7%
Tumour Size (mm, invasive component)			
(<10)	762 (4)	680	89.2%
(10-20)	3702 (22)	3154	85.2%
(20-50)	6465 (38)	4844	74.9%
(>50)	862 (5)	555	64.4%
Missing	5338 (31)	722	13.5%
Nodal Status			
Negative	5107 (30)	4847	94.9%
Positive	3881 (23)	3480	89.7%
Missing	8141 (47)	1628	20.0%
TNM Stage			
I	4215 (25)	3412	80.9%
II	6617 (38)	5097	77.0%
III	1295 (7)	877	67.7%
Missing	5002 (29)	569	11.4%
Bloom Richardson Grade			
1	2720 (16)	1783	65.6%
2	8567 (50)	5516	64.4%
3	3200 (19)	2385	74.5%
Missing	2642 (15)	271	10.3%

Table 4.5: Characteristics of the included population.

4.5.3. Treatment by deprivation

Rates of surgical treatment decrease with increasing deprivation, a finding also described by Lavelle and colleagues in their prospective cohort of 800 women [375]. The average difference in absolute rates of surgery between the top and bottom quintiles was 13.5% for each age at diagnosis in this range. For women aged over 85, no deprivation effect was observed. Similar to age, increasing deprivation has been shown to be associated with increasing levels of comorbidity [443] and affluence is also associated with lower levels of smoking, greater longevity and education [444], thereby promoting better health and discussion of treatment options.

4.5.4. Treatment according to levels of comorbidity

Increasing levels of comorbidity were associated with decreasing rates of surgical treatment, a finding reported by other studies [105, 375]. Again this is unsurprising as increasing rates of comorbidity result in a reduction in life-expectancy, thereby decreasing the benefit of more aggressive treatments for breast cancer, such as surgery [106].

4.5.5. Treatment according to method of diagnosis

Over 95% of women recorded as presenting via screening were treated surgically, though it should be noted that screening was not routinely offered to this population [445]. It has been shown that there is a positive association with screening adherence, higher educational attainment [101, 446] and higher income [447, 448]. These factors in turn may promote better health status and treatment discussion.

4.5.6. Treatment according to tumour factors

Tumour factors were also associated with treatment type, with larger, node positive tumours being less likely to be treated surgically which may represent patients and clinicians trying to avoid more major surgery, such as mastectomy and axillary node clearance. These results corroborate and update those found by Lavelle and colleagues in their study of 23 038 women aged 65 years and over between 1997 and 2005 [374].

Higher tumour grade was associated with increasing rates of surgery, this may represent the assumption that more aggressive disease should be treated with more aggressive treatment, i.e. surgery.

4.5.7. Treatment rates at hospital level

4.5.7.1. Unadjusted treatment rates at hospital level

The unadjusted rates of surgery varied substantially between hospitals (see figure 4.2a), with 25 of 68 (36.8%) falling outside of the outer 99% limits, and 39 of 68 (57.4%) falling outside of the inner 95% limits on the funnel plots, meaning that they statistically differ from the expected norms (that is the average overall rate of surgery).

4.5.7.2. Adjusted treatment rates at hospital level

Taking account of patient level characteristics and adjusting for case mix did not significantly reduce the variation in surgery rates between hospitals, with 15 of 68 (22.1%) still falling outside of the outer 99% limits and 30 of 68 (44.1%) falling outside of the inner 95% limits on the funnel plot (see figure 4.2b).

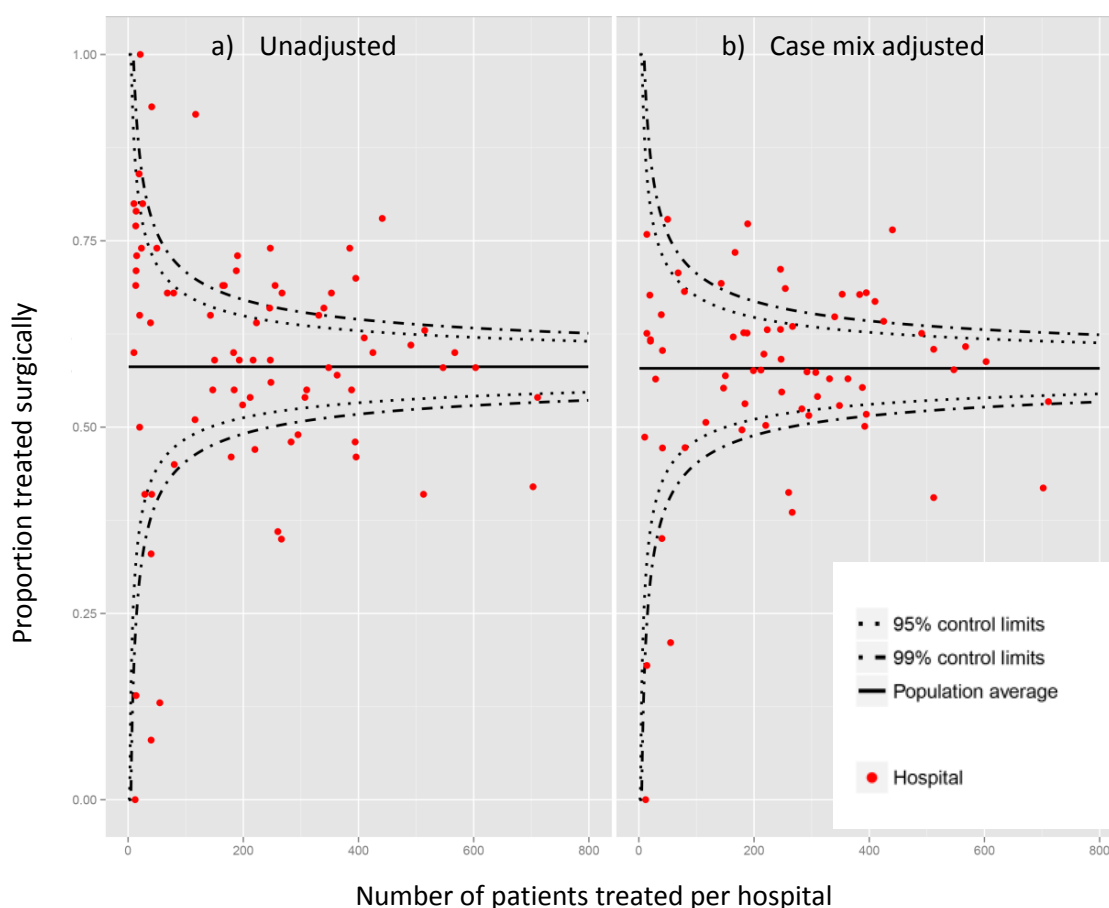


Figure 4.2: Funnel plots showing the proportion of patients treated surgically by each hospital. Hospitals falling outside the control limits show greater than expected variation in practice. Figure (a) shows the unadjusted rates and figure (b) shows the rates following adjustment for case mix.

4.5.8. Treatment rates at clinician level

4.5.8.1. Unadjusted treatment rates at clinician level

The unadjusted rates of surgery varied substantially between clinicians (see figure 4.3a), with 36 of 167 (21.6%) falling outside of the outer 99% limits, and 73 of 167 falling outside of the inner 95% limits on the funnel plots, meaning that they statistically differ from the expected norms.

4.5.8.2. Adjusted treatment rates at clinician level

Adjusting for case mix did appear to reduce the variation in surgery rates at clinician level, with 7 of 167 (4%) falling outside of the outer 99% limits and 17 of 167 (10.2%) falling outside the inner 95% limits on the funnel plot (see figure 4.3b). It was felt that this may be a result of the smaller numbers of cases per individual consultant, making any variation by clinician too small to identify. It may also reflect a cluster effect where consultants working within the same hospital unit have similar practices, thereby reducing any individual clinician-level variation.

4.5.9. Effect of dementia on treatment

Matched HES comorbidity data were available for 14 380 (83.9%) of the 17 130 eligible patients. Of these, 246 (1.7%) had a recorded diagnosis of dementia. Patients without a match in HES tend to be older and the majority are treated non-surgically. Table 4.6 shows the age and treatment of those patients (n=2750) who were unmatched in HES.

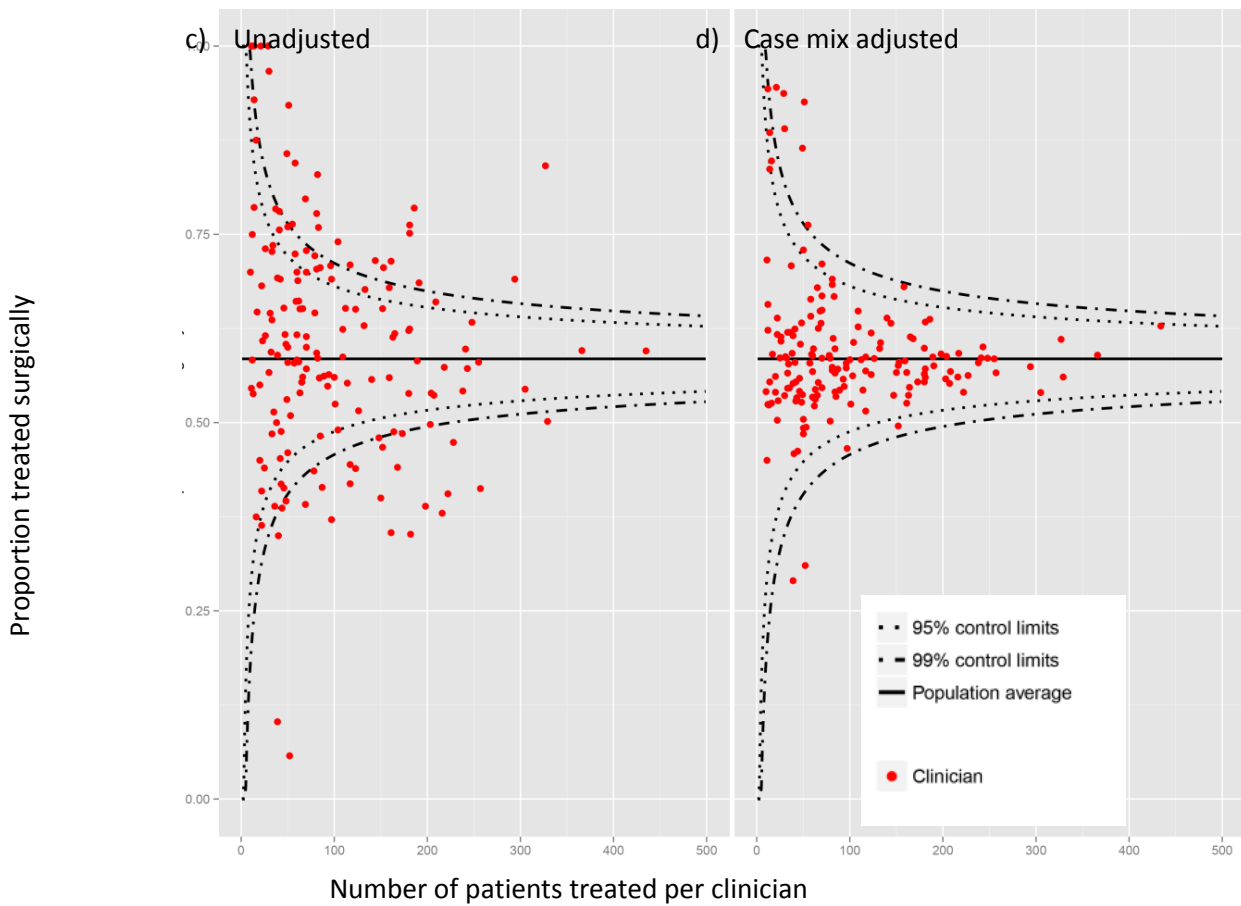


Figure 4.3: Funnel plots showing the proportion of patients treated surgically by each clinician. Clinicians falling outside the control limits show greater than expected variation in practice. Figure (a) shows the unadjusted rates and figure (b) shows the rates following adjustment for case mix.

Age	70-74	276
	75-79	410
	80-84	746
	85-89	766
	90+	552
Treatment	Surgery	292
	PET	2458

Table 4.6: Age and treatment of the 2750 patients without a matched HES record.

Patient characteristics of both dementia and control groups are shown in table 4.7.

		Control		Dementia		Total	
		n	%	n	%	n	%
Number of patients		14134	-	245	-	14379	-
Age	70-79	8420	59.6	52	21.2	8472	58.9
	80-89	4940	34.9	153	62.5	5093	35.4
	90+	774	5.5	40	16.3	814	5.7
	median	78	-	84	-	78	-
Surgery	Yes	9632	68.1	31	12.7	9663	67.2
	No	4502	31.9	214	87.3	4716	32.8
Income deprivation quintile	1 (least)	2320	16.4	22	9.0	2342	16.3
	2	2927	20.7	47	19.2	2974	20.7
	3	2792	19.8	33	13.5	2825	19.6
	4	3012	21.3	61	24.9	3073	21.4
	5 (most)	3082	21.8	82	33.4	3164	22.0
	Missing	1	0.0	0	0.0	1	0.0
Charlson Comorbidity Index (excluding dementia)	0	12160	86.0	158	64.5	12318	85.7
	1	1095	7.7	42	17.1	1137	7.9
	2	587	4.2	22	9.0	609	4.2
	>2	292	2.1	23	9.4	315	2.2
Screen detected	Yes	1062	7.5	0	0.0	1062	7.4
	No	13072	92.5	245	100.0	13317	92.6
Tumour diameter (mm)	< 10	692	4.9	5	2.0	697	4.9
	10-20	3388	24.0	19	7.8	3407	23.7
	20-50	5761	40.8	67	27.3	5828	40.5
	>50	769	5.4	6	2.5	775	5.4
	Missing	3524	24.9	148	60.4	3672	25.5
Nodal Status	Negative	4853	34.3	20	8.2	4873	33.9
	Positive	3718	26.3	15	6.1	3733	26.0
	Missing	5563	39.4	210	85.7	5773	40.1
Grade	1	2268	16.0	40	16.3	2308	16.1
	2	7247	51.3	107	43.7	7354	51.1
	3	2911	20.6	23	9.4	2934	20.4
	Missing	1708	12.1	75	30.6	1783	12.4

Table 4.7: Characteristics of the control population compared with the dementia population.

Due to the high proportion of missing data in the dementia group it was not possible to reliably test whether or not there are differences in baseline disease characteristics between the dementia and control groups, however the distributions of tumour size, nodal status and grade appear similar

between the groups for whom data is available. Patients recorded as having dementia are more likely to have additional co-morbidities (87/246, 35.4%) than the control group (1 974/14 134, 14.0%, $p < 0.001$).

Patients with a diagnosis of dementia were significantly less likely to receive surgery compared to those without (12.7% vs 68.1%; $p < 0.001$, see figure 4.4).

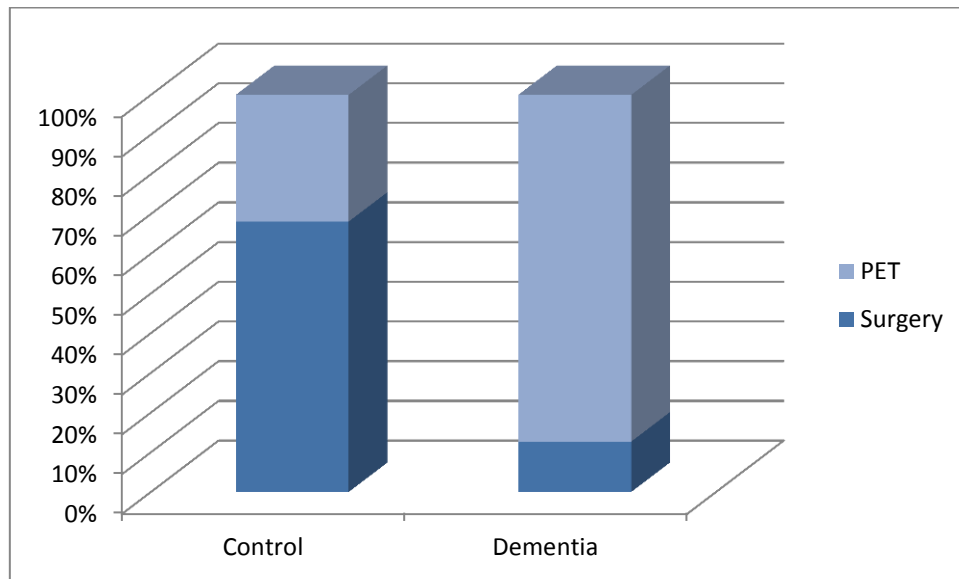


Figure 4.4: Treatment according to Dementia status, ($p < 0.001$).

4.6. Discussion

4.6.1. Effect of patient and tumour factors on surgery rates

Between 2002 and 2010, 17 129 women were treated for assumed operable, ER+ breast cancer in the regions of the West Midlands and Northern & Yorkshire registries. Of these, 9 955 were treated surgically, with the remaining 7 174 (41.8%) having non-surgical management – this figure is in keeping with the rate of PET for these two registry areas in previous studies [73].

The analysis demonstrates that increasing age at diagnosis is associated with a reduced likelihood of receiving surgical treatment which is consistent with other similar studies [68, 84, 89, 90, 375, 398]. Deprivation level was also associated with treatment type, with the most deprived group being less likely to undergo surgical management, a finding also described by Lavelle and colleagues in their prospective cohort of 800 women [375]. This may be due to the fact that affluence is associated with lower levels of comorbidity and smoking, and greater longevity and education [444], thereby promoting better health and facilitating discussion of treatment options. Higher levels of comorbidity were also associated with non-surgical treatment, which is also consistent with other published studies, where co-morbidity is stated as a major reason for choosing PET over surgery [128, 362, 365]. Tumour factors were also associated with treatment type, with larger, node positive tumours being less likely to be treated surgically which may represent patients and clinicians trying to avoid more major surgery, such as mastectomy and axillary node clearance. These results corroborate and update those found by Lavelle and colleagues in their study of 23 038 women aged 65 years and over between 1997 and 2005 [374].

4.6.2. Effect of case mix correction on surgery rates

There was considerable variation in the rates of surgical treatment across the 68 hospitals and this variation persisted, despite case-mix adjustment, with 44.1% of units remaining outside the 95% limits on funnel plot analysis. Sixteen hospitals had significantly higher and 14 hospitals had significantly lower rates of surgery than could be explained by the case mix information available.

There was also substantial variation in rates of surgical treatment between 167 clinicians, although this variability lessened with case-mix adjustment, with only 10.2% falling outside the 95% limits on funnel plot analysis. However, this still showed that 12 clinicians had significantly higher and 4 had significantly lower rates of surgery than could be explained by case mix alone. It should be noted that there were much smaller numbers available for analysis at clinician level and so these results are less reliable than the hospital level data. It is possible that the persistence of variability in

treatment at hospital level but not at clinician level is a result of a “cluster effect” – in that clinicians working within the same hospital are likely to have trained locally, will work together within a multi-disciplinary team and may subscribe to a local protocol, thereby having similar practices, resulting in magnified effect at hospital level when the data from individuals is combined.

4.6.3. Persistent variability may be due to multiple factors

This persistence of variation in the treatment of older women with operable, ER+ breast cancer at hospital level is due to factors not included in the case-mix adjustment. One possible cause is clinician preference for either treatment. Current guidelines on the use of PET in the older breast cancer population state it should only be used in patients with a short life expectancy (less than 2-3 years), when significant comorbidities preclude surgery, or in patients who refuse surgery [9, 127]. It is left to the treating clinicians’ judgement as to which patients should be offered PET as an alternative treatment option to surgery. Patient preference or refusal of surgery is also often stated as a possible reason for variation in treatment, which may reflect clinician preference and how the treatment options are presented, as was proposed by Hamaker et al [373]. Qualitative research in this older group of patients has suggested more passive decision-makers, relying on the advice of healthcare professionals [226, 279].

This persistent variation at hospital level may also be a result of other unobserved patient factors not taken into account by case-mix adjustment, for example frailty, level of education, being married or widowed, or caring for an unwell spouse may all impact on treatment decisions for older breast cancer patients.

4.6.4. Effect of dementia on treatment

The findings of the sub-group analysis demonstrate that older breast cancer patients with a diagnosis of dementia were less likely to receive surgery. However it is important to note that no adjustment was made for disease characteristics, including stage at diagnosis, due to high rates of missing data in the dementia group. Previous studies have shown that patients with dementia may present with later stage disease [449] and this may be in part due to poor symptom recognition and impaired communication among these patients [450, 451]. They are also unlikely to volunteer for screening which is associated with better disease stage [452].

It is perhaps unsurprising that patients with dementia are less likely to be treated with surgery, given the direct impact of dementia on life expectancy and the link to other comorbid diseases. Similar

patterns are seen in other types of cancers where patients with dementia are less likely to receive standard treatment, including surgical resection and adjuvant chemotherapy for colorectal cancer [453]. It is also more technically challenging to treat patients with dementia surgically. They may not be able to cooperate with surgery under local anaesthesia or with the induction phase of general anaesthesia. In addition anaesthetic and post-operative analgesic drugs may cause anxiety and confusion which may be distressing. Admission to hospital may also have a destabilising effect.

A similar study conducted in the USA also demonstrated lower rates of surgery in dementia patients, however as PET is not a widely used treatment option in the USA the reported rates of surgery were considerably higher for both dementia and control populations (96.4% and 99.0%, respectively) [449]. A population-based study of breast cancer patients in the Netherlands demonstrated less extensive treatment for patients with co-existing illnesses, including but not limited to dementia. They reported that patients aged over 80 years with comorbidities were more likely to be treated with PET than those without comorbidities (21% vs. 14%) [105].

Registry studies conducted elsewhere have reported a comparably low prevalence of dementia, with Gorin and colleagues reporting a rate of 3.8% and Louwman and colleagues reporting 2.7% [105, 449], although both figures are higher than found in our study population (1.4%). These figures however represent substantially lower proportions than are reported to exist in the general UK population where the rate is thought to be 7.1% of over 65 year olds [454]. One possible explanation for this is the HES-based method used to identify patients with dementia within our study population. For a patient to be categorised as having dementia, they must have been hospitalised in the 18 months prior to and including their breast cancer diagnosis, and at least one admission must have been associated with an ICD-10 diagnostic code indicating dementia. The majority of patients with dementia are treated in the community setting and so will not be recorded in HES unless they are admitted to hospital for another cause, with their dementia coded as a co-existing comorbidity. This analysis will therefore have selected out those with either more severe dementia or dementia linked to other comorbidities severe enough to require admission which may have biased the analysis to the more extreme end of the disease spectrum.

It is unclear whether the differences in treatment are a result of active decision-making by healthcare professionals to omit treatment for dementia patients, or a conscious choice made by patients and/or their families, or a mixture of the two. It is recognised that quality of life issues may influence treatment decisions and that older cancer patients may opt for less invasive therapies for these reasons [415]. However, there are no guidelines or data available to help clinicians, patients and their families to make informed choices and decisions about breast cancer treatment.

4.6.5. Strengths and weaknesses of this analysis

Cancer registry data allows analysis of large cohorts of women treated in everyday, normal clinical practice. The routine nature of data collection through hospital coding teams makes this type of observational data less prone to selection bias. However, this method is hampered by missing data and potential coding inaccuracies which is a limitation of this component of the study. Multiple imputation is less prone to bias than other commonly used methods to account for missing data, such as complete case analysis or inclusion of “missing” as a category in factor variables [437]. However, whilst exploratory analysis of the imputed data suggested that the values were plausible, it is not possible to verify the extent to which the distribution of the imputed data accurately represents that of the missing values. By using 25 imputations, uncertainty around the missing data is incorporated into the probabilities used to adjust for case mix which mitigates against any small biases due to problems with the imputation model.

Data were only obtained from two of the UK’s 11 cancer registration regions and these two regions have been shown to have higher PET rates than other regions [73] which may potentially limit the generalisability of these results. However the population analysed represents a quarter of all breast cancer cases in the UK and the areas covered by these registries are demographically representative of the UK as a whole, making it reasonable to cautiously extrapolate these findings to the UK population generally.

Despite this model containing several clinically-relevant variables, not all covariates could be included due to large quantities of missing data, e.g. HER2 and progesterone receptor (PR) status. Additionally, assumptions had to be made regarding the ER status of the patients, with the resulting proportion of ER+ patients in the population being considerably smaller than reported in other studies [44].

Another limitation of this analysis is the proxy Charlson score using HES data. Data are only available from HES if a patient who has had a hospital admission in the year preceding their cancer diagnosis and relies heavily on accurate and complete coding of the relevant co-morbidities at the hospital level, and the accuracy of coding within both HES and cancer registries has previously been questioned [455]. This method may under-score patients who have chronic co-morbidities which are well-controlled and managed in the community, such as diabetes or dementia, as these alone are unlikely to precipitate a hospital admission.

The case-mix adjustment may also have been inadequate, due to lack of data on important covariates, such as frailty, which are not captured by registry data. Detailed data on every aspect of a patient's care that could influence treatment choice cannot be collected in this setting, so factors such as frailty, patient choice, family input, social circumstances and clinician preference have not been included but may all play a part when deciding on a treatment modality in the older population. It is therefore possible that some other variables are confounding the results presented in this analysis.

In the dementia sub-group analysis 14.3% of patients were not matched with a HES record, and therefore their comorbidity data are missing and they cannot be assigned to either the dementia or control group. This group of patients is older and were more likely to have been treated non-surgically than the matched control group. It is possible that some of these patients will have had dementia at the time of diagnosis but it is not possible to verify this from the current data. The high proportion of patients treated non-surgically would be consistent with an elevated proportion of dementia in this subgroup. In order for this issue to change our conclusion that dementia is associated with a lower probability of surgical treatment, the prevalence of dementia in this unmatched subgroup would have to be lower than that for the matched cohort. It is not expected that this would be the case.

4.7. Summary

This study demonstrates that whilst the majority of UK hospitals and clinicians have similar decision-making practices, there are some units where practice varies substantially from this norm and is not compensated for by case mix adjustment. Many factors influence treatment choice, as discussed above and examining how these vary in relation to treatment may provide evidence to help explain the variability in treatment of older patients across the UK. Whilst this study has identified outlying practice, it is not clear why they are out-with normal practice, nor whether this outlying practice is unreasonable. Outlying status could be explained by data quality or confounders as previously discussed. However this variation should not be ignored, but further research to determine why practice varies forms further components of this research thesis in Section II below.

Further work is also required to determine how much treatment allocation for dementia patients is a result of active decision-making by healthcare professionals to omit treatment for dementia patients and this also forms further components of this research thesis which will be discussed in subsequent chapters.

Significant variation in practice is important, particularly in view of the fact that literature on this topic suggests that patients who are treated with PET have inferior outcomes compared to those treated with surgery [78, 83-85, 88, 390]. Continuation of this varying practice may result in a post-code lottery and further guidelines on the management of older women with operable breast cancer are urgently needed.

Section II: Why does the variation in treatment across the UK exist?

Chapter 5: Semi-structured Qualitative Interviews with Healthcare Professionals

5.1. Abstract

5.1.1. Introduction

Current guidelines on the management of older women with operable breast cancer provide little guidance to HCPs on which patients may be unfit for surgical management and as such it is left up to them to determine which patients may be offered alternative treatment modalities, such as PET. Additionally, it may be appropriate to offer PET to some older patients as an alternative treatment and allow them to decide which is best for them. There is currently little in the published literature examining how HCPs determine which older patients should be offered surgery, PET or a choice of either.

5.1.2. Methods

Semi-structured qualitative interviews were undertaken with specialist HCPs from regions of high and low PET rates across the UK. Data analysis was performed using the Framework method to identify themes in the data.

5.1.3. Results

Thirty-four HCPs (20 breast surgeons; 13 nurse specialists; 1 geriatrician) were interviewed from 14 sites across the UK. There was an overriding view that PET is not suitable for patients under the age of 80 unless there are significant comorbidities. Opinion was split regarding the best way to treat patients with dementia. Opinion varied on whether patients over the age of 70 should be offered PET as an alternative treatment option.

5.1.4. Conclusions:

Opinions differ on the best way to treat women over 70 with operable breast cancer, especially if they have co-existing dementia, as well as whether they should be offered PET as a treatment option. This may be a significant cause of treatment variation in the UK.

5.2. Introduction

Current guidelines from the National Institute of Clinical Excellence (NICE) state that PET should only be used where there is “significant comorbidity that precludes surgery” [9] and recommendations from the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) suggest that PET should only be offered to patients with a “short estimated life expectancy (<2-3 years), who are considered unfit for surgery... or who refuse surgery” [127]. However, neither specify which comorbidities may preclude surgery or what constitutes being unfit for surgery. As such it is left to the treating clinician to decide which breast cancer treatments a patient should be offered. This may be a causative factor in the considerable variability in the treatment practice for older women with breast cancer across the UK, where rates of non-surgical management range from 12-40% depending on region [73].

Rates of local control are inferior in patients treated with PET compared to those treated surgically [402]. In addition disease progression with PET may necessitate a change in management when the patient is less fit [222, 340, 362]. Despite this, no survival disadvantage has been demonstrated between surgical and PET patients, except in the youngest age sub-groups (70-75 years) in meta-analysis of randomised trial data although cohort studies do suggest a small survival advantage for surgery [402, 404]. Furthermore, quality of life studies and patient opinion studies show that both treatment types are well tolerated by this age group [226, 240] and evidence suggests that some older patients may prioritise quality of life over quantity [415]. In today’s health service, where there is a greater emphasis placed on shared decision-making (SDM) and ensuring patients are fully informed about their possible treatment options [268, 277, 456], for some older women it may be appropriate to offer PET as an alternative to standard surgical treatment and allow them to ultimately make the choice about their personal preference.

To date, there is little in the published literature examining how clinicians determine which older patients should be offered surgery, PET or a choice of both. This chapter describes the findings from interviews with health care professionals (HCPs) specifically, breast surgeons, breast clinical nurse specialists (CNS), oncologists and geriatricians, exploring factors deemed important when determining what treatment options to offer older patients with operable breast cancer. The interviews also examined HCP views and experience on the use of both surgery and PET in this population, as well as investigating their subjective opinions on the decision-making process.

5.3. Methodology

5.3.1. Choice of qualitative interviews

Qualitative research broadly has several overriding objectives and may be used to [457]:

- Define concepts.
- Record the range and nature of phenomena.
- Generate typologies or classifications.
- Uncover associations.
- Find explanations.
- Develop strategies.

Which strategy is employed depends on the original questions under investigation. This phase of the study aimed to record the variation in views of HCPs, uncover possible associations related to the decision-making in the treatment of older women and ultimately identify potential explanations for these varying opinions.

Semi-structured interviews are a common way of acquiring rich qualitative data that may be used to examine a topic of interest [458]. They also provide an opportunity to explore additional themes that emerge from the participants themselves (emergent themes). It was felt this approach would lend itself to this type of research as it allows analysis within and between participants, facilitating investigation of complex inter-related themes [457].

5.3.2. Qualitative data analysis options

There are a number of qualitative analysis approaches and several were considered in the early stages of this study. These included the framework approach [459-461], content analysis [462] and grounded theory [463].

Content Analysis involves coding and counting the frequency of codes to determine where the emphasis lies as well as identifying relationships between these codes and applying statistical analysis.

Grounded Theory involves coding before grouping these codes into concepts and categories which form the basis for the creation of a theory or reverse engineered hypothesis.

Table 5.1 shows a comparison of these methods.

Content Analysis	Framework Approach	Grounded Theory
Devoid of theoretical base.	Investigational objectives set in advance so thematic framework identified a priori.	Theory isn't applied to data, data generates theory. Theory is discovered rather than verified.
More open enquiry. Can allow for both quantitative and qualitative analysis.	More structured data collection to address specific questions.	Formulaic in nature as opposed to open enquiry.
Inherently reductive, and disregards the context that produced the text, particularly with complex texts.	Reductive but maintains the integrity of participants' narrative.	Reductive – data is deliberately fractured to open up new avenues of data analysis.
More anecdotal, descriptive and less reflective.	Allows analysis across participants and themes. Can identify associations and provide explanations.	Generates new theory that is "grounded in" the data collected.
		Can what is generated really be considered theory?

Table 5.1: Comparison of qualitative analysis methods.

5.3.2.1. The framework approach

The framework approach is a matrix-based method to manage and analyse qualitative data developed by social policy researchers at the National Centre for Social Research in the 1980s [460]. It is an interpretive process which can provide insight into complex epistemological issues, developing meaningful themes to expand on or test existing theory [461].

It was viewed as a rigorous, structured, organised approach to data collection and analysis based on the needs of the research. It was an approach that enabled the researcher to explore the breadth and depth of large volumes of textual data but with an emphasis on maintaining the transparency of the process and the links between each stage of analysis. The use of the matrix to allow data analysis enables exploration of the data at many levels; thematic; participant; rates of PET; and hence the framework approach was felt to be the appropriate choice for the qualitative analysis of this study.

5.3.2.2. The method of framework approach

The framework approach is a systematic analytic process that guides the researcher through the principles of qualitative analysis in a series of structured, interconnected stages to elicit and manage the data [460]. It allows organisation and classification of the data collected according to key a priori ideas, as well as emerging concepts, in condensed and manageable chunks prior to further analysis.

Despite its structured approach, the analysis relies on the researcher's ability to interpret meaning, salience and connections [457, 464].

The framework approach has several key characteristics:

- It has the capacity to analyse large quantities of descriptive textual data, allowing all information to be comprehensively and systematically included.
- It is grounded in the original data; it retains the participants' 'voice' as the participants' own words are summarised into 'in-vivo' codes [460], thus staying true to the source data. This is a fundamental principle of the framework approach.
- It is dynamic, with the series of interconnected stages allowing the analyst to move back and forth between the data until an overall picture emerges [460].
- It is straightforward and accessible, the logical and systematic process remains visible throughout and maintains rigor in the analytic process.
- It allows direct comparison between datasets facilitating identification of relationships between themes; data is extracted in two dimensions from the outset (participant characteristics, etc. vs. theme) and then arranged in a matrix, facilitating exploration of the data within and across themes and cases in a flexible way.
- There is an emphasis on transparency of the analytic process; links are retained between the comments and the source data, as well as between each stage of the analysis [459-461]. This "audit trail" ensures findings are more credible due to the rigor of the processes [460].

The process of framework analysis is performed in a step-wise fashion with five key processes [457, 464]:

1. Familiarisation

This stage is undertaken at the start of the analysis that involves full immersion into the raw data by listening to recordings, reading transcripts and observational notes as well as studying the aims and objectives of the research proposal. In this way, the researcher gains an overview of the body of material gathered as a whole and becomes familiar with the range and diversity of ideas, attitudes, behaviours and motivations within the data. By focussing on *a priori* and recurring issues, views and experiences that emerge from the data, the initial themes and concepts can be identified and outlined, beginning the process of abstraction and conceptualisation.

2. Identifying a thematic framework

Once the key issues, concepts and themes have been identified in step 1, a detailed index, or 'framework' is constructed. This stage permits data to be examined and referenced in a systematic way. Some index categories may follow the interview questions and are regarded as *a priori* issues that are introduced by the researcher through the topic guide. Others are emergent issues, raised by the participants themselves, or analytic themes which arise from recurrent opinions or other patterns within the data. These initial themes are then sorted into broader, higher order categories, ensuring that the original research questions are being addressed. This process of devising and refining the conceptual framework requires analytical, logical and intuitive thinking on the part of the researcher, who will need to make inferences and judgements regarding the relevance and meaning of the data.

3. Indexing/Coding

The thematic framework developed in stage 2 is then applied to all the transcripts in a systematic manner. Texts are re-read and annotated with indexing references recorded in the margins. In this way, data can be linked back to the original transcripts, making the process visible and accessible to others. Inferences and judgements are made regarding the relevance and meaning of the emerging data.

4. Charting

In this stage, data is lifted from its original context. It is then distilled into summaries of the opinions and experiences of the participants, before being rearranged and brought together according to the appropriate thematic reference within a framework chart. This process then allows the researcher to build up a picture of the entire dataset. The information within the chart should contain enough information to draw meaning without losing content or context so as to prevent having to go back to the original interview. However it should not be so detailed as to be unreadable and therefore requires care and judgement. Every attempt should be made to keep data in the participants own words so as to retain the language of the participants and page references and quotes should be marked to allow source data to be traced. Some themes overlap and therefore data occasionally appear in more than one thematic column. Equally, some thematic columns may be blank, perhaps if a particular question was not asked to all participants or certain issues were not relevant to every participant, however this should be documented within the chart to indicate the reasons for absent data.

5. Mapping and interpretation

The entire dataset can now be analysed as a whole with reference to the research question by reviewing concepts, associations and patterns and exploring possible explanations. This systematic process of detection allows the researcher to examine the individual interview content as well as its position within the dataset in its entirety in order to draw necessary conclusions. The researcher explores descriptive accounts, identifying similarities and differences in an attempt to understand how and why accounts are similar or different, leading to the identification of factors describing clinician's opinions, preferences and practice. The researcher can then investigate explanatory accounts, where an explanation is sought as a cause for the identified variation. Explanations may be explicit – where conclusions are drawn based on the participants own explicit statements; or implicit – where conclusion are based on the interpretation of the data by the analyst. The researcher may also seek wider applications for the explanations generated by the analysis.

5.3.3. Ensuring quality within qualitative research

With all the different approaches to qualitative research methodology there have been widespread concerns about quality and the importance of ensuring robust and rigorous research practice. Several quality frameworks [464-468] have been produced to aid researchers in the pursuit of this. In order to develop this part of the study, these guidelines, were thoroughly examined and use as a guide throughout.

Table 5.2 summarises the points in the Quality Framework Assessment [464] of qualitative research, together with how these have been met within this study.

	Appraisal Question	How addressed
Findings	How credible are the findings?	The data on which the findings are based can be viewed in Appendix 15. Corroborating evidence is used to support and refine the findings within the broader thesis in this MM study.
	How has knowledge/ understanding been extended by the research?	Full literature review has been performed summarising the knowledge and key issues raised by previous research. Findings are discussed in context with what is previously known and compared with other strands of the study. Discussion of limitations of the study and further research required can be found in sections X and X.
	How well does the evaluation address its original aims and purpose?	Study aims and objectives clearly stated. Review of findings chapter (chapter X) links findings back to the purposes of the study. Discussion of limitations of the study can be found in sections X.
	Scope for wider inference	Use of MM design in order to generalise QUAL findings to the wider UK breast HCP population. Use of purposive sampling from wide areas across UK, including high/low PET units to increase applicability of findings to wider population. Limitations on drawing wider inference discussed in section X.
Design	How defensible is the research design	See section X for discussion of how the overall research strategy was designed to meet aims of study, together with the rationale for study design.
Sample	How well defended is the sample design?	Details of the sampling process and a description of how and why this was chosen can be found in section X.
	Sample composition – how well is the eventual coverage described?	Table 2.1.2 documents the actual versus expected recruitment per site and reasons for non-participation.
Data Collection	How well was the data collection carried out?	Audio recordings and verbatim transcripts were used. Full details of data collection methods and charting/transcription conventions can be found in section X.
Analysis	How well has the approach to, and formulation of, the analysis been conveyed?	Use of NVivo data management tool. Development of themes from original coding can be found in Appendix 14.
	Contexts of data sources – how well are they retained and portrayed?	Framework method using NVivo facilitates within and across case description and analysis whilst preserving context by electronically linking summarised text within the framework matrix back to the original transcript.

	How well has diversity of perspective and content been explored?	Purposive sampling used to encourage diversity of perspectives and examination of these within the context of HCP profession type and high/low PET regions to identify differences.
	How well has detail, depth and complexity (i.e. richness) of the data been conveyed?	Explorations of both explicit and implicit explanations (for example when examining the influence of age – see section X). Representative quotes used throughout to demonstrate the data complexity.
Reporting	How clear and coherent is the reporting?	Findings fully reported (see section X) and linked back to the aims and objectives in the study in the Review of findings section (chapter X).
Reflexivity & Neutrality	How clear are the assumptions/theoretical perspectives that have shaped the form and output of the evaluation?	Full discussion of the ideological perspectives and philosophies of the researcher can be found in section X. Reflections on the impact of the researcher on the research process can be found in the discussion chapter (section X).
Ethics	What evidence is there of attention to ethical issues?	Full ethical approval was sought (see section X). Written consent was obtained from all participants (section X). Discussion of confidentiality and data handling can be found in section X.
Auditability	How adequately has the research process been documented?	Strengths and weakness of the study are discussed in sections X. Copies of all study documents can be found in Appendices 6, 7, 8, 9, 10, 11, 12 and 13.

Table 5.2: Ensuring quality within the qualitative interview strand of the project using the Quality Framework Assessment [464].

5.4. Methods

5.4.1. Research Governance

5.4.1.1. Ethics approval

The study was undertaken in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the World Medical Association General Assembly, Seoul, Korea, October 2008. Informed written consent was obtained from the clinicians prior to entry into the study. The right of a participant to refuse participation without giving reasons was made explicit and respected. The participants remained free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. The study was conducted in accordance with the principles of GCP according to EU Directive 2005/28/EC [469].

Research Ethics Committee (REC) approval was not required for this study as the participants were NHS staff recruited by virtue of their profession. The study protocol was reviewed by the University of Sheffield Medical School's Ethics Review Committee and approval was granted on 22nd November 2012 (ref: SMBRER243; see Appendix 6 & 7).

5.4.1.2. Research and development approval (R&D)

Approval was sought from the R&D department of each NHS trust participating in the interview phase of the study via the national Integrated Research Application System (IRAS) system (see Appendix 8 & 9).

5.4.1.3. Informed consent

Fully informed written consent was taken from each participant before commencement of the interviews. A copy of the consent form can be found in the study protocol, in Appendix 10.

5.4.1.4. Confidentiality

Interview transcripts were pseudo-anonymised to protect participant identifiers. Databases were password protected and stored in a locked office in the university in accordance with the Data Protection Act 1998. The list of participant names was stored separately from participant details, again in accordance with the Data Protection Act 1998. No information that would allow clinicians to be identified was released into the public domain. If a participant withdrew consent for their data to

be used then it would have been confidentially destroyed. However this did not occur within this study.

5.4.2. Sample and setting

5.4.2.1. Sampling

In order to gain insight into the variation seen across the UK, breast units were purposively sampled from within UK regions known to be high and low in terms of their use of non-surgical treatment of older women according to the national BCCOM audit [73] – the average (mean) PET rate across all regions was 23% - those regions above this level were classified as “High” and those below “Low”. This information was then inserted into the framework so it could be analysed across themes.

Units were also purposively selected on the basis of geography to ensure representation of units from both the North and South of the UK.

Semi-structured interviews were conducted with both breast surgeons and breast clinical nurse specialists (CNS), with the aim of recruiting at least one surgeon and one CNS per site. In practice this was not feasible due to the availability of both researcher and participants, no response from potential participants, administrative difficulties and delays obtaining research and development approvals for some sites.

5.4.2.2. Saturation of themes

Recruitment continued until saturation of themes was reached. The size of purposive samples typically relies on the concept of “saturation” – the point at which no new information or themes are observed in the data [470-472]. There are no guidelines as to how many qualitative interviews will produce saturation of themes and in general the rule of recruitment is to keep going as long as you are getting different answers [471]. In this case, saturation occurred at around 30 interviews which is a similar number to that found by Mason [470] in his study examining 560 qualitative PhD studies.

5.4.2.3. Inclusion/exclusion criteria

Inclusion criteria:

- Permanent staff within the breast unit, e.g. consultant breast surgeon, associate specialist, breast CNS.

- Other permanent staff regularly involved in the treatment of newly diagnosed breast cancer in older women, e.g. geriatrician or oncologist in specialised older patient breast clinics.

Exclusion criteria:

- Non-permanent staff, e.g. training specialist registrars who move from unit to unit.
- Staff not regularly treating older women with newly diagnosed breast cancer.

5.4.3. Interview schedule

An interview schedule was developed based on review of the relevant literature [226] and members of the wider study steering committee which included breast surgeons and oncologists (see figure 5.1). The schedule was designed to act as a prompt sheet to enable the interviews to explore key issues but also give opportunity for free expression of views with open questions.

5.4.4. Recruitment and data collection

5.4.4.1. Recruitment

The local NHS Trust principle investigator (PI) (see Appendix 11) was identified by direct contact by e-mail. The PIs were asked to provide a list of names of suitable HCPs (including breast surgeons, breast clinical nurse specialists, oncologists, geriatricians) working within their local breast units who would be happy to be contacted by email to receive information about the study. Identified individuals were sent a study pack by e-mail containing a participant information sheet (PIS) and an outline of the topics to be covered (see Appendices 12 & 13). Interviews were conducted in person and a date was scheduled by e-mail that was convenient for both the HCP and the researcher (JM).

A total of 20 trusts were approached and agreed to take part in the study. However, due to problems of obtaining local research and development approval or closure of the study due to saturation of themes, 14 Trusts took part in this phase of the study. These included eight teaching hospitals and six district general hospitals

What treatment options would you normally consider for an older woman (over 70) with operable primary breast cancer?	
Prompts:	Would surgery form part of your potential management plan in all patients? Is PET an option for all patients in this group?
What do you feel are the risks and benefits of surgery and PET for this age group?	
Prompts:	Morbidity and mortality of surgery Local recurrence risks, local control Compliance
What factors influence your choice of management for a particular patient with primary operable breast cancer?	
Prompts:	Age of patient at diagnosis Frailty of patient Co-morbidities, including dementia Anaesthetic considerations Optimisation of other health issues Patient choice Carer preferences Guidelines Stage/operability of cancer Cancer biology (e.g. ER and HER2 status, mucinous subtype) Pre-operative assessment: anaesthetic assessment, formal geriatric assessment, "end of the bed" assessment
Are there any other factors that influence your overall practice in this patient group?	
Prompts:	Influence of cancer targets Influence of costs
If in such patients there is the potential for choice of either surgery or primary endocrine therapy, what level of involvement does the patient play in the management decision?	
What factors have influenced your personal strategy for dealing with these patients?	
Prompts:	Literature evidence Patient preference Experience of cases over the years Unit policy Training and mentoring Breast care nurse input
What affects the amount of information you relay to a patient following a diagnosis of breast cancer?	
Prompts:	Patient wishes Patient cognitive status Relative and carers information needs
What do you think older women feel about primary endocrine therapy?	
Prompts:	Easier than having surgery Safer than having surgery Less certainty of a cure Less hassle
What do you think older women feel about having surgery?	
Prompts:	Fear of death Disfigurement or loss of the breast Fear of hospitalisation Burden on others Loss of independence Complications (e.g. arm swelling)
Any additional comments the participant would like to add	

Figure 5.1: Interview schedule.

Table 5.3 shows the sites according to their allocated site number, with the number of participants recruited.

Trust (high/low PET rate)	Number invited			Number recruited			Issues
	Surgeon	CNS	Other	Surgeon	CNS	Other	
T001 (high)	3	1	0	2	1	0	
T002 (low)	1	1	0	1	1	0	
T003 (low)	2	1	0	2	1	0	
T004 (high)	2	1	0	1	0	0	
T005 (high)	2	1	0	2	1	0	
T006 (low)	1	1	0	0	1	0	
T007 (high)	2	2	0	1	1	0	
T008 (high)	1	1	1	1	1	1	
T009 (high)	2	1	0	1	1	0	
T010 (high)	2	1	0	2	1	0	
T011 (low)	2	1	0	1	1	0	
T012 (low)	1	1	0	2	1	0	
T013 (high)	2	0	0	2	1	0	
T014 (low)	2	1	0	2	1	0	
T015 (low)	-	-	-	0	0	0	Delay with R&D
T016 (high)	-	-	-	0	0	0	Delay with R&D
T017 (low)	-	-	-	0	0	0	No response
T018 (low)	-	-	-	0	0	0	No response
T019 (high)	-	-	-	0	0	0	No response
T020 (high)	-	-	-	0	0	0	Delay with R&D
Total	25	14	1	20	13	1	Grand Total: 34

Table 5.3: Interview recruitment per site.

5.4.4.2. Data collection

All participants were contacted the day before their interviews to ensure they still wished to proceed and were given the opportunity to decline if they so wished. It was explained to all interviewees that they could terminate or pause the interview at any point without stating a reason for doing so and that their participation was entirely voluntary. Fully informed, written consent was taken prior to the interview. Interviews were conducted by one researcher (JM) at a location convenient to the participant. Questions were initially focussed around the interview schedule, however as the study progressed, further topics were raised (emerging themes) and participants views pertaining to these were also explored.

All interviews were digitally recorded with the participants consent and these were then transcribed verbatim. All data collected was pseudo-anonymised.

5.4.4.3. Data analysis

Framework analysis was undertaken on the transcripts using the steps described (see section 5.3.2.2). Familiarisation and initial coding was performed on paper whilst themes were emerging – the initial coding categories and their relationship to the final themes and subthemes can be found in Appendix 14. Ten percent of transcripts (three in total) were double coded by a second researcher (MB) to ensure inter-rater reliability and a more rigorous analysis. Formal coding and charting was performed using QSR NVivo 10 software – this software had the facility to electronically link summarised text within the framework matrix back to the original transcript so the charted text was read in context (see figure 5.3) – this removed the need for including page numbers within the framework matrix.

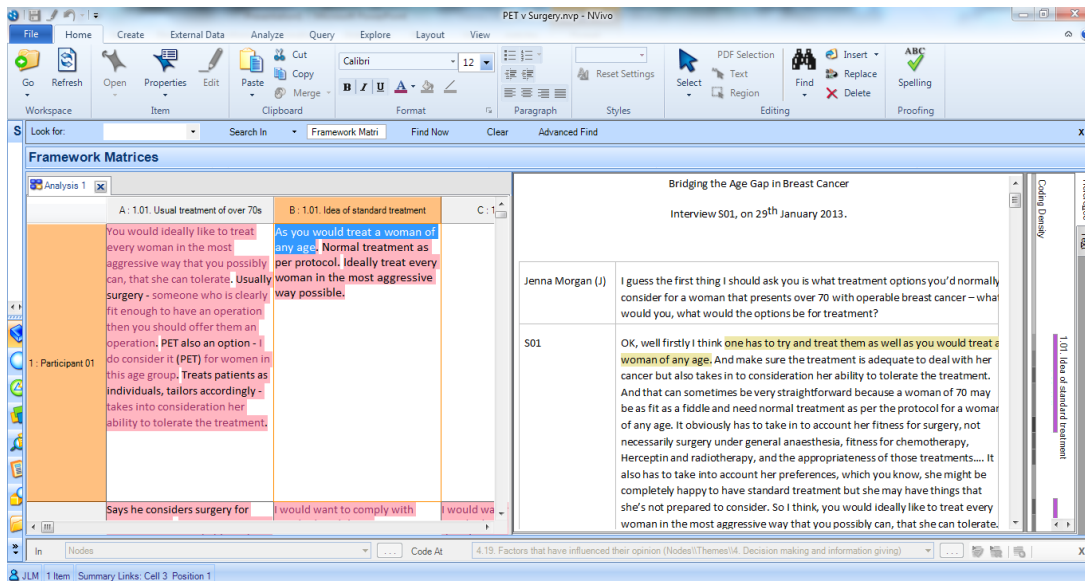


Figure 5.2: QSR NVivo 10 screen shot demonstrating linked text.

Once charting was complete, mapping and interpretation could be performed by analysing the dataset in its entirety. The main interpretations were concerned with:

- mapping the range and nature of the data
 - Identifying the range of responses across themes to identify the range of HCP opinions and map polarities regarding the treatment of older women with operable breast cancer.
- Finding associations
 - Recognising patterns of responses and identifying certain characteristics which may produce a certain view – for example, linking specific patterns of opinion to the HCPs role (surgeon vs. CNS) and regional PET rate (high or low)
- Providing explanations
 - Explaining and illuminating HCP’s attitudes, experiences, behaviours and beliefs.

5.4.4.4. Charting conventions

During the charting process, attempts were made to condense the text whilst retaining the meaning and the voice of the participant. Table 5.4 shows the adopted charting conventions.

Font & Format	Meaning
Black text highlighted	Summarised verbatim text, linked to original transcript in NVivo
Purple text highlighted	Direct quote, linked to original transcript in NVivo
Green text	Researchers comments, analysis
N.B. transcript page numbers are not shown within the matrix as NVivo software doesn't use page numbers but directly links quotes back to the original paragraph of the transcript.	
Abbreviations	
PET / ET / HT	Primary Endocrine Therapy / Endocrine Therapy / Hormone Therapy
Rx	Treatment
Pt	Patient
BC	Breast Cancer
Mx	Mastectomy
WLE	Wide Local Excision
RTx	Radiotherapy
Op	Operation
Info	Information
HCP	Healthcare professional
BCN / CNS	Breast care nurse / Clinical nurse specialist
Tam	Tamoxifen
Comorbs	Comorbidities
DM	Decision-making

Table 5.4: Adopted charting conventions.

The full framework can be viewed in Appendix 15.

5.4.4.5. Transcription conventions

In order to clarify direct quotation in the results section, table 5.5 shows the transcription conventions that were adopted.

Formatting	Meaning
<i>Italics</i>	Direct quotation
Bold	Indicates a word emphasised by the participant.
(S02-MH) (N06-FL)	Appears after a quotation and indicates the participant from whom the quotation was taken and their characteristics (S = surgeon, N = nurse, G = geriatrician; M = Male, F = Female; H = High PET unit, L = Low PET unit).
...	Ellipsis points have been use to identified where a quotation has been abridged
[word]	A word within square brackets within a quotation indicates a note of clarification by the author.
N.B. transcript page numbers are not shown following a quotation as NVivo software doesn't use page numbers but directly links quotes back to the original paragraph of the transcript.	

Table 5.5: Transcription conventions.

5.5. Results

5.5.1. Recruitment

Thirty-four healthcare professional (HCP) interviews were undertaken. These included 20 surgeons, 13 breast clinical nurse specialists (CNS) and one geriatrician with a specialist interest in women with newly diagnosed breast cancer. All interviews were conducted by the primary researcher (JM).

Interviews lasted between 15:05 and 57:39 (minutes: seconds), with a mean time of 33 minutes, 11 seconds. Data continued until saturation of themes occurred. HCP characteristics are shown in table 5.6 below.

HCP identifier	Profession	Sex	Unit PET rate	Interview length (minutes:seconds)
S01	Surgeon	Female	High	29:02
S02	Surgeon	Male	High	18:44
S03	Surgeon	Male	Low	15:05
S04	Surgeon	Male	Low	28:27
S05	Surgeon	Male	Low	44:42
N06	CNS	Female	Low	16:33
S07*	Surgeon	Female	High	24:06
S08	Surgeon	Male	High	24:08
N09	CNS	Female	High	31:42
S10	Surgeon	Male	High	21:47
N11	CNS	Female	Low	39:27
N12	CNS	Female	High	23:51
N13	CNS	Female	High	34:47
S14	Surgeon	Male	High	21:34
S15	Surgeon	Female	High	55:40
G16	Geriatrician	Male	High	55:23
N17	CNS	Female	High	47:08
S18	Surgeon	Female	High	29:49
N19	CNS	Female	High	32:41
S20	Surgeon	Male	High	45:41
S21*	Surgeon	Female	High	32:33
N22	CNS	Female	High	33:13
N23	CNS	Female	Low	57:39
S24	Surgeon	Male	Low	29:30
S25	Surgeon	Female	Low	34:42
S26	Surgeon	Male	Low	36:13
N27	CNS	Female	Low	20:15
S28	Surgeon	Female	Low	27:23
S29	Surgeon	Female	Low	41:20
N30	CNS	Female	Low	26:26
N31	CNS	Female	High	46:32
S32*	Surgeon	Female	High	42:19
S33	Surgeon	Female	High	25:13
N34	CNS	Female	High	34:47

Table 5.6: HCP interviewee characteristics; *denotes double coded by a second researcher (MB).

Copies of two sample interview transcripts can be found in Appendix 16.

5.5.2. Findings

Four key themes were raised during the interviews and these can be seen in table 5.7.

Theme	Subthemes
Attitudes towards treating older women with breast cancer	Impact of age on the treatment of breast cancer
	Factors influencing treatment in older patients
	Assessment of older patients
	Variation in treatment of older patients
Experience of surgical treatment in older women with breast cancer	Opinions on surgery as a treatment in older patients
	Pros and cons of surgical treatment for older patients
	Perceptions of older patients views of surgery
	Their experience of older patients refusing surgery
	Opinions regarding the use of local anaesthetic surgery
Experience of Primary Endocrine Therapy as a treatment for older women with breast cancer	Opinions on PET as a treatment in older patients
	Pros and cons of PET as a treatment for older patients
	Perceptions of older patients views of PET
	Practicalities of treating older women with PET
Views on the decision-making process in older women	Patients preconceptions & prior knowledge
	Information giving
	Decision-making in older women
	Their experience of older patients refusing treatment
	Influence of healthcare professional on the DM process
	Offering choice
	Making recommendations
Timing	

Table 5.7: Themes (and their subthemes) raised during healthcare profession interviews.

5.5.2.1. Views regarding the treatment of older women with breast cancer

Impact of age of the treatment of breast cancer

Most HCPs (n=19) were of the view that it was important to treat an older patient in the same way that you would treat any patient and most said that age itself was not a factor when deciding treatment. In some cases, it seemed that HCPs were keen not to be seen as being prejudiced against older patients or considered “ageist”.

“You give the patient treatment that the cancer deserves and not an age deserves... I would never differentiate on age because I wouldn't want that to be done to me and so why would I do it to someone else?” (S05-ML).

However despite this, some (n=9) HCPs, particularly those from High PET units (n=7), contradicted themselves by describing age-related cut-offs for discussing non-standard treatment and a couple implied subconscious age-related bias by comparing older patients to “normal” patients. Only a minority (n=3) felt that clinicians were inherently biased towards older patients and acknowledged

that age was actually an important factor when deciding what treatment they would consider for this age group. This group felt it was important to account for age due to its effect on tumour biology, patient physiology and life expectancy – this was commonly termed “biological age” as opposed to chronological age.

“everyone does take age into account, and you can’t help it. But it’s correct to encourage people to make decisions based on, you know this thing known as biological age... if you’re in your 90s your physiological reserve renal function is 25% of what it was when you were in your 20s, which has a huge impact on your ability to withstand certain treatments, including surgery” (S02-MH)

HCPs talked about less aggressive treatment in some older patients, with limited use of reconstruction, trying to avoid axillary clearance and offering PET as an alternative. These HCPs felt older patients would not tolerate these or they would significantly impact on their quality of life.

“If you do an op and you rid them of the cancer but you leave them with a very poor quality of life because of the after-effects then you’ve achieved nothing” (S25-FL)

There was also an overriding opinion that the definition of “old” has changed and that decisions between surgery and PET were no longer appropriate for those under the age of 80.

“I would say 70’s not really my cut off now, it’s more like 80... This kind of drive to do more surgery for elderly patients has actually raised the definition of ‘elderly’ from 70 to 80” (S24-ML)

Factors influencing treatment of older patients

HCPs mentioned many factors that influenced their decision-making and opinion regarding appropriate treatment for older women with breast cancer. These included:

- Tumour factors such as degree of ER-positivity, PR status, HER2 status, suitability for breast-conserving surgery and the histological sub-type (specifically mucinous types).
- Patient factors such as their fitness or level of co-morbidity, presence of dementia, frailty, functional status, social circumstances and their preferences.
- Other external factors, such as family opinion, cultural issues and the opinion of other HCPs such as their anaesthetist.

Most important were the patient factors, particularly fitness for surgery which was an issue raised by nearly all of the participants.

“Often boils down to... is this patient fit for standard treatment” (S15-FH)

There was variation in HCP opinion on what constituted being fit or unfit for surgical treatment. Some (n=18) HCPs equated this to the co-morbidity status of the patient and others emphasising the importance of frailty (n=16) although there was no clear definition for this. In terms of which co-morbidities were considered important, again this varied considerably amongst HCPs. One said they operated on all patients unless they had a significant other cancer that would limit their life-expectancy to a few months whereas others mentioned more chronic conditions such as hypertension, cardio-respiratory disease, diabetes and even arthritis.

Another factor that divided opinion of the HCPs was that of women with breast cancer AND a diagnosis of dementia. Approximately half of the HCPs interviewed were of the view that patients with dementia should be treated surgically due to issues with compliance and distress around continued follow-up. The other half of HCPs felt that PET was the preferred treatment of choice (as opposed to surgery) as there was no distress associated with admission and being away from their own environment, coupled with the problem of informed consent.

“Dementia is the one indication for PET in my book” (S24-ML)

“These patients [with dementia] need double consenting and surgery” (S03-ML)

Many of the HCP interviewed stated that life expectancy was the most important factor in deciding which treatments to offer, with other factors, such as comorbidity, frailty and dementia only being relevant because they impacted on a patient’s expected life expectancy and, consequently, the benefit derived from standard treatment.

“If you’ve got... a predicted survival of less than two to three years there’s no additional benefit from surgery” (S02-MH).

Several HCPs (n=13) stated patient preference was one of the most important factor in deciding treatment; even those who didn’t offer a choice of treatment claimed they would use PET if a patient refused to undergo surgery.

“Patient views obviously have the primacy” (S01-FH)

Assessment of older patients

Most HCPs did not use any form of comprehensive geriatric assessment in their routine practice. The main form of assessment to determine whether a not a patient is deemed fit for surgery was an

anaesthetic assessment. Some stated that this was to gain a clearer understanding of the surgical risk rather than determine which treatment they should undergo since they often had already made that decision. Some however, seemed to defer the decision as to whether or not to operate to the anaesthetist.

“...we leave it to the anaesthetists to decide” (S25-FL)

However, as one surgeon pointed out, different anaesthetists also have different opinions.

“Different anaesthetists have different thresholds for who’s fit for a GA” (S01-FH)

Many surgeons (n=14) explained that the decision to operate was based on an “end of the bed” type of assessment.

“There’s a lot of patients you can eyeball, if they can go up a flight of steps, they can walk from the entrance to your clinic, you know they’ll be ok for a GA” (S28-FL)

Some HCPs thought that more formal assessments might provide impartiality in the DM process, however one in particular felt these assessments had potential limitations.

“...you ask... ‘can you walk upstairs?’ and they say ‘no, I live in a bungalow’... you can very easily take their independence away from them.” (N17-FH)

Variation in treatment of older patients

HCPs raised several important factors that were deemed to contribute to the variation in the treatment in the older breast cancer population, including the heterogeneity within the population combined with the need to individualise treatment.

“...you’ve got your tennis playing 75, 78, 80 years olds and you’ve got your decrepit 71 year olds” (S33-FH)

Others commented on the variation in opinions of clinicians and whether patients are offered a choice and how that choice is offered.

“you have a surgeon who always operates... and you have someone who would always... puts them on medication – I’ve got a feeling that we should blame the HCPs more rather than the patients” (S20-FL)

5.5.2.2. Experience of surgical treatment in older women with breast cancer

Opinions on surgery as a treatment in older patients

Most HCPs (n=24) were of the view that surgery was considered a safe and superior treatment option for most patients.

“Surgery is the gold standard” (N12, FH)

The two main benefits of surgery over PET were stated as providing superior local control and increased survival benefit, although these were deemed more relevant in the younger, fitter older breast cancer population.

“what the surgery gives you is enhanced local control” (S01-FH)

“surgery probably does have a (survival) benefit as long as you haven’t got severe co-morbidities” (S02-MH)

However, despite these perceived benefits of surgery, HCPs were also mindful of the possibility of “over-treatment” in this group of patients, commenting that most patients would die with their cancers rather than because of them.

“People say that you can get any patient through breast cancer surgery, though why would you want to if she’s not likely to benefit?” (S15-FH)

Pros and cons of surgical treatment for older patients

Although the general consensus was that surgery is safe with low complication rates, some HCPs felt that there were potential risks when operating on older patients. These included general complications of breast surgery, such as bleeding, infection and the development of lymphoedema, as well as those more likely to occur in the older population, such as myocardial infarction and loss of independence. However some HCPs commented that although breast cancer surgery can usually be performed as a day case procedure, recovery may not be as straightforward in older patients.

“A complication... causes a much bigger set-back and a much bigger impact on their quality of life” (S33-FL)

The effect of surgery, in particular of mastectomy, on a patient’s body image was also mentioned within a number of the interviews. This was particularly raised by the nurses at interview, with surgeons seeming to deem it less important in the older compared to the younger breast cancer population.

“...there’s a small number of people, despite their age, still would feel a great sadness at losing their breast and having an altered body image” (N19-FH)

“At that stage of life most women are less concerned about disfigurement” (S25-FL)

Perceptions of older patients views of surgery

Most HCPs (N=17) felt that surgical management was a source of anxiety for older patients, particularly in relation to the anaesthetic and the risks of complications.

“having surgery is scary... having an anaesthetic, they worry, are they going to come round from it? Having an, in their eyes, a “big” operation, if it’s a mastectomy... the recovery’s going to be harder... if they’re isolated... that panics them more” (N06-FL)

It was felt that those who do have it are pleasantly surprised by how easy it is.

“Patients’ perceptions about the risks are completely different from the actual risk” (S04-ML)

A few (n=6) commented that some patients simply considered surgery to be a hassle and they would rather choose, what they deemed as, an easier option.

“you offer them an operation and they go “no, I really don’t want one... I don’t want any more messing, just leave me alone”... they just don’t want to be bothered, they just don’t want an operation” (S07-FH)

Their experience of older patients refusing surgery

Almost all HCPs had experienced older patients who had refused surgical treatment for their breast cancer and of those HCPs who claimed they didn’t get many patients refusing surgery, most were from low PET units (n=3 versus n=1).

What was interesting was the variation in response to this type of refusal. Some accepted that this was a valid treatment choice and so would use PET in these circumstances. There were others however, who felt strongly that surgery was the best treatment and so would try and convince patients that this was the best treatment, especially for younger, fitter older patients.

“They are the ones I would like to persuade towards surgery” (S28-FL)

Use of local anaesthetic surgery

When asked about the use of local anaesthetic surgery performed on older patients, there were a variety of responses, with some never using this technique, as they felt it was inferior in terms of being unable to perform axillary surgery, and others performing it on a regular basis.

“Majority of my elderly patients will have their wide local excision under local” (S24-ML)

5.5.2.3. Experience of PET as a treatment in older women with breast cancer

Views on PET as a treatment in older patients

HCP opinion on PET as a treatment varied, with some considering it a valuable treatment option and others viewing it as the inferior option.

“It does seem to be a fairly long-term good treatment” (N13-FH)

“I feel... PET is writing somebody off” (S28-FL)

One HCP explained that he didn't even consider PET a treatment for breast cancer.

“I see endocrine therapy as adjuvant, and sometimes neo-adjuvant but I don't see it as a stand-alone treatment” (S04-ML)

A common theme that emerged from the data was the issue of variability in both the response rate and duration of response. Interestingly, HCPs from high PET units tended to think PET had a longer duration of response than HCPs from low PET units.

“you see women who are on tamoxifen for 10 years without a single sign of the tumour re-growing and no problems at all... but then for some women... two years down the line they're worse off... but you don't know at the outset... you can't tell can you?” (S07-FH)

Pros and cons of PET as a treatment option for older patients

The main benefit of PET over surgery was that it avoided an operation and the need for admission to hospital.

“It avoids them coming into hospital, having an operation, avoids radiotherapy” (S15-FH)

A few (n=7) mentioned there being the potential for non-compliance, but the main disadvantage of PET that nearly all (n=27) HCPs talked about was the risk of disease progression at a later date when surgery may no longer be a viable option.

“Endocrine therapy is going to stop working, and they’re going to be a couple of years older, maybe not fit for surgery at that point” (N17-FH)

Also mentioned by around half of HCPs, were the potential side-effects of PET, including osteoporosis and deep vein thrombosis, although a couple pointed out that this was not really a disadvantage of PET over surgery as patients having surgery will also be having adjuvant endocrine therapy.

Perceptions of older patients views of PET

HCP’s were of the view that the majority of older patients who received PET were pleased and relieved about not having an operation.

“I think those ladies that are on primary endocrine therapy are happy to be on primary endocrine therapy because I think they’re generally the people who have, kind of, steered clear of surgery” (N12-FH)

It was also thought that older women considered PET low-risk in comparison to surgery.

“they all think that PET is great because it’s the no risk scenario in some respects, certainly to start with” (S01-FH)

However, nearly half of the HCPs felt that patients may be uncomfortable with the idea of PET as the cancer remains in-situ.

“They don’t like the idea that they still have a cancer within the body” (N13-FH)

In contrast, around half of the HCPs felt that older women are reassured if they can feel a palpable lump shrink and soften. Many suggested that older women are usually just relieved that they do not need an operation as it is seen as the easier option.

Practicalities of treating older women with PET

Although most specified that they would use letrozole as a first line for PET, there were HCPs that used alternatives including anastrozole and tamoxifen.

There was also considerable variation in the methods of tumour assessment, with some HCPs using US scanning to perform a volume assessment, others using bi-dimensional caliper measurements whilst others just measured the size of the lump informally on clinical examination. Timings of follow-up also varied, with some bringing patients back on an intensive regime, every three months until the patients achieve a good response, and then patients were seen six-monthly or yearly for

the duration of treatment. There were others, however, who discharged patients after 6 months or a year from follow-up, leaving it to the GP to review the response in the community.

Many of the participants commented on the variability in duration of response to PET, although there was variation in the average duration HCPs believed PET usually maintained control for. HCPs from high PET units tended to believe that PET had a longer duration of control than those from low PET units.

“Some women obviously go a long time on endocrine therapy and others don’t even get that first response” (N12-FH)

There was also variation in the reaction of HCPs when patients did experience loss of tumour control during treatment with PET. Some believed that patients with progressive disease should undergo surgery straight away if they were still fit enough. Others would simply try an alternative anti-oestrogen and others commented that they occasionally used radiotherapy as second-line treatment, especially if patients were no longer fit enough for an operation.

5.5.2.4. Views on the decision-making process in older women

Information giving

The amount of verbal information provided by HCPs varied, with most stating they tailored it to the individual, depending on their preferences for information as well as their ability to absorb it.

“See how the patient is accepting or digesting the information, some of them are happy to accept everything, so I tell them everything. Some of them, they don’t like it, they like just ‘cancer’ or ‘not cancer’, ‘give me the treatment, let me go home’ ” (S10-MH)

In terms of written information, several HCPs mentioned that they had standard packs of information that they tended to give out to all patients.

“We have a standard pack and then we give additional information on top of that... some of which are not relevant for every patient” (N06-FL)

There was a suggestion that HCPs felt that older patients required less information than younger patients, although there were no reasons why this might be.

“A lot of the older population I feel, don’t want information... They don’t want to be empowered with information like the younger population” (N12-FH)

The breast CNSs appeared to do the majority of the information-giving with patients, as they were able to spend longer with them.

“In a busy clinic, as a surgeon, I can do only so much from that [information-giving] point of view. I’ll make sure that my specialist nurse is sitting with me... then we’ve got a separate room whereby she goes and explains a bit more” (S26-ML)

Decision-making in older women

HCPs varied on their opinions regarding the DM styles of older women; some believed older patients preferred a more doctor-centred approach whilst others felt they wanted a more patient-centred DM approach.

“They want the surgeon... to tell them what is the best option, they don’t want to make decisions about their care... I find that a lot in the older population” (N12-FH)

“I think elderly patients are usually quite switched on. They’ve often already made up their mind... so they’ve made a decision which is not necessarily that well informed but they’ve nevertheless made a clear decision. It can be extremely difficult to change their mind once they’ve got a set opinion” (S18-FH)

Patients’ preconceived ideas about themselves, breast cancer and cancer treatments were identified by HCPs as factors that influenced patients’ treatment preference. Particular issues raised included a belief by patients that they were too old for treatment (particularly surgery), the notion that quality of life was prioritised over quantity, and the impact of previous experiences of cancer, either themselves or of family and friends.

Experience of older patients refusing treatment

Almost all HCPs had experience of older patients refusing treatment, particularly surgical treatment. Most of those who didn’t feel this was a common problem were from low PET units. There was a feeling that older patients didn’t want to be bothered with surgical treatment.

There was however variation in the way HCPs, and in particular surgeons, responded to this refusal, with some simply respecting their choices and others trying to convince them, especially younger, fitter patients, to undergo what they considered the optimal treatment.

“As a physician, if you tell them what’s best for them they would eventually come around to your point of view” (S05-ML)

“A lot is about what they want and even the fittest people don’t want something doing and you know it’s about not judging that and just doing what they want you to do” (N13-FH)

Influence of healthcare professional on DM process

This theme raised some interesting aspects in terms of contradictions within the interviews. Most HCPs declared that the treatment decision was down to the patient.

“It’s a patient-driven decision, rather than a surgeon-driven decision” (S05-ML)

However, the same HCPs also admitted that although the ultimate decision was left with the patient, there was an acknowledgement that the framing of the way in which the information about either treatments enabled older women to make their treatment decision. This is crucially important in terms of a patient deciding between two treatment options if only one option is provided.

“It always depends on how a surgeon puts it... if I want to take them down the endocrine route only – then they’d go with it. Or if I said you need to have surgery, then they’d go with that” (S05-ML)

Interestingly, the nurses that were interviewed seemed more aware of patients being led by the clinicians than the surgeons themselves.

“a personal opinion can sway people’s approach, a lot of the time I do feel it’s to do with the preference of the surgeon” (N11-FH)

“I think doctors these days are getting better at talking about all of the options but possibly steering them more now towards the surgical option” (N12-FH)

Offering choice

There was considerable variation between HCPs regarding whether or not older patients with operable breast cancer should be offered a choice of treatments between surgery or PET. The majority (n=20), who tended to be from high PET units (n=14), felt that there were a sub-group of patients, who tended to be older, frailer and less fit, who were suitable to be offered a choice as it would not impact on their overall survival. However, a few HCPs from units with lower rates of PET (n=5), felt that, as they considered it an inferior option, it was not appropriate to offer PET as a choice.

“that group of patients where we’re uncertain whether surgery’s going to have a benefit or not, it’s definitely an issue for patient choice. So no pressure on the patient for making a decision... and genuinely trying to advise them that it’s an equivocal decision” (S02-MH)

“I give my advice...The literature suggests that at the moment, if they’re operable they should be offered an operation and so that’s what I offer them. So I don’t give them a choice between surgery and primary endocrine therapy” (S04-ML)

Making recommendations

The majority of HCPs felt comfortable recommending surgery to most older patients as it was seen as the superior treatment option. However when patients were offered a choice of treatment but were deemed to be passive decision-makers, willingness to recommend in this scenario varied - some were quite happy to advise patients and others felt very uncomfortable with it.

“...’no doctor, you decide what’s best for me, I don’t know, I’m not the expert’ I mean I’ve had that said to me many times and in that situation you say ‘Well I’ll tell you a little bit and let you have a little think about it and then if you want me to decide then I’ll decide for you’ ” (S01-FH)

“If they ask me well what do I think, I will tell them... ‘You choose what is right for you, not what is right for me... I don’t know how I will choose if I was sitting where you’re sitting so it really is your choice’ ” (S21-FH)

“I think deciding for them is uncomfortable for me” (S33-FH)

Timing

Giving the patient time to reach a treatment decision was viewed as important by HCPs.

“Giving them time to think through it, the pros and cons, is very important” (S28-FL)

Some HCPs also used PET as a method of “buying time” whilst the patient took time to think about whether or not they wanted to have an operation.

“...there’s no harm in most of them in starting them on the tablets and giving them some time to think” (S01-FH)

5.6. Discussion

This study reports new findings on the factors underlying treatment decision-making by HCPs in relation to older women with operable breast cancer and their views regarding the use of PET and surgery in this group.

5.6.1. Factors considered in the treatment decision-making process

Several factors were considered by HCPs when deciding what treatment to offer older patients with operable breast cancer. Although initial responses were generally consistent with current guidelines [8, 127], particularly with regards to the influence of age, further investigation revealed variation from the UK recommendations, with many HCPs offering less aggressive treatments, including PET, to the older and frailer, less fit patients. This may in part be due to the fact that increasing age is inextricably linked to both decreasing life-expectancy and increasing comorbidity rates, which in turn may decrease the survival advantage of more aggressive breast cancer therapies [106]. Both comorbidity and life-expectancy were also considered important in their own right.

5.6.2. Variation in clinician opinion regarding factors considered

HCPs unanimously agreed that “fitness for surgery” was an important consideration in treatment decision-making for older patients. However there was considerable variation among clinicians regarding key features that constituted being fit for surgery. This was specifically the case in older women with breast cancer and dementia. There are currently no guidelines pertaining to the treatment of cancer patients with dementia and this variation in opinion may reflect this. A further explanation for such differing views may be that dementia was not defined, and HCPs clinical judgement of dementia may vary in the absence of formal assessments.

Another source of variability was the assessment process by which HCPs determined fitness of their patients. This is unsurprising as the older population make up a very heterogeneous group and as SIOG points out that although CGA may be useful, it is not clear which patients will benefit nor which method is best [127].

5.6.3. Variation in clinician opinion regarding treatment options

As with any real world situation, the findings demonstrated a broad spectrum of beliefs, attitudes and behaviours. Perhaps the most striking division of opinion was regarding the use of PET as a treatment for older patients with operable breast cancer, with some HCPs believing it a valuable

treatment option and others declaring they did not consider it a treatment at all. This may reflect uncertainty in the published evidence to date and the variability in response and duration of benefit, with the length of time to progression varying greatly from nine to 132 months [337, 339, 341, 364, 401].

Another point of variability was in the use of local anaesthetic surgery. Despite the fact that the use of local and regional anaesthesia for breast surgery in patients who are unable to undergo GA is well-established [473], some HCPs did not utilise this option with their patients, instead tending to treat them with PET.

5.6.4. Variation in clinician opinion regarding choice

Evidence suggests that older patients may prioritise quality of life over quantity [415] and patient choice is commonly stated as a reason for treating patients with PET [128, 369]. SDM dictates that patients should be informed of their treatment options and allow the patient to decide what is best for them [277], however there was considerable variation in the importance placed on offering treatment choices and informing patients (particularly those who are fit and healthy) that PET may be an alternative they may wish to consider. There was also clear evidence from numerous HCPs that the practice of steering a patient towards their preferred choice, whilst paying lip service to offering SDM, was widespread.

5.6.5. Variation between high and low PET regions

There appeared to be some variation in opinions of HCPs from high and low PET units, with those from high units tending to use more age-related cut-offs for discussing PET as a treatment option. HCPs from high PET units also tended to be more likely to offer a choice of treatments, with those from low units tending to feel that offering PET as an option was not appropriate. This latter opinion is in contrast with SDM ideals that have become more important in today's NHS [268, 277, 456], particularly since evidence suggests that older patients may prioritise quality of life over quantity [415].

Interestingly, HCPs from low PET units stated that they had less experience of older patients refusing surgical treatment for their breast cancer. This may in part be due to the fact that these HCPs tended not to offer choice and so patients may not have known there was an alternative. Indeed, it has been suggested that clinician preference and how treatment options are presented are significant in determining treatment [373] and there was clear evidence of this in these interviews.

HCPs from high PET units also tended to believe that PET had a longer duration of control than those from low PET units. One of the major drawbacks of PET is the short duration of response and most patients will suffer a relapse [227] with recurrence or progression of their disease after a mean duration of 18-24 months [216]. However long-term follow-up studies have shown that over one third of women treated with PET had disease control for more than 5 years, and more than 15% still had control up to 10 years [219]. It may be that HCPs using PET more often have experience with patients who have been on PET for longer periods or that this difference in opinion regarding the duration of clinical benefit is the reason why HCPs either do or don't use PET.

This variation in opinion between individuals from high and low PET units may be a contributing factor to some of the variation seen in the UK.

5.6.6. Strengths and weaknesses of this analysis

Semi-structured qualitative interviews have provided a rich data source, enabling documentation of unique first-hand perspectives of HCPs that would be difficult to gather by any other method.

Utilising open-ended questions and a conversational style has allowed flexibility within the interview schedule and has aided the collection of emerging themes in addition to pre-determined ones.

However this method of data collection and analysis can be prone to bias. In view the fact that all participants were contacted via personal communication by the lead researcher (JM), this may have led to selection bias, however this was minimised by purposively selecting from units across the country and including individuals that were both known and not known to the researcher prior to the study. A further source of bias can be considered as the interviewer themselves as they lead the questions and, whilst it cannot be said that participants intentionally wish to mislead, they may try and respond in a way that they think the interviewer wants them to.

Interviews of peoples experiences is also prone to potential recall bias due to retrospective recollection, although all HCPs involved were currently practicing in the area of study. Additionally, it has previously been shown that most UK breast surgeons do not formally audit their practice in terms of PET [128], so it may be possible that for some questions participants have used a best-guess that may inaccurately represent their current clinical practice.

5.7. Summary

In conclusion, HCP opinions differ on the most appropriate way to treat older women with operable breast cancer, especially if they have co-existing dementia, and whether they should be offered PET as a treatment option. This may be a significant cause of the variation in treatment of older women with breast cancer in the UK and is explored further in later chapters of this thesis to identify whether some of the themes raised here are generalizable to the UK as a whole.

Chapter 6: Clinician Questionnaires – Survey of Opinion

6.1. Abstract

6.1.1. Introduction:

PET may be a viable alternative to surgery in selected older women but there are no reliable evidence-based guidelines on which to base this decision and rates of surgery vary widely. This component of the study aimed to quantify and generalise the findings from the previous interview study in relation to factors underpinning the treatment decision-making in older women with operable breast cancer.

6.1.2. Methods:

A bespoke questionnaire was developed based on the results from a systematic literature review, expert opinion and qualitative interviews with HCPs. The final questionnaire was administered by post, distributed via the UK Association of Breast Surgery (ABS).

6.1.3. Results:

Of the 641 questionnaires distributed, 258 were returned (40.2%). The presence of comorbidities was considered the most important factor in determining how to treat older women with operable breast cancer with age being considered as one of the least important factors. Dementia was considered an important factor in determining treatment but opinion was divided as to whether these patients should be treated with PET (41.1%) or surgery (58.9%). Only around a quarter 65/244 (26.6%) felt that all patients over the age of 70 should be offered PET as an alternative treatment option.

6.1.4. Conclusions:

HCP opinion regarding the treatment of older women with operable breast cancer differ particularly regarding the optimal way to treat patients with co-existing dementia and as to whether patients should be offered both surgery and PET as a treatment option. These factors may be having an impact on the variation in the treatment of older women with breast cancer across the UK.

6.2. Introduction

As previously discussed, PET may be a viable alternative to surgery in selected older women with a limited life expectancy. However, currently there are no reliable evidence-based guidelines on which to base this decision and rates of surgery vary widely across the UK, Europe and the world. Chapter 5 explored some of the issues which clinicians take into account when making this treatment choice (between PET and surgery) using qualitative interviews. This identified a number of factors which were viewed as important. A questionnaire was developed based on the systematic review and the issues raised within the qualitative phase of the study. The aim being to examine the relative importance of each factor identified through these stages and to increase the generalisability of these findings.

A similar survey of specialist HCPs was published during the recruitment phase of this part of the study [128]. Wylie and colleagues aimed to examine UK practice of PET in the treatment of patients 70 years or over with surgically resectable early breast cancer. Their study only surveyed breast surgeon members of the Association of Breast Surgery (ABS) and had a response rate of 228/489 (47%). They found that the vast majority of surgeons used PET in older women who were unfit for surgery or owing to patient preference and that three-quarters used letrozole. The percentage of older patients treated in this way varied considerably (<10-70%) and the majority of surgeons had not formally audited their practice. In addition, Wylie and colleagues also found that the over 70% of surgeons underestimated the expected life expectancy of an average 80 year old woman [128]. Their study had a response rate that would be expected for this population based on other similar questionnaire studies [474], however the authors have limited their study to surgeons only, thereby excluding other potential useful opinions of HCPs also involved in the care of these patients. There is also no discussion in their report as to how the questions within the survey were designed and chosen. Their study reports findings mainly related to clinical practice and do not explore opinions or reasons why HCPs practice in this way, excepting one question on estimating life-expectancy, the results of which are quite interesting in this context.

The study presented in this chapter aimed to investigate specialist HCP opinion relating to factors they consider important when choosing treatment, examined both PET and surgery as treatment options and included breast CNSs and other HCPs involved in the care of older breast cancer patients in order to gain a greater breadth of knowledge on this subject. It aimed to complement the qualitative interviews by quantifying the factors that were found to underlie treatment decision-making among HCPs relating to older women with breast cancer and optimise the generalisability of the findings.

6.3. Methodology

6.3.1. Choice of Questionnaire Surveys

Questionnaire surveys are a common method of gathering information from a population on their knowledge, beliefs, attitudes and behaviours [475, 476], and can be used to quantify findings collected as part of a mixed methods study in order to give breadth and generalisability to the findings [477]. They have the advantage of being cheap and easy to administer and can collect data efficiently from a large population [475, 478].

6.3.1.1. Response rates

Care must be taken when designing questionnaires to ensure they are acceptable and understandable to the participants in order to obtain an adequate response rate. Questionnaires that are overly long, incomprehensible or offensive are unlikely to be successful. Several techniques may be employed to increase response rates [475, 479-481], including:

- Using official headed paper.
- Using a covering letter or participant information sheet.
- Addressing the mail to the participants personally.
- Using stamps rather than mass franking.
- Enclosing a stamped-addressed reply envelope.
- Having the survey sponsored or endorsed.
- Ensuring anonymity and confidentiality of responses.
- Sending out reminders when response rates drop off.

6.3.1.2. Question design

Questions should be short and clear, avoiding ambiguous words such as “often, regularly or some” as perceptions vary between individuals [481]. The decision to use closed or open questions should also be considered – closed questions are more straightforward to analyse however they may restrict the depth of responses [478].

Likert scales are ordinal scales that measure levels of agreement/disagreement and can be particularly useful in determining preference or opinions [478, 482]. There is some controversy regarding whether or not to include a neutral point, e.g. neither agree nor disagree, as whilst

excluding it forces participants to make a choice, removing it may lead to irritation and non-response bias [482].

How the questions are framed is also important in terms of avoiding bias in results. Questions may be positively or negatively framed [483] depending on whether the focus of the question is centred on gains or losses. Framing has been shown to influence people's choices, preferences, attitudes and behaviours differently [484]; people tend to be more risk-averse when considering gains but are risk-seeking when considering losses [483-486]. As such, it is important to use a combination of framing styles within a questionnaire to avoid bias from framing.

6.3.2. Questionnaire psychometrics

Questionnaires should be reliable, valid and acceptable and these attributes may be assessed by the use of pilot studies.

Reliability refers to the ability of a questionnaire to yield consistent results so that any differences yielded result from differences between participants and not from how the questions are understood or interpreted [481, 487]. The reliability of a questionnaire can be assessed by applying the instrument to the same individual at different time points (test-retest reliability) or by asking the same question in different ways within the same questionnaire (internal reliability) [487]. When designing the questionnaire, similar questions using both positive and negative framing can be included to ensure reliability and the pilot phase can be used to apply the questionnaire to the same individuals twice over a period of time to ensure test-retest reliability.

Validity refers to the ability of a questionnaire to measure what it claims to measure [475]. There are several types of validity:

- **Content validity** refers to the ability of a questionnaire to measure all elements of the topic being studied. It assesses whether the questions within the instrument are a well-balanced sample of the content domain to be measured [475]. In order to ensure content validity it is important to research the subject area being studied in depth prior to constructing the instrument.
- **Face validity** is similar to content validity but assesses whether the questionnaire appears to measure what it is supposed to measure and is evaluated by the individuals being assessed [487]. This is an important element to be assessed during the pilot study.
- **Criterion or concurrent validity** refers to how well the questionnaire compares with other similar or validated instruments [475, 487].

- **Construct validity** applies when abstract constructs, such as intelligence, are being studied and refers to how well the questionnaire results compare with a set of theoretical assumptions [475]. This has little application in this study where the area being studied is not an abstract concept.

Acceptability refers to whether the questionnaire is tolerated by the individuals being tested – for example, it doesn't take too long to complete and the questions are worded so as to not cause offence – it is assessed qualitatively by the individuals who complete the questionnaires [487] and should also be evaluated during the pilot phase.

Section 6.4.2.3 demonstrates how these psychometrics have been addressed within the study.

6.4. Methods

6.4.1. Research Governance

6.4.1.1. Ethics approval

Research Ethics Committee (REC) approval was not required for this study as the participants were NHS staff recruited by virtue of their profession. The study protocol was reviewed by the University of Sheffield Medical School's Ethics Review Committee and approval was granted on 22nd November 2012 (ref: SMBRER243; see Appendices 6 & 7).

6.4.1.2. Consent

Individual participant consent was implied by the return of the questionnaire to the study team. A covering letter explaining the study and informing the individual that participation is voluntary was included with the questionnaire pack (see Appendix 17).

6.4.1.3. Confidentiality

Questionnaire responses were anonymous unless individual participants requested personal feedback about publication of the study results, in which case their identities were anonymised for purposes of analysis.

Databases, including the list of names and addresses of ABS members, were password protected and stored in a locked office in the university in accordance with the Data Protection Act 1998. No information that would allow clinicians to be identified was released into the public domain.

6.4.2. Questionnaire design

6.4.2.1. Pre-piloting phase

A preliminary questionnaire was developed by the primary researcher (JM) based on the literature review (Chapter 3), the results of the qualitative interviews and the expert opinion of the members of the study team and the extended "Bridging the Age Gap in Breast Cancer" study team (LW, MWR, KC, MB, LC, RAA, KLC, TGR) to ensure content validity. Table 6.1 shows the topics explored within the questionnaire and the sources used to develop them.

Questionnaire topic	Source from which derived
Effect of patient age on treatment	Literature, Interviews, Expert opinion
Effect of tumour biology on treatment	Literature, Interviews, Expert opinion
Effect of tumour stage on treatment	Literature, Interviews, Expert opinion
Effect of patient factors (such as frailty, function, comorbidity) on treatment	Literature, Interviews, Expert opinion
Effect of patient preference on treatment	Literature, Interviews, Expert opinion
Effect of dementia on treatment	Literature, Interviews
Effect of family members on treatment	Interviews, Expert opinion
Variability in clinical practice	Literature, Interviews, Expert opinion

Table 6.1: Sources use to construct questionnaire.

6.4.2.2. Piloting phase

This preliminary questionnaire was then piloted with members of the surgical team locally in Sheffield and those on the “Bridging the Age Gap in Breast Cancer” trial management team, to maximise content and face validity, comprehensibility and usability. During piloting, individuals were asked to examine the length, acquiescent response set, flow, salience, ease of administration and response and acceptability [481]. Specifically, participants were asked to indicate how long it took them to complete the questionnaire and were invited to comment on any questions which were difficult to interpret or to answer. The results of the pilot phase are shown in table 6.2 below, including the feedback received and remedial action taken to address each of the comments.

6.4.2.3. Psychometrics of the questionnaire

As part of the piloting phase, the psychometrics of the questionnaire were assessed.

- **Reliability:** Similar questions using both positive and negative framing were included, particularly in section 3 of the questionnaire using the Likert scales to ensure internal reliability. However, some of these questions had to be removed upon receiving feedback from the wider study team who felt they were too repetitive, in order to balance internal reliability with acceptability. Test-retest reliability was not examined due to the small number of individuals within the pilot study.
- **Content validity:** The questionnaire was designed following a full systematic literature review, in collaboration with experts in the field and after performing exploratory interviews with a sample of potential participants in order to ensure content validity.

Pilot HCP	Comments	Remedial Action
Surgeon, Female	<p>Questionnaire seems too long and each section should be on a separate page.</p> <p>Delete repeat questions in section three.</p> <p>Remove year of qualification and shorten options for profession in section one.</p> <p>Remove 4 questions from section two.</p> <p>Remove neutral option from section three.</p> <p>Less options for % patient treated with PET.</p> <p>Remove four questions from section four.</p>	<p>Repeat questions removed and formatted so each section begins on separate page.</p> <p>Number of questions in section three halved.</p> <p>Questions removed from section one.</p> <p>Questions removed from section two.</p> <p>Neutral option removed from section three.</p> <p>% options changed from 5% increments to 10%.</p> <p>Questions removed from section four.</p>
Surgeon, Male	<p>Too many repeats of the same question asked in different ways.</p> <p>Too many HER2+ scenarios in DCE.</p> <p>Undecided category should be changed to “no preference” or similar.</p> <p>Takes about 20 minutes to answer.</p>	<p>Number of questions in section three halved.</p> <p>Orthogonal design altered to include 3 levels in tumour biology section to reduce this.</p> <p>Changed to “prefer both equally”.</p>
Surgeon, Male	<p>Change last category of maintenance of control to 5+ years as literature states can maintain control for up to 10 years.</p> <p>Two of the DCE scenarios not clinically realistic.</p> <p>Takes 15-20 minutes to complete.</p>	<p>Changed last category to “5 years or more”.</p> <p>DCE scenarios removed.</p>
Surgeon, Male	<p>Reads well and is self-explanatory.</p> <p>Consider use of ET to down-stage to make operable?</p>	<p>Decided not to include questions on neo-adjuvant as the study is mainly concerned with PET.</p>
Surgeon, Male	<p>No comments on content or lay-out.</p> <p>Takes around 20 minutes to fill in.</p>	
Geriatrician, Male	<p>Standardise age criteria across questionnaire (currently >70, over 70) – should be ≥70.</p> <p>Remove neutral option from section three questions.</p> <p>Three DCE scenarios unrealistic.</p> <p>Predicted life-expectancy given for each of the DCE scenarios.</p>	<p>Changed to ≥70.</p> <p>Neutral option removed.</p> <p>Scenarios removed.</p>

Table 6.2: Feedback received from the questionnaire pilot phase.

- **Face validity:** Face validity was ensured during the pilot phase when members of the study team were asked to comment on whether the questionnaire appeared suitable for the purposes of the study and whether they felt anything was missing.
- **Criterion or concurrent validity:** In this case, there are no other validated questionnaire instruments available and so this was not assessed.
- **Construct validity:** This has little application in this study where the area being studied is not an abstract concept and so was not assessed.
- **Acceptability:** This was assessed by the pilot study in terms of length of time taken to complete, comprehensibility and usability. Specific comments relating to increasing acceptability can be seen in table 6.2.

6.4.2.4. Final instrument design

Based on the feedback, final modifications were made to the design and content of the questionnaire and a final version was submitted for ethical approval along with the letter of invitation. These documents and the letter granting approval can be found in Appendices 6, 7, 17 and 18.

The final questionnaire consisted of five sections and is shown below:

1. Background and demographic information of the participant.
2. Factors considered when discussing treatment options with older women with operable breast cancer.
3. Questions regarding HCPs views about the choice between surgery and PET.
4. Questions relating to the HCPs personal experience of treating older women with operable breast cancer
5. Discrete choice experiment scenarios (this section will be discussed in Chapter 2.3).

Where categorical choices were used, for example “respondent profession”, an “other” option was included with space for free text to ensure full and complete data collection.

Where Likert style questions were used, only four options were included and the “opt out” middle category (e.g. no preference/unsure) was removed to encourage participants to make a choice as advised by two of the experts in the pilot study.

The full and final questionnaire can be seen below.

Sheffield Teaching Hospitals **NHS**

NHS Foundation Trust



The
University
Of
Sheffield.



Sheffield
Hallam University

SHARPENS YOUR THINKING



University of
Leicester

Variation in Clinician Preferences for Treatment of Older Women with Operable Breast Cancer

Health Care Professional Questionnaire

All information that you provide will remain strictly confidential

When you have finished please post the questionnaire back in the FREEPOST envelope provided. You do not need a stamp.

If you have any queries about this questionnaire or the study, please contact Lynda Wyld (Senior Lecturer and Consultant Breast Surgeon), EU36, University of Sheffield Medical School, Beech Hill Road, Sheffield. Telephone 0114 2268640.

This sheet is intentionally blank.

Section One

This section requires you to give brief information about your professional background

1. What is your age in years?

2. What is your gender? (please tick appropriate box)

Male

Female

3. What is your profession or speciality? (please tick appropriate box)

Breast Surgeon

Oncologist

Breast Care Nurse Specialist

Other (specify).....

4. Which area do you currently work in? (please tick appropriate box)

Eastern

North West

Northern & Yorkshire

Northern Ireland

Oxford

Scotland

South West

Thames

Trent

Wales

West Midlands

Other (specify).....

Section Two

The table below contains factors that may be considered when discussing treatment options with an older patient with operable breast cancer. Please rate the importance of each of these factors in shaping your advice regarding treatment options in an older woman (≥ 70) in whom you are considering the choice between surgery and primary endocrine therapy.

For each factor place your tick in the relevant box that best describes how important you think each factor is. Please only tick one box per question.

Patient Characteristic	Very important	Important	Some importance	Not important
Patient age	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Breast cancer ER positivity	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Breast cancer Her 2 receptor status	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Size of tumour (e.g. suitability for WLE)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Presence of axillary nodal disease	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Suitability for surgery under local or regional anaesthesia in a frail patient	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Estimated life expectancy of the patient	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's preference for operation or PET	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Functional status (level of independence, ability to perform)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Cognitive function (dementia)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Co-morbidity (are they fit and well or do they have multiple health problems?)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's anxiety level about breast cancer	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's anxiety levels about an operation	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Family member/carer preference for operation of PET	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄

Section Three

The following questions relate to your views about the choice between surgery and primary endocrine therapy.

For each of the statements below please circle one box to indicate your views about the validity and accuracy of the statement:

1) All women ≥ 70 with operable breast cancer should be offered an operation, regardless of age.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

2) All women ≥ 70 with operable ER+ve breast cancer, who have multiple co-morbidities such that anaesthesia may carry an increased risk of morbidity and mortality, should be treated with PET.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

3) All women ≥ 70 with operable ER +ve breast cancer, who have significant dementia, (unable to give informed consent) should be treated with PET.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

4) Primary endocrine therapy may be offered to any woman ≥ 70 with ER+ve disease as there is no proven survival disadvantage.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

5) Surgery is almost always possible for older women ≥ 70 with operable breast cancer under local or regional anaesthesia.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

6) Most older women ≥ 70 , if given a choice of treatment would prefer to have non-surgical treatment for their breast cancer.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

Section Four

The following questions relate to your experiences with treating older women ≥ 70 with operable breast cancer. For each of the questions below please tick the box of the answer that is most similar to your experiences.

1) What percentage of women ≥ 70 receive PET in your unit?

- | | | | |
|---------------|--------------------------|-----------|--------------------------|
| Less than 10% | <input type="checkbox"/> | 10 to 20% | <input type="checkbox"/> |
| 20 to 30% | <input type="checkbox"/> | 30 to 40% | <input type="checkbox"/> |
| More than 40% | <input type="checkbox"/> | | |

2) In your experience, how long on average does PET maintain local control?

- | | | | |
|-----------|--------------------------|-----------|--------------------------|
| 6 months | <input type="checkbox"/> | 12 months | <input type="checkbox"/> |
| 18 months | <input type="checkbox"/> | 24 months | <input type="checkbox"/> |
| 3 years | <input type="checkbox"/> | 5 years | <input type="checkbox"/> |

3) What action would you take if your first line anti-oestrogen failed to achieve a response in a patient being treated with PET?

- | | | | |
|----------------------------------|--------------------------|-----------------------------|--------------------------|
| Start second line anti-oestrogen | <input type="checkbox"/> | Advise operative management | <input type="checkbox"/> |
| Advise radiotherapy | <input type="checkbox"/> | Other (specify)..... | <input type="checkbox"/> |

4) In your experience, are anaesthetists in your unit happy to perform regional blocks to allow you to undertake surgical excision in women ≥ 70 who have multiple co-morbidities where a general anaesthetic may carry increased risk or morbidity and mortality?

- | | | | |
|---|--------------------------|--|--------------------------|
| Never perform regional blocks in this group | <input type="checkbox"/> | Rarely perform regional blocks in this group | <input type="checkbox"/> |
| Regularly perform regional blocks in this group | <input type="checkbox"/> | | |

5) In your experience, is surgery under general anaesthesia well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

6) In your experience, is surgery under local anaesthesia well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

7) In your experience, is PET well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

6.4.3. Recruitment

Recruitment to this part of the study was via the Association of Breast Surgery (ABS). The ABS is the association representing HCPs (breast surgeons and breast CNS) treating malignant and benign breast disease in the UK, Ireland and worldwide. It focuses on education, audit and guidelines to enhance the treatment of patients with breast disease. This recruitment strategy was viewed as being a potentially appropriate and effective method in which to contact the majority of HCPs treating older women with breast cancer in the UK. The president of the ABS was contacted by personal communication by the study lead (LW) and permission was granted to contact members. The questionnaire was posted to all 641 members of the Association of Breast Surgery (ABS).

Questionnaire packs were prepared and included the finalised questionnaire (see Appendix 18), a letter of invitation to participants written on headed paper (see Appendix 17), and a stamped addressed return envelope. These were then mailed to each individual member of the ABS personally in a stamped envelope to try and increase recruitment.

A record of the number of packs sent out was kept and correlated with the number returned to give the response rate. An electronic reminder was sent out by the ABS after eight weeks to remind members who had not completed the questionnaire to do so. No further reminder was sent although during the study period the questionnaire study was presented to the ABS meeting to raise its profile and a poster was put up at the meeting. However this seemed to have little effect (see table 6.3).

Recruitment phase	Response rate
Total population of ABS: 641	-
Initial posting of questionnaires	229 (35.7%)
Electronic reminder	11 (1.7%)
Presentation at ABS meeting	18 (2.8%)
Total	258 (40.2%)

Table 6.3: Response rate at each phase of recruitment.

6.4.3.1. Power calculation

Given the sample population (641 members of the ABS) and using standard 95% confidence levels, it was calculated using sample size calculation software that we would need at least 240 responders to the survey for the results to be reasonably precise (confidence interval of +/-5%) [488]. This means that if 41% of the participants agree with a questionnaire statement, we can be 95% sure that the actual figure of the total population that would agree with this statement lies between 36% and 46% (41% +/- 5%).

It was estimated, based on previous similar studies, that 240 responders would be an achievable response rate [128, 474].

6.4.4. Data handling and statistics

6.4.4.1. Data handling

Data were initially entered into a Microsoft Excel 2010 spreadsheet and coded before being transferred to IBM SPSS (version 21) for analysis. Graphs were drawn in Microsoft Excel 2010.

6.4.4.2. Statistical analysis

Descriptive questions were analysed using percentages, median responses and ranges. Chi-squared test and Fisher's exact test were used to identify associations between preferences indicated and the demographic categories of participants. All statistical analyses were performed in IBM SPSS (version 21).

6.5. Results

6.5.1. Response rate

Of the 641 questionnaires distributed, 258 were returned (40.2% response rate). Of these, 6 were not completed at all, leaving 252 for analysis (39.3% of those distributed), and a small percentage were not completed in full, meaning that some questions have small numbers of missing data (<5%). However, despite this, the response rate was still high enough for the study to be adequately statistically powered based on the calculations above (see section 6.4.3.1.) and based on previous similar studies, this rate was judged to be reasonable [128, 474].

Table 6.4 shows the characteristics of participants and the percentage response by region compared with the percentage distribution of surgeons within these regions [73], demonstrating that each region is relatively well represented.

Characteristic	n (%)	Number of surgeons (and % for comparison) eligible to take part in each region (based on the Year 3 BCCOM figures [73]).	Region of high or low PET rate as based on the rate of non-surgical treatment in the Year 3 BCCOM figures [73].
Age	Median 50 years Range 28-69 years		
Sex	Male	115 (45.6)	
	Female	134 (53.2)	
Profession	Breast surgeon	190 (75.4)	
	Clinical nurse specialist	55 (21.8)	
	Oncologist	2 (0.8)	
	Breast physician	1 (0.4)	
	Plastic surgeon	2 (0.8)	
Region (based on UK cancer registration regions)	Eastern	26 (10.3)	42 (8.6%) High
	North West	23 (9.1)	66 (13.5%) Low
	Northern & Yorkshire	37 (14.7)	55 (11.3%) High
	Northern Ireland	6 (2.3)	16 (3.2%) High
	Oxford	5 (2.0)	18 (3.7%) Low
	Scotland	20 (7.9)	46 (9.4%) High
	South West	37 (14.7)	56 (11.5%) Low
	Thames	42 (16.7)	77 (15.7%) Low
	Trent	14 (5.6)	35 (7.2%) High
	Wales	14 (5.6)	28 (5.7%) Low
	West Midlands	22 (8.7)	49 (10.0%) High

Table 6.4: Characteristics of questionnaire participants.

6.5.2. Findings

6.5.2.1. Factors considered when discussing treatment options with older women with operable breast cancer.

The presence of comorbidities was the most important factor determining treatment decisions for older women with operable breast cancer. All HCPs 248/248 (100%) rated this factor as having at least some importance (see figure 6.1). Age was considered as one of the least important factors considered by HCPs when making decisions about surgery vs PET, with only 12/245 (4.9%) rating it as very important and a further 59/245 (24.1%) rating it as important (see figure 6.1). Other patient factors that were considered important included patient preference, life expectancy and functional status and these were rated as either important or very important by 236/249 (94.8%), 208/245 (84.9%) and 217/249 (87.1%) respectively.

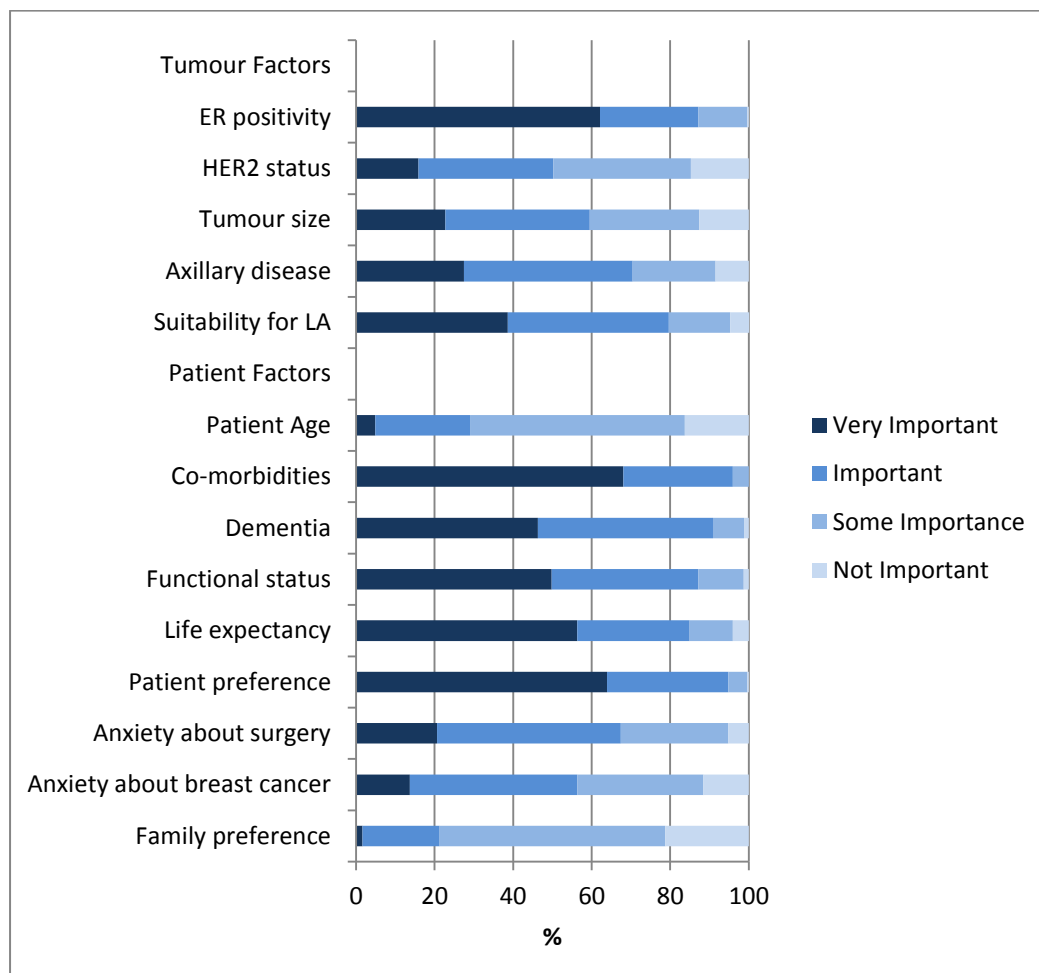


Figure 6.1: Patient and tumour characteristics and their importance in shaping the advice HCPs would give to an older patient in whom a choice of PET and surgery may be considered (n=252).

Tumour factors, such as stage and size of the disease were viewed as being less important in determining treatment than patient health and fitness measures (see figure 6.1) as although 216/247 (87.4%) rated tumour factors as of at least some importance, only 56/247 (22.7%) regarded it as very important. Axillary disease was rated as slightly more important with 68/247 (27.5%) HCPs rating it as very important. This may be due to the fact that surgery is likely to be more extensive in patients with axillary disease or higher tumour stage. ER status was regarded as important or very important by most surgeons (216/248; 87.1%) but HER2 status much less so (123/245; 50.2%). This may be explained by the fact that HER2 tumours are less responsive to anti-oestrogens [489].

6.5.2.2. Views regarding the choice of PET vs surgery

Over three quarters (199/249) of HCPs agreed with the statement “All women ≥ 70 with operable breast cancer should be offered an operation regardless of age” (see figure 6.2). However only 65/244 (26.6%) agreed that PET may be offered to any older woman with ER positive disease as there is no proven survival advantage (see figure 6.3). There was also a predominant but not universal view (217/247; 84.6%) that older women, if given the choice between PET or surgery, would choose surgery.

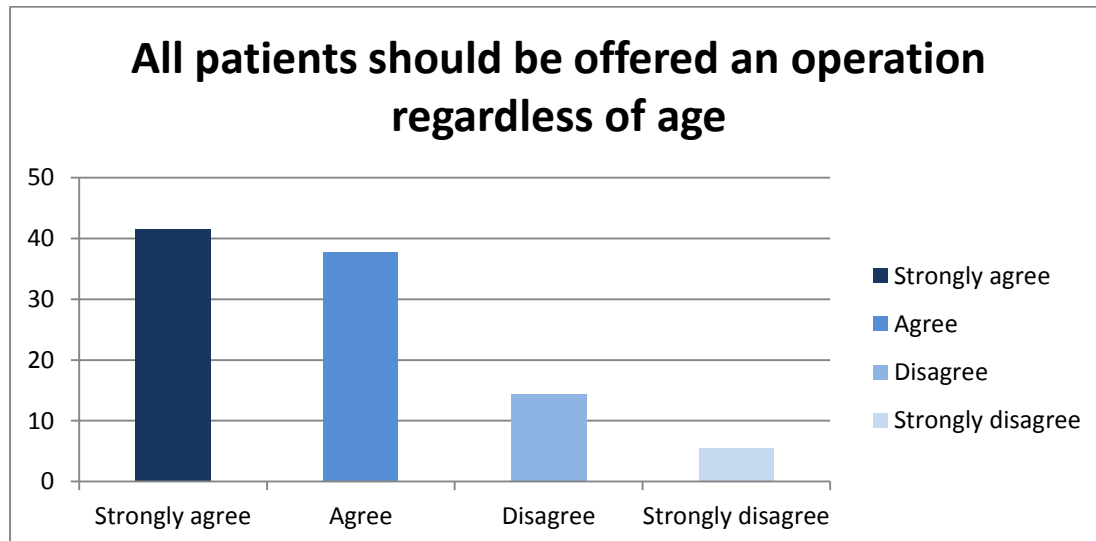


Figure 6.2: HCP opinion regarding offering all patients an operation, regardless of age.

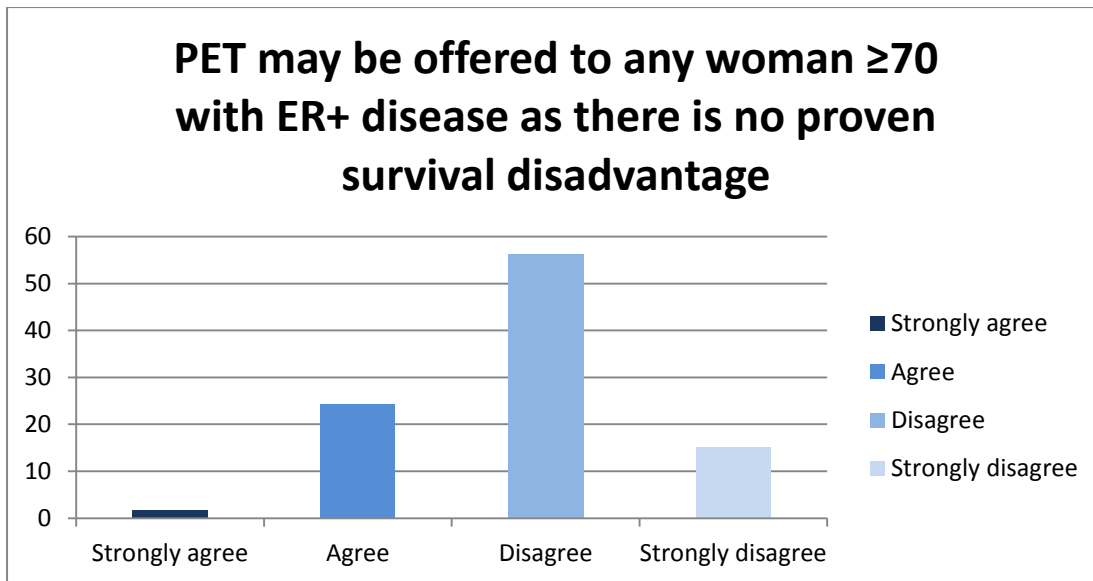


Figure 6.3: HCP opinion regarding offering PET to any woman over 70 years.

Again, comorbidities were considered important, with nearly two thirds (155/246; 63.0%) agreeing with the statement “All women ≥ 70 with operable ER+ breast cancer, who have multiple comorbidities such that anaesthesia may carry an increased risk of morbidity and mortality, should be treated with PET” (see figure 6.4).

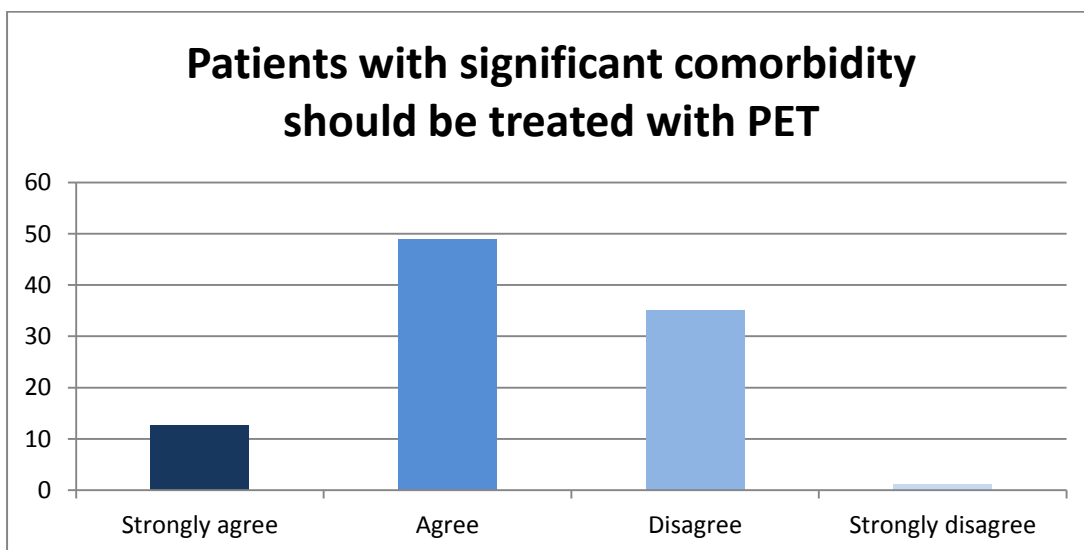


Figure 6.4: HCP opinion regarding treating patients with significant comorbidity.

In terms of dementia, whilst 220/245 (89.8%) rated the presence of dementia as very important or important in making treatment decisions, opinion regarding the best treatment for these patients appeared to be divided, with 102/248 (41.1%) agreeing with the statement “all women ≥ 70 with

operable ER+ breast cancer, who have significant dementia (unable to give informed consent) should be treated with PET” and the remainder (146/248; 58.9%) disagreeing (see figure 6.5).

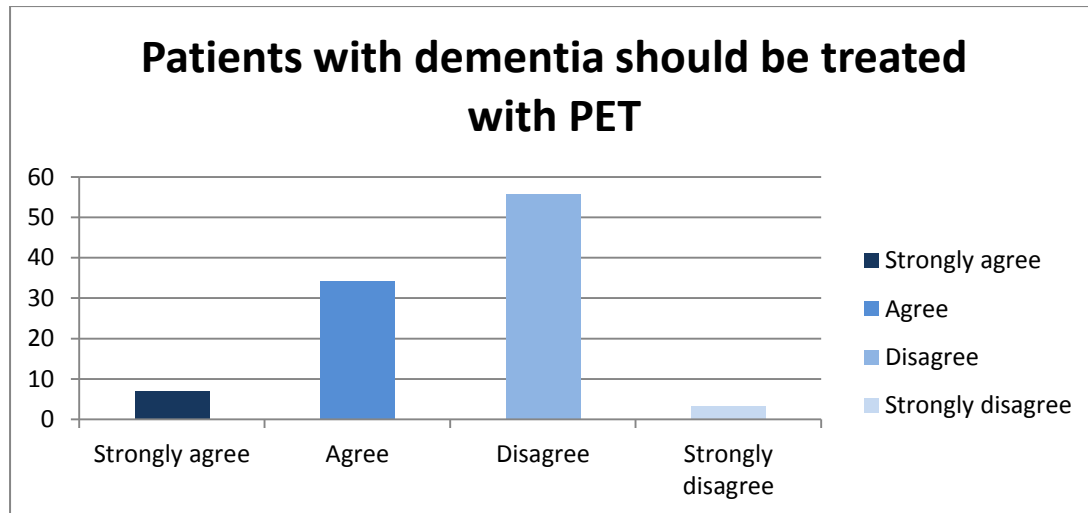


Figure 6.5: HCP opinion regarding the treatment of patients with dementia.

6.5.2.3. Personal experience of treating older women with operable breast cancer

Almost all (241/245; 98.4%) HCPs stated that in their experience, surgery under GA was well tolerated in older women. However, experience with the usage of local anaesthetic (LA) and regional techniques was more variable, with only 43/244 (17.6%) stating that they had an anaesthetist who would happily perform regional blocks to allow surgical excision in patients where GA may carry an increased risk. Nearly two-thirds (156/244; 63.9%) felt that surgery under LA was well tolerated in older women and 148/246 (60.2%) agreed with the statement “surgery is almost always possible for older women ≥ 70 with operable breast cancer under local or regional anaesthesia”.

Despite this, PET is still used to treat women across the UK, although its use is variable, with 17/240 (7.1%) stating that more than 30% of women ≥ 70 were treated this way, 65/240 (27.1%) stating that 20-30% of women ≥ 70 were treated with PET, 67/240 (27.9%) stating that 10-20% of women ≥ 70 received PET and 91/240 (37.9%) stating that PET was used in less than 10% of women ≥ 70 years (see figure 6.6).

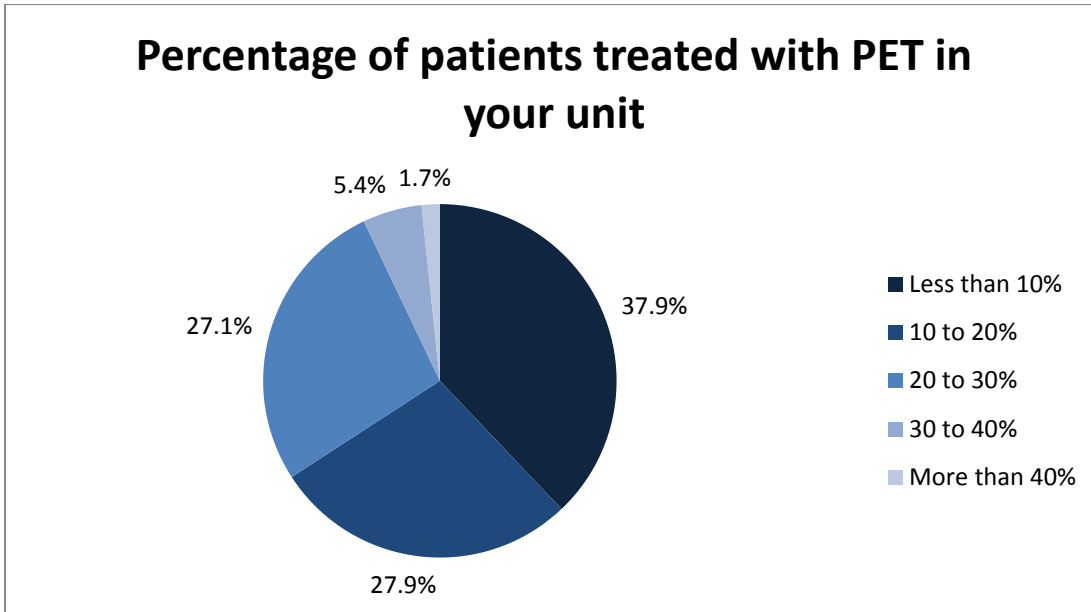


Figure 6.6: HCP experience of PET use in their breast unit.

There was variation regarding how long HCPs felt that PET was effective in maintaining local tumour control, with 64/238 (26.9%) stating 5 years or more; 74/238 (31.1%) stating 3 years, 70/238 (29.4%) stating 2 years and 30/238 (12.6%) stating 18 months or less (see figure 6.7).

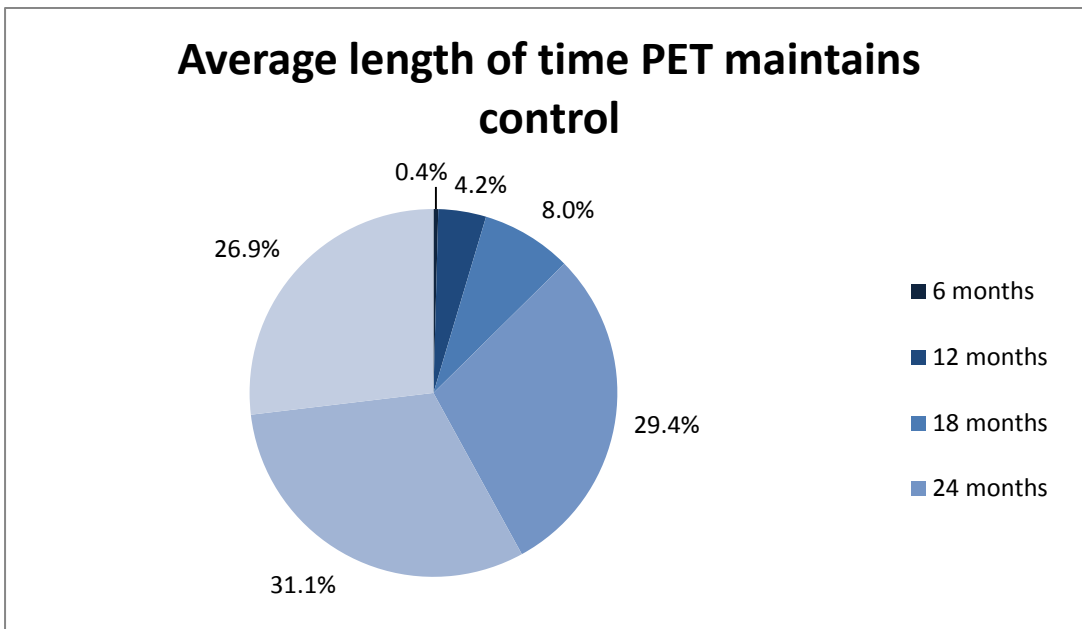


Figure 6.7: HCP experience of how long PET maintains tumour control on average.

Additionally, opinion was divided regarding what action to take if first-line anti-oestrogen failed to achieve a response, with 146/245 (59.6%) opting for a second-line anti-oestrogen, 61/245 (24.9%) advising operative management, 4/245 (1.6%) opting for radiotherapy and 34/245 (13.9%) choosing

“other” – most HCPs in that ticked “other” commented that they would consider more than one of these options or the decision would depend on the individual patient (see figure 6.8).

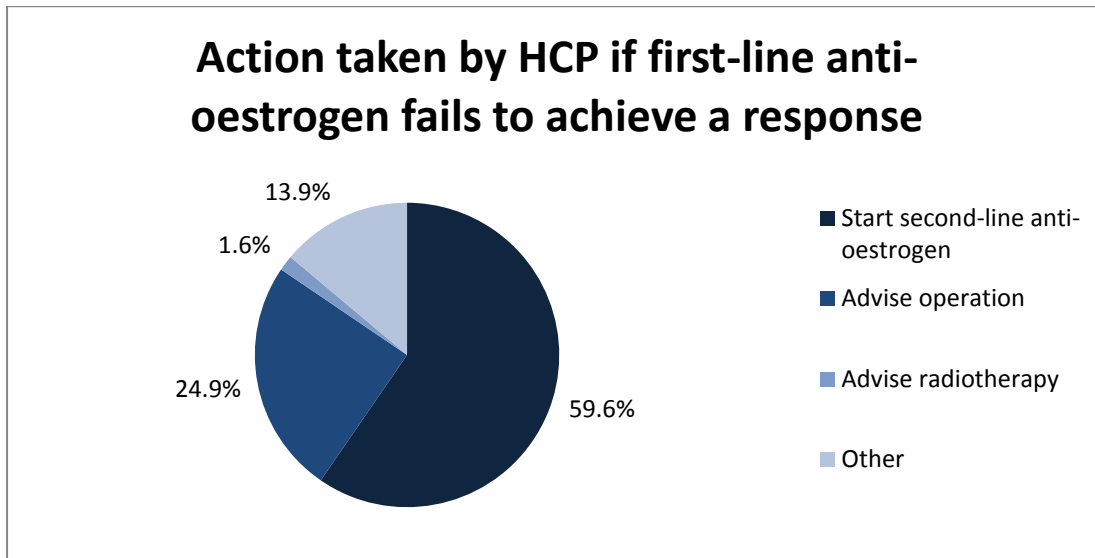


Figure 6.8: Action taken by HCP if first-line anti-oestrogen failed to achieve a response in a patient being treated with PET.

6.5.2.4. Effect of HCP demographics on responses

Participant responses were examined according to gender, age category, profession and region (categorised as high and low PET rates according to the cancer registration region, see figure 6.8) [73].



Figure 6.8: Regions according to High (red) or Low (blue) PET rates [73].

There were no significant differences between answers given by male and female HCPs in the majority of questions. Gender appeared to make a difference in how important HCPs felt age was when making a treatment decision for older patients with operable breast cancer, with men tending to think age was more important than women ($p=0.006$). Additionally, women also appeared to rate patient anxiety as more important than men, both patient anxiety over breast cancer ($p=0.001$) and patient anxiety over surgery ($p=0.22$).

There were statistically significant differences between the responses given by doctors compared to nurses: nurses rated cancer size ($p=0.009$), axillary disease ($p=0.012$), patient anxiety – both regards to breast cancer ($p=0.001$) and surgery ($p<0.001$), and preference of family ($p=0.001$) as more important when deciding treatment compared to doctors. Conversely, doctors rated life expectancy ($p=0.005$) as more important when deciding treatment in comparison to nurses.

There were no significant differences between responses from participants working in regions of high or low PET rates, except that they felt patients would always choose PET if given the choice. HCPs from low PET regions were more likely to agree that patients would always choose PET if they were given the choice compared with HCPs from high PET regions (21.2% vs 10.5%, $p=0.022$). HCPs from low PET regions also appeared to have more access to regional blocks compared to those from high PET regions ($p=0.030$), see table 6.5.

Age of participants appeared to have no effect on the answers provided.

Use of regional blocks	Low PET region	High PET region
Never use	21.8%	38.3%
Rarely use	56.3%	49.2%
Regularly use	21.8%	13.3%

Table 6.5: Use of regional anaesthetic blocks by region.

6.6. Discussion

6.6.1. Factors considered in the treatment decision-making process

In 2008 the UK's Department of Health established the National Cancer Equality Initiative (NCEI) aimed at lowering the inequality in cancer outcomes for all, including those of older patients [94]. Recent guidelines suggest that PET should only be offered to patients with a "short estimated life expectancy (<2-3 years), who are considered unfit for surgery... or who refuse surgery" [127] and that PET should only be used where there are "significant comorbidities that precludes surgery" [9]. The HCPs studied here appear to be adhering to these guidelines when considering treatment options offered to older patients with operable breast cancer. Although several studies have explored the issue of increasing age being associated with "under treatment" of older women with operable breast cancer [68, 84, 90, 375], these results show that HCPs consider age one of the *least* important factors in determining which treatment options to offer. However, as age increases so rates of comorbidities rise, both of which have an impact on life expectancy and so may to potentially reduce the survival advantage of more aggressive breast cancer therapies [106] and comorbidities are often stated as a reason for treating patients with PET [128, 362]. It is not surprising then that the presence of comorbidities was the most important factor HCPs considered when deciding treatment options for older patients with operable breast cancer. These results also show that life-expectancy was also considered relatively important. However a recent UK questionnaire study found that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [128].

Tumour factors were considered less important in treatment decision-making than patient factors, even though larger tumours are more likely to require mastectomy rather than breast conservation surgery. Nodal status was considered slightly more important and this may be due to the fact that surgery to clear the axilla under local anaesthesia is not technically possible and therefore surgery to clear an involved axilla would be precluded in women who were too frail to undergo GA. Despite the fact that HER2 positive cancers are known to be generally less likely to respond to endocrine therapy [489], it was considered much less important than ER status.

6.6.2. Offering choice

Patient preference was stated as one of the most important factors that HCPs take into account when deciding which treatment options to offer older patients with operable breast cancer, and patient choice is commonly stated as a reason for treating patients with PET [128, 369]. Some

evidence suggests that older patients may prioritise quality of life over quantity [415] however, in this study, there was a strong view that older women, if given the choice, would choose surgery over PET. Whether this statement's response would have changed had the questionnaire contained a different, older, age cut-off we are unable to confirm but current UK practice would suggest this to be the case.

However, in order for patients to express a preference for a particular treatment, they must first be informed of the different treatment options as advocated in shared decision-making (SDM) [277], which means that for some older women it may be appropriate to offer PET as an alternative to 'standard' surgical treatment and allow the patient to decide what is best for them. These results show that only around a quarter of HCPs agreed that PET may be offered to any older woman with ER positive disease as there is no proven survival advantage, suggesting that not all older patients are able to take part in SDM, although the number here is more than three times the number found by Wylie et al [128]. In addition, not all older patients want to engage in SDM, with many preferring a more passive role [88, 278-280] so it is perhaps for this reason why not all patients are offered a choice of the two treatments.

6.6.3. Variation in practice

The use of PET for the treatment of older breast cancer patients across the UK is variable [73] and this study supports these findings, with over a third of HCPs stating they treat less than 10% of this population in this way and over a third of HCPs stating they treated more than 20% of this population with PET.

This component of the study also identified major variation in the way PET is used in respect of the type of first-line anti-oestrogen prescribed, the assessment methods and follow-up regimen used. This corroborates the findings by Wylie et al [128] and is most likely due to a lack of guidelines on its usage. A recent review on this subject advocates the use of AIs for PET, unless otherwise contraindicated [403] but there have been no studies that determine how best to follow these patients up.

The major drawback of PET is the risk of development of progressive disease which most patients will eventually suffer from [227] although the length of time to progression varies greatly from nine to 132 months [337, 339, 341, 364, 401]. The duration of response is generally shorter in women who have only exhibited a partial response to PET, compared to those with a complete response

[217, 337]. This may explain why there was so much variation in these results of HCP opinion as to how long PET maintains tumour control.

The use of local and regional anaesthesia for breast surgery in patients who are unable to undergo GA is well-established [473], with nearly two thirds of HCPs feeling that surgery in older patients was well-tolerated under LA. However, it seems that a limiting factor in the utilisation of regional techniques is the availability of a suitably-experienced anaesthetist.

6.6.4. Opinions on patients with dementia

For those older breast cancer patients who are unable to make a decision due to significant dementia, opinion was divided regarding the best treatment approach. Although it appeared to be an important factor affecting treatment decision-making for HCPs, around 40% felt patients with dementia should be treated with PET with the remainder feeling they should be treated with surgery. As dementia predominantly affects older age groups, this represents a significant problem in this population. Studies show that older patients with dementia are less likely to receive standard cancer therapies [449] and that this is often stated as a reason for selecting PET over surgery [69, 368]. However, there are currently no guidelines for the treatment of operable breast cancer in this complex group of patients which may reflect the lack of consensus amongst HCPs surveyed here. A further explanation for such differing views may be that dementia was not defined in terms of severity in the survey, and HCPs clinical judgement of dementia may vary in the absence of formal assessments.

6.6.5. Strengths and weaknesses of this analysis

Limitations of this study include the low response rate to the questionnaire, although this is comparable with other similar studies [128, 474], but limits the generalizability of the results.

Additionally, it has previously been shown that most UK breast surgeons do not formally audit their practice in terms of PET [128] and so will have had to have estimated in some areas, such as the percentage of patients treated with PET.

The findings from this survey component of the study support those found in the interview of component, helping to generalise these findings to the wider UK breast HCP population.

6.7. Summary

In conclusion, HCP opinions regarding the treatment of older women with operable breast cancer differ, particularly regarding the optimal way to treat patients with co-existing dementia. There is also divided opinion as to whether patients should be offered both surgery and PET as a treatment option. These factors may impact on the variation in the treatment of older women with breast cancer across the UK.

Chapter 7: Clinician Questionnaires – A Discrete Choice Experiment

7.1. Abstract

7.1.1. Introduction:

Despite current guidelines that state PET should only be used for patients with “significant comorbidity” or “reduced life expectancy”, there are many factors which HCPs consider important when determining treatment for older breast cancer patients.

7.1.2. Methods:

A Discrete Choice Experiment (DCE) was used to determine the impact of key variables on healthcare professionals’ (HCP) treatment preferences for operable breast cancer among older women.

Distribution was by postal questionnaire via the Association of Breast Surgery (ABS) to their professional membership. Multinomial logistic regression was used to identify associations between treatment and clinical characteristics (patient age, comorbidity, cognition, functional status, cancer stage, cancer biology).

7.1.3. Results:

Forty percent (258/641) of questionnaires were returned. Five variables (age, co-morbidity, cognition, functional status and cancer size) independently demonstrated a significant association with treatment preference ($p < 0.05$). On multivariable analysis, functional status was omitted from the model due to collinearity, with all other variables correlating with a preference for operative treatment over no preference ($p < 0.05$). However, only co-morbidity, cognition and cancer size correlated with a preference for PET over no preference ($p < 0.05$).

7.1.4. Conclusion:

The majority of HCPs selected treatment in accordance with current guidelines, however in some scenarios, opinion was divided. Additionally, age did appear to be an independent factor that HCPs considered when making a treatment decision in this population. This study demonstrates that HCP preferences for managing older breast cancer patients are not uniform, which may contribute to the treatment variation seen in this population.

7.2. Introduction

As demonstrated in previous chapters, HCPs take a variety of factors into account when determining treatment options for older women with operable breast cancer, and vary in their opinions on how this population should be treated. Despite current guidelines stating that PET should only be used for patients with “significant comorbidity” or “reduced life expectancy” and that age itself should not be taken into account [9, 127], there is evidence that age is one of the many key variables that HCPs consider important when determining treatment for older breast cancer patients [68, 89, 90].

As discussed in Chapter 1.2, case mix does not seem to fully explain the wide variation in practice that can be seen across the UK [73]. Variation in clinician preference and opinion may be a source of some of this variation [373] and this may exert a potent influence on patient choice [88].

The aim of this component of the study was to use Discrete Choice Experiment (DCE) methodology to determine the impact of key variables on healthcare professionals’ (HCP) treatment preferences for the management of operable breast cancer in older women and to further quantify the importance of these factors.

7.3. Methodology

7.3.1. Choice of Discrete Choice Methodology

There are several methods of eliciting preference in surveys, including Discrete Choice Experiment (DCE) and Conjoint Analysis which are types of stated preference techniques. Table 7.1 shows a comparison of these two methods.

DCE	Conjoint Analysis
Measures preferences at an individual level	Measures preferences at an individual level
Allows estimation of trade-offs an individual is willing to make when evaluating several attributes together	Allows estimation of trade-offs an individual is willing to make when evaluating several attributes together
Individuals must choose between alternatives – in this case, choose a treatment based on the scenario characteristics.	Individuals rank scenarios – in this case, rank the scenarios according to how likely they are to offer a particular treatment, e.g. surgery.
More realistic and more closely resembles clinical practice.	Unrealistic, does not resemble clinical practice as HCPs consider patients on an individual basis and not together.

Table 7.1: A comparison of DCE and Conjoint Analysis.

A DCE design was chosen for this component of the study as it is a rigorous survey methodology capable of eliciting individuals' preferences in controlled experimental conditions, through responses to hypothetical scenarios. It was felt it had superiority over other stated preference techniques, such as conjoint analysis in this research area in its ability to establish the relative importance of difference variables according to individuals HCPs [490] and would provide more clinically realistic choices [491], making the survey more acceptable to HCPs.

7.3.2. The methodology of DCEs

Discrete choice experiments are based on the assumptions that the healthcare intervention, service or in this case, the patient, can be described by their characteristics or attributes and that an individual's (in this case the HCP) valuation depends on the levels of these characteristics [492].

Discrete choice scenarios provide information on the relative weights individual professionals attach to the various dimensions (variables) involved in the decision-making process and how willing they are to trade these off against each other in reaching a decision.

7.3.2.1. Establishing variables

The initial step in development of a DCE tool is to identify the main characteristics or variables [493] which depends on the researchers ability to correctly identify the relevant attributes. This requires an understanding of the situation to be studied and of the target population's perspective [494, 495]. Methods for developing variables include: literature review and expert review, however it is highly recommended that exploratory qualitative work is also carried out [496].

There are no restrictions on the number of variables that can be included in a DCE, however most contain less than 10 to prevent the questionnaire becoming unwieldy and to prevent participants from adopting a simplified approach to answering the questions [497].

7.3.2.2. Assigning attribute levels

The levels within a variable should be exhaustive, so as to reflect the range of situations HCPs might expect to experience [498]. There must also be a finite number of mutually exclusive levels, in order for the analysis to be meaningful. Ensuring realistic and meaningful levels within an attribute increases the precision of the analysis [495].

7.3.2.3. Designing the scenarios

In determining the choice sets, in this case, the patients scenarios, the hypothetical alternatives must be generated and combined [498]. A full factorial design which lists all possible combinations of the variable levels may be generated, however in is usually impractical to use all possible combinations, as for example a DCE with 5 attributes each with four levels will produce 1024 possible scenarios (4^5). As such a selection of scenarios are usually produced as a choice set using an orthogonal factorial fractional design which aims to produce a choice set that is both orthogonal (statistically independent) and balanced with minimal overlap [499, 500].

It is important to consider how many scenarios participants can view before boredom sets in, and this will depend on their complexity and the characteristics of the target population [498].

It is also important to clinically review the scenarios to ensure they are clinically realistic (for example in this case to have a scenario with a woman with severe dementia but who was living independently is not realistic).

7.3.2.4. Designing the questionnaire

The majority of DCEs in the healthcare setting provide two options for the participants to choose between, in this case, recommending the treatment options of either PET or surgery. However it is recognised that decision-making in healthcare is more complex and an opt-out response may be required to improve realism and therefore response rates. This type of opt-out response is usually a “prefers neither” response [501].

The questionnaire should be piloted to ensure the content is plausible to potential participants and contains realistic scenarios comprised of attributes that individuals are willing to trade between to arrive at a decision. In addition, if the questionnaire is to be self-administered, it is important that a clearly presented and understandable introduction is included with the scenarios [498].

7.4. Methods

7.4.1. Research Governance

7.4.1.1. Ethics approval

Research Ethics Committee (REC) approval was not required for this study as the participants were NHS staff recruited by virtue of their profession. The study protocol was reviewed by the University of Sheffield Medical School's Ethics Review Committee and approval was granted on 22nd November 2012 (ref: SMBRER243; see Appendices 6 & 7).

7.4.1.2. Consent

Individual participant consent was implied by the return of the questionnaire to the study team. A covering letter explaining the study and informing the individual that participation is voluntary was included with the questionnaire pack (see Appendix 17).

7.4.1.3. Confidentiality

Questionnaire responses were anonymous unless individual participants requested personal feedback about publication of the study results, in which case their identities were anonymised for purposes of analysis.

Databases, including the list of names and addresses of ABS members, were password protected and stored in a locked office in the university in accordance with the Data Protection Act 1998. No information that would allow clinicians to be identified was released into the public domain.

7.4.2. Establishing variables and levels

The DCE method was chosen to establish HCP preferences in controlled experimental conditions using hypothetical scenarios. Key variables were identified and selected using the relevant literature and previous qualitative research with a selection of the target population of HCPs (see Chapter 5). These variables were subsequently subdivided into levels of clinical severity based on clinical expert peer review by members of the study team. Table 7.2 shows the variables and levels.

Variable	Levels			
Patient age	70-74	75-79	80-84	85+
Co-morbidity	None	Mild	Moderate	Severe
Cognition	Normal	Mild impairment	Moderate Impairment	Severe Impairment
Functional status*	Independent	Mild dependence	Moderate dependence	Severe dependence
Cancer size	Small tumour, node negative	Small tumour, node positive	Large tumour, node negative	Large tumour, node positive
Cancer biology	ER positive, HER2 positive	ER positive, HER2 negative	ER strongly positive, HER2 negative	

*denotes not included in final model analysis

Table 7.2: Discrete choice variables and levels.

7.4.3. Determining the choice sets

Based on previous research done in our unit, it was felt that HCPs could potentially review up to 25 scenarios with 5 factors (with up to five levels for some of the factors) before the questionnaire becomes unacceptably long for participants [474, 502]. Twenty-five scenarios were randomly generated using IBM SPSS version 21 Orthoplan software out of 3,072 potential scenarios. For each scenario the participants were asked to indicate a preference for recommending either PET or operative treatment for a hypothetical older woman with operable breast cancer. In order to optimise reality in clinical practice, an “opt out” option was included, whereby participants could indicate no preference for either treatment choice [503], which would be equivalent to offering the patient a choice of both treatments. It was felt that this would more closely reflect clinical decision-making and therefore enhance response rates compared to the more conventional pair-wise choice design [501].

7.4.4. Piloting the scenarios

To be effective, scenarios must be plausible and so the questionnaire was piloted with a selection of experienced clinicians who identified eight of the 25 scenarios as being unrealistic. These were excluded from the final instrument.

An experienced geriatrician examined the plausible scenarios and estimated the predicted life-expectancy for each hypothetical patient based on their age, levels of co-morbidity, cognition and functional status, which were categorised as <2 years, 2-5 years and >5 years. Life expectancy of less than 2 years would be an indicator that primary endocrine therapy would be a good choice with minimal morbidity in a woman in whom the breast cancer is unlikely to contribute to the cause of

death. Conversely as literature suggests that the median duration of disease control with PET is 2 years, use of this treatment option for a woman with an estimated life expectancy of more than 5 years would be unlikely to result in long term disease control without change of management. The predicted life expectancy of each patient scenario was NOT shown to the questionnaire participants as this information would not be routinely available in normal clinical practice. Figure 7.1 illustrates a scenario example.

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	SEVERE IMPAIRMENT		
For Operation	[]	For PET	[]
Prefer both equally	[]		

Please indicate your preferred choice of recommendation for treatment (i.e. in favour of operative treatment or primary endocrine therapy (PET), by placing a tick (✓) in the relevant box below the scenario description. Please assume that each hypothetical patient has asked you to advise them on what treatment option they should choose.

Figure 7.1: DCE scenario example.

7.4.5. The final DCE instrument

The final 17 discrete choice scenarios were incorporated into a postal questionnaire that was mailed to all clinician and nurse members of the UK Association of Breast Surgery (ABS) – see Chapter 6 for further details. A copy of the DCE section of the questionnaire can be found below (also found in Appendix 18). The DCE section of the questionnaire contained a detailed explanation of the task and variable levels to aid self-completion of the questionnaire. An electronic reminder was sent via email to all members after four months and the study was advertised at the national ABS conference after this in order to try and increase response rates (see Chapter 6 for further details).

7.4.6. Statistical Analysis

Since the outcome for each scenario had three nominal levels (“prefer operation”, “prefer PET”, “prefer both equally”) multinomial logistic regression was used to identify associations between the outcome variable (treatment preference) and the various clinical characteristics given in the scenarios (patient age, comorbidity, cognition, functional status, cancer stage, cancer biology). A multinomial logistic model was fitted in Stata (Statacorp version 13) with “prefers either” as the reference category.

With a 3-level nominal categorical outcome, the multinomial logistic model will estimate two sets of regression coefficients: one for the effect of preferring operation versus prefers both options equally, and another for prefers PET versus prefers both options equally. These regression coefficients (relative risk ratios; RRR) correspond to the probability of each treatment preference (for operation or PET) relative to the base category (prefers either) and are calculated for each unit of change in the corresponding variable (clinical characteristic) against the reference level for each variable (the reference unit was taken as the first level of each clinical characteristic: 70-74 for age, no comorbidity, no cognitive impairment, functionally independent, small node negative tumour, ER+HER2+).

The cluster option was used to calculate confidence intervals and P-values since outcomes were clustered by participant to take into account the lack of response independence (as each participant answered 17 scenarios).

Section Five: Introduction

This section comprises a series of 20 clinical scenarios on which you are asked to make a hypothetical decision. They are concerned with the importance that you place on various factors influencing your preferred option for surgery or PET in individual women ≥ 70 with operable breast cancer. **PLEASE NOTE:** the option for surgery may include operations under General, Regional or Local anaesthetic if this is how you would treat the patient.

Please tear out this double-sided sheet to use as a reference when working through the scenarios

- 1. Patient age (years)** **Divided into the following age bands:**

70 – 74	75 – 79
80 – 84	85 and over

- 2. Co-morbidity** **Divided into the following:**
 - 1) No co-morbidity
 - 2) Mild co-morbidity, e.g. arthritis, hypertension
 - 3) Moderate/well-controlled co-morbidity, e.g. diabetes, coronary heart disease, moderate COPD
 - 4) Severe co-morbidity, e.g. disabling stroke, congestive cardiac failure, severe COPD

- 3. Cancer Stage** **Divided into the following:**
 - 1) Small tumour, no nodal involvement
 - 2) Small tumour, nodal involvement
 - 3) Large tumour, no nodal involvement
 - 4) Large tumour, nodal involvement

- 4. Cancer Biology** **Divided into the following:**
 - 1) ER++/HER2- (ER strongly positive, HER2 negative)
 - 2) ER+/HER2- (ER moderately positive, HER2 negative)
 - 3) ER+/HER2+ (ER moderately positive, HER2 positive)

- 5. Functional Status** **Divided into the following:**
 - 1) Fully independent
 - 2) Mild dependence; requires weekly help for domestic activities, e.g. shopping
 - 3) Moderate dependence; requires daily help with washing, dressing, continence management, etc.
 - 4) Severe dependence; requires 24 hour care, e.g. resides in a residential or nursing home

- 6. Cognitive Function** **Divided into the following:**
 - 1) Normal cognitive function
 - 2) Mild cognitive impairment; functions normally in society
 - 3) Moderate cognitive impairment; unable to cope without help
 - 4) Severe cognitive impairment; requires daily social services input or lives in residential or nursing home

Section Five: Patient Scenarios

For each of the 20 scenarios below, based on the information provided, please indicate your preferred choice of recommendation for treatment (i.e. in favour of operative treatment or primary endocrine therapy (PET), by placing a tick (✓) in the relevant box below the scenario description. Please assume that each hypothetical patient has asked you to advise them on what treatment option they should choose.

Scenario 1

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	SEVERE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 2

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	SEVERE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 3

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 4

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	MILD		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 5

PATIENT AGE (YEARS)	75-79		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 6

PATIENT AGE (YEARS)	80-84		
CO-MORBIDITY	MILD		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 7

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 8

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	SEVERE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 9

PATIENT AGE (YEARS)	75-79		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 10

PATIENT AGE (YEARS)	80-84		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 11

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	MILD DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 12

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	MILD		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 13

PATIENT AGE (YEARS)	80-84		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	MILD DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 14

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 15

PATIENT AGE (YEARS)	80-84		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 16

PATIENT AGE (YEARS)	70-74		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	SEVERE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 17

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	MILD DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

7.4.7. *A priori* sample size calculation

We calculated that in order to estimate the preference for a given scenario with a reasonable degree of precision of +/-6% (assuming a 50% preference) i.e. 95% confidence interval 44% to 56% would require 250 responders to the survey.

7.4.8. Ethical considerations

University of Sheffield Research Ethics Committee approvals were obtained (SMBRER243) (see Appendix 7).

7.5. Results

7.5.1. Response rate

Questionnaires were sent out in February 2014. Of the 641 questionnaires distributed, 229 (35.7%) were initially returned before the reminder was sent out. After this a further 29 were returned, meaning a total of 258 were returned (40.2% response rate): 45.6% male, 53.2% female, 75.4% breast surgeons, 21.8% clinical nurse specialist, 2.0% others (oncologists, breast physician, plastic surgeons). The median age of participants was 50 years (range 28-69 years). Of these, 4 did not complete the DCE section as they were oncologists or plastic surgeons and therefore did not routinely make these treatment decisions.

7.5.2. Findings

7.5.2.1. Preference for surgery vs. PET

The 258 responders answered 4,281 of the 4,386 scenarios (258 x 17). In 53% (2,279/4,281) of the scenarios responders' preferred operative treatment, 25% (1063/4281) PET and 22% (939/4281) preferred both equally. Seventy-eight percent (199/254) of responders demonstrated a preference for operative treatment in the majority of the scenarios they rated, 9% (22/254) a preference for PET, and 13% (33/254) an equal preference for surgery and PET. Table 7.3 summarises the results by scenario.

There was no relationship between participant age, gender or region and their preference for treatment. However participant profession did demonstrate an association with treatment preference, with surgeons more likely to prefer surgery over choice (RRR=1.33, p=0.039) and PET over choice (RRR=1.64, p=0.002) when compared to nurses. That is nurses were more likely to be undecided or offer choice when compared to surgeons, which is perhaps unsurprising in view of their role in helping patients with decision-making.

Five of the six variables (age, co-morbidity, cognition, functional status and cancer size) independently demonstrated a statistically significant association with treatment preference on univariate analysis (p<0.05). The variable cancer biology (receptor status) was associated with a treatment preference for operation over no preference (p<0.001) but not for PET (p=0.966) i.e. had a weaker effect on preference than the other variables. However, it should be noted that all options were ER positive so this is not surprising.

On multivariable analysis, functional status had to be omitted from the model due to collinearity; this is most likely due to the close association between this variable and the variables co-morbidity and cognition (e.g. a patient with moderate or severe co-morbidity and or cognitive dysfunction must inevitably also have moderate or severe functional dependence) and so the model could not determine whether an observed effect was due to functional status or co-morbidity/cognition. Table 7.4 summarises the multivariable analysis results. Overall, all five variables in the model were associated with a preference for operative treatment over no preference. However, only co-morbidity, cognition and cancer size were associated with a preference for PET over no preference.

The goodness of fit of the multivariable model in table 7.4 can be assessed by the pseudo R_2 value. In this case, the pseudo R_2 value for the model is 0.31, suggesting this model including these five covariates is better than a model including no covariates by 31%, but is worse than the theoretical perfect fitting model (which would have a pseudo R_2 value of 1.0).

Scenario	Patient Age	Co-morbidity	Cognition	Functional status	Cancer size	Cancer biology	Predicted life expectancy	Preference for Surgery	Preference for PET	Prefer both equally
1	85+	Severe	Normal	Severe dependence	Small, node negative	ER+, HER2+	<2 years	15 (5.9%)	218 (86.2%)	20 (7.9%)
2	85+	None	Severe impairment	Moderate dependence	Small, node positive	ER++, HER2-	<2 years	32 (12.6%)	155 (61.3%)	66 (26.1%)
3	70-74	Severe	Normal	Moderate dependence	Large, node negative	ER+, HER2+	<2 years	64 (25.3%)	111 (43.9%)	78 (30.8%)
4	80-84	None	Moderate impairment	Severe dependence	Small, node negative	ER+, HER2+	<2 years	63 (25.1%)	108 (43.0%)	80 (31.9%)
5	70-74	None	Severe impairment	Severe dependence	Large, node negative	ER+, HER2-	<2 years	30 (12.0%)	156 (62.2%)	65 (25.9%)
6	85+	Moderate	Moderate impairment	Mild dependence	Large, node negative	ER++, HER2-	2-5 years	33 (13.1%)	115 (45.6%)	104 (41.3%)
7	75-79	Moderate	Normal	Severe dependence	Large, node positive	ER++, HER2-	2-5 years	55 (22.0%)	100 (40.0%)	95 (38.0%)
8	80-84	Moderate	Mild impairment	Moderate dependence	Small, node negative	ER+, HER2-	2-5 years	98 (39.2%)	39 (15.6%)	113 (45.2%)
9	85+	None	Mild impairment	Independent	Large, node positive	ER+, HER2+	2-5 years	172 (68.3%)	20 (7.9%)	60 (23.8%)
10	70-74	Mild	Moderate impairment	Moderate dependence	Large, node positive	ER+, HER2-	2-5 years	182 (72.2%)	16 (6.3%)	54 (21.4%)
11	70-74	None	Normal	Mild dependence	Large, node positive	ER+, HER2-	>5 years	231 (92.0%)	6 (2.4%)	14 (5.6%)
12	85+	Mild	Normal	Independent	Small, node negative	ER+, HER2-	>5 years	198 (78.3%)	3 (1.2%)	52 (20.6%)
13	80-84	None	Normal	Mild dependence	Small, node positive	ER+, HER2-	>5 years	210 (83.7%)	2 (1.2%)	39 (15.5%)
14	70-74	Moderate	Normal	Independent	Small, node positive	ER+, HER2+	>5 years	227 (90.4%)	2 (0.8%)	22 (8.8%)
15	70-74	None	Normal	Independent	Small, node negative	ER++, HER2-	>5 years	251 (99.2%)	0 (0.0%)	2 (0.8%)
16	75-79	None	Mild Impairment	Independent	Large, node negative	ER+, HER2-	>5 years	223 (88.1%)	5 (2.0%)	25 (9.9%)
17	80-84	Mild	Normal	Independent	Large, node negative	ER++, HER2-	>5 years	195 (77.4%)	7 (2.8%)	50 (19.8%)

*highlighted area demonstrate participants overall preference for surgery, PET or both equally by scenario

Table 7.3: Results by DCE scenario (maximum N=254 responders).

Variable	Levels	Surgery vs equal preference			PET vs equal preference		
		RRR	95% C.I.	P-value	RRR	95% C.I.	P-value
Age	70-74	Ref	-	-	Ref	-	-
	75-79	0.12	0.06-0.22	<0.001	2.05	0.88-4.77	0.096
	80-84	0.06	0.03-0.11	<0.001	2.48	0.98-6.25	0.055
	85+	0.11	0.06-0.19	<0.001	1.84	0.78-4.34	0.166
Co-morbidity	None	Ref	-	-	Ref	-	-
	Mild	0.67	0.46-0.99	0.043	0.24	0.12-0.46	<0.001
	Moderate	0.11	0.07-0.17	<0.001	0.95	0.33-2.74	0.923
	Severe	0.05	0.03-0.09	<0.001	20.70	8.44-50.73	<0.001
Cognition	Normal	Ref	-	-	Ref	-	-
	Mild impairment	2.46	1.63-3.72	<0.001	0.74	0.35-1.55	0.424
	Moderate impairment	0.32	0.24-0.42	<0.001	3.67	2.07-6.48	<0.001
	Severe impairment	0.01	0.01-0.03	<0.001	21.45	7.01-65.57	<0.001
Cancer size	Small, node-	Ref	-	-	Ref	-	-
	Small, node+	1.77	1.22-2.56	0.003	0.18	0.09-0.40	<0.001
	Large, node-	0.47	0.30-0.76	0.002	0.53	0.29-0.97	0.039
	Large, node+	0.25	0.15-0.43	<0.001	1.68	0.81-3.44	0.161
Cancer biology	ER+,HER2+	Ref	-	-	Ref	-	-
	ER+, HER2-	1.44	1.11-1.86	0.006	1.41	0.76-2.60	0.273
	ER++, HER2-	4.51	2.26-8.98	<0.001	2.27	0.53-9.72	0.269

N = 248 responders; RRR = Relative Risk Ratio

Table 7.4: Influence of DCE variable over treatment choice.

7.5.2.2. Factors influencing treatment preference

Influence of age on treatment preference:

Figure 7.2 and table 7.4 illustrate how HCPs' preference for treatment is influenced by a patient's age. The upper section of figure 7.2 compares a preference for surgery against no preference for either treatment (which will be considered to prefer to offer the patient a choice); the lower section compares a preference for PET against no preference/choice. Along the vertical axis, treatment preferences for patients of increasing age are compared with those in the 70-74 year old category. Boxes represent the relative risk ratios (RRR), whiskers the 95% confidence intervals (CI); those not crossing the vertical line at 1 are statistically significant. To the left of the vertical line 1, HCPs are more likely to prefer to offer the patient a choice of treatment; to the right of the vertical line 1, HCPs prefer the specific treatment option (surgery in the upper section, PET in the lower section).

As can be seen in figure 7.2, age has a statistically significant influence on treatment preference ($p < 0.001$), with HCPs being less likely to prefer surgery as age increases. There is also the suggestion that HCPs are more likely to prefer PET with increasing age, although this is less marked than when choice and surgery are compared and does not reach statistical significance.

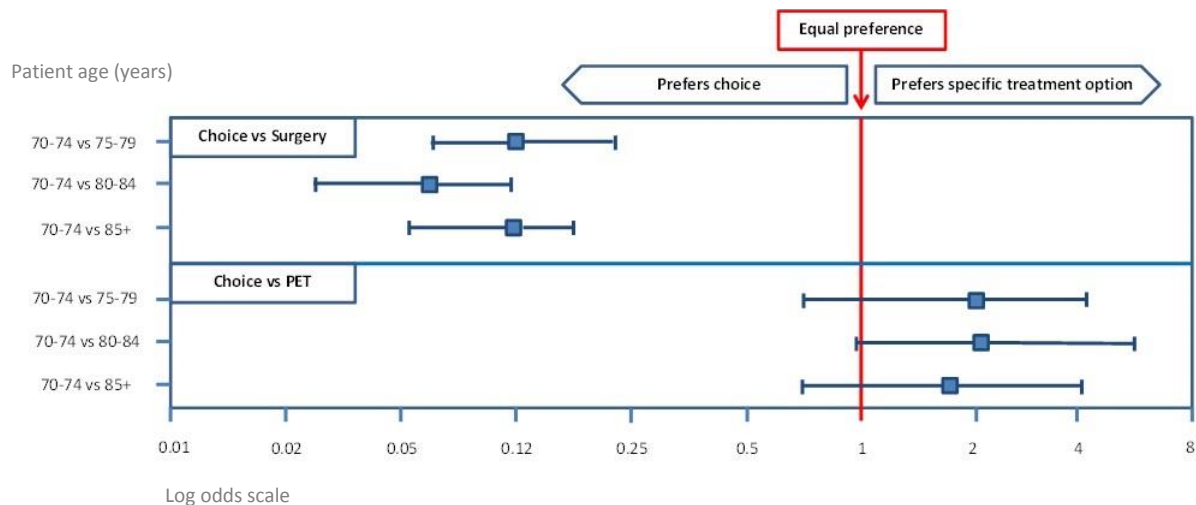


Figure 7.2: Impact of patient age on treatment preference. Boxes represent RRR, whiskers the 95% CI; statistically significant results do not cross 1. Results to the left of 1 represent a preference of choice and to the right of 1 a preference of surgery (upper section) or PET (lower section).

Influence of comorbidity on treatment preference

Comorbidity significantly influenced HCPs treatment preference ($p < 0.05$). With increasingly severe comorbidity, HCPs demonstrated an increasing preference for choice rather than surgery (none vs. severe comorbidity; $RRR = 0.05$, $p < 0.001$) and PET rather than choice (none vs. severe comorbidity; $RRR = 20.70$, $p < 0.001$). Interestingly, when comparing patients with mild comorbidities to those with none, HCPs favoured choice over both surgery and PET ($RRR = 0.67$, $p = 0.043$ and $RRR = 0.24$, $p < 0.001$ respectively). Figure 7.3 and table 7.4 illustrate the effect of comorbidity on treatment preference.

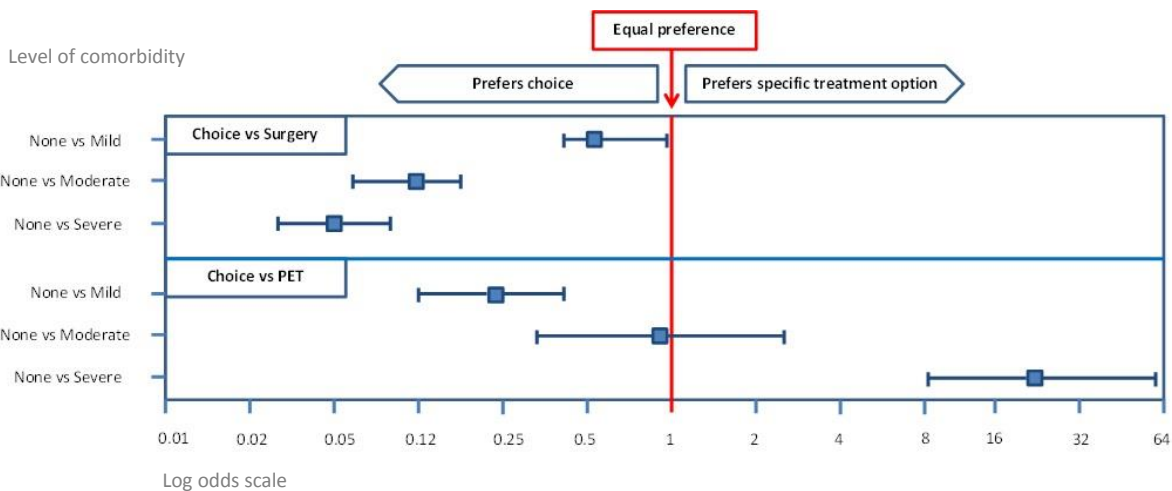


Figure 7.3: Impact of patient comorbidity on treatment preference..

Influence of cognition on treatment preference

Cognitive impairment significantly influenced HCPs treatment preferences ($p < 0.001$). With increasingly severe levels of cognitive impairment, HCPs were less likely to prefer surgery (none vs. severe impairment; $RRR = 0.01$, $p < 0.001$) and more likely to prefer PET (none vs. severe impairment; $RRR = 21.45$, $p < 0.001$). However when comparing patients with milder cognitive impairment to those without impairment, HCPs were more likely to prefer surgery over choice (none vs. mild impairment; $RRR = 2.46$, $p < 0.001$) and seemed to also prefer choice over PET, although this did not reach statistical significance. Figure 7.4 shows how cognition affects HCPs' preference for treatment.

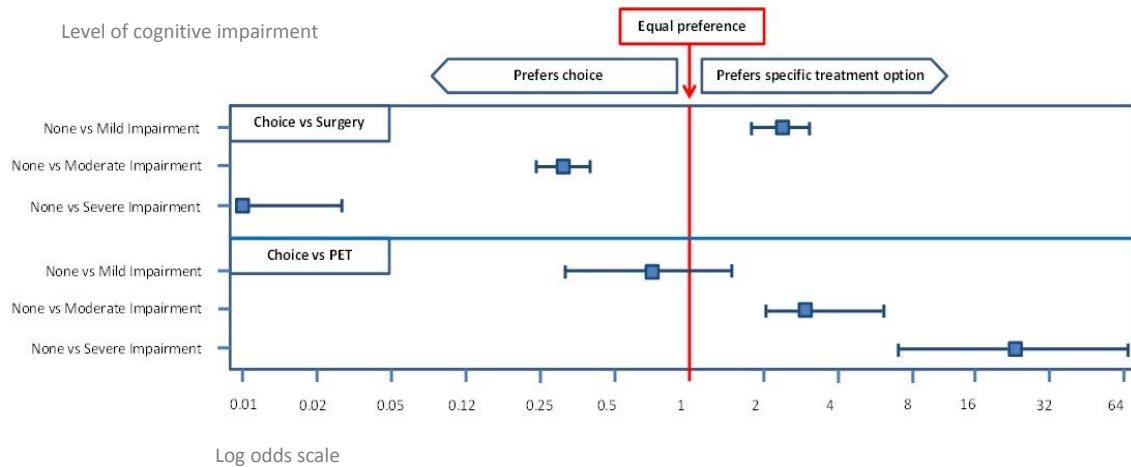


Figure 7.4: Impact of patient cognitive impairment on treatment preference.

Influence of tumour stage on treatment preference

Tumour stage significantly influenced HCPs treatment preferences ($p < 0.001$). Large, node positive tumours were associated with an increasing preference for choice over surgery (small, node negative vs large, node positive; $RRR = 0.25$, $p < 0.001$) and also for PET over choice, although this was not statistically significant. When comparing smaller, node positive tumours with small, node negative tumours, HCPs were more likely to prefer surgery over choice ($RRR = 1.77$, $p = 0.003$) and choice over PET ($RRR = 0.18$, $p < 0.001$). When comparing smaller, node positive tumours with larger, node negative tumours, HCPs were more likely to prefer choice over both surgery and PET ($RRR = 0.47$, $p = 0.002$ and $RRR = 0.53$, $p = 0.039$ respectively). Figure 7.5 shows how tumour stage affects HCPs' preference for treatment.

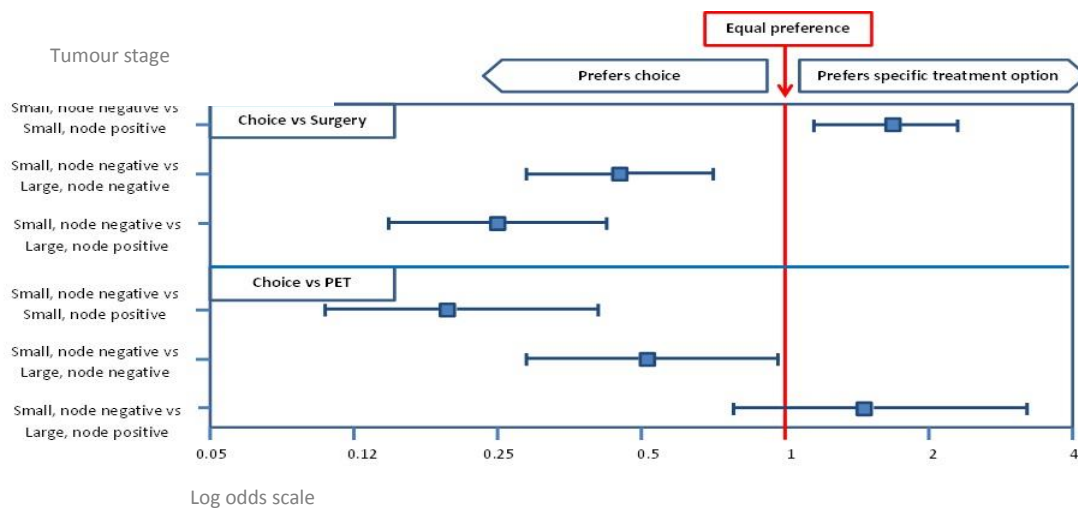


Figure 7.5: Impact of tumour stage on treatment preference.

Influence of tumour biology on treatment preference

Tumour biology significantly influenced HCPs treatment preferences ($p < 0.001$). Comparing HER2 negative tumours with ER positive/HER2 positive tumours, HCPs preferred surgery over choice and also seemed to prefer PET over choice, although this was not statistically significant. Figure 7.6 shows how tumour biology affects HCPs' preference for treatment.

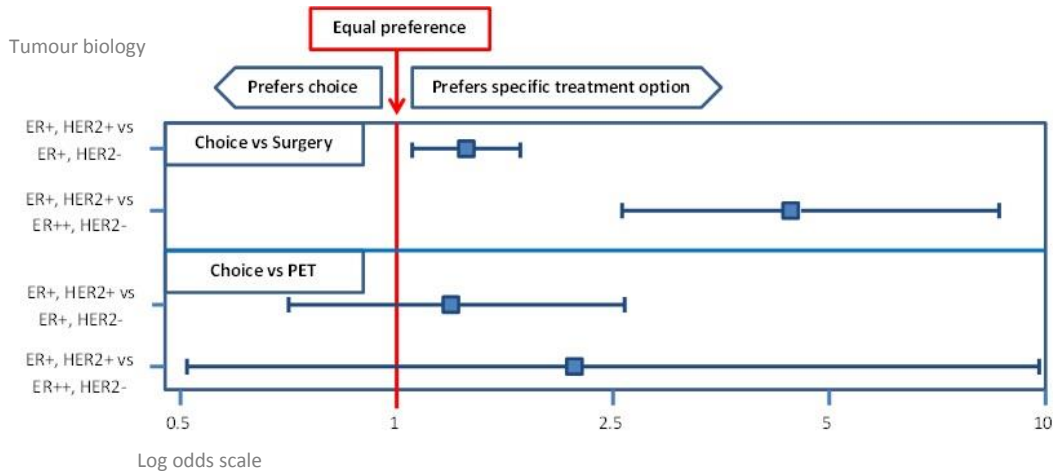


Figure 7.6: Impact of tumour biology on treatment preference.

Influence of functional status on treatment preference

Functional status could not be included in the multivariate logistic model due to collinearity – the model could not distinguish between the effects due to functional status and those due to comorbidity and cognition. However independently, functional status had big impact on treatment preference as can be seen in table 7.5; with increasingly severe dependence HCPs were less likely to prefer surgery and more likely to prefer PET (independent vs severe dependence; RRR = 0.10, $p < 0.01$ and RRR=12.77, $p < 0.01$ respectively).

Response		RRR	P value	Lower 95% CI	Upper 95% CI
Prefers Either	Baseline category				
Prefers Operation	Independent	Ref	-	-	-
	Mild dependence	0.50	<0.01	0.42	0.61
	Moderate dependence	0.20	<0.01	0.16	0.25
	Severe dependence	0.10	<0.01	0.08	0.14
Prefers PET	Independent	Ref	-	-	-
	Mild dependence	4.47	<0.01	2.83	7.05
	Moderate dependence	5.89	<0.01	3.71	9.35
	Severe dependence	12.77	<0.01	7.87	20.71

Table 7.5: Univariate analysis of the effect of functional status on treatment preference.

7.5.2.3. Treatment preference and predicted life expectancy

The majority of HCPs selected treatment in accordance with the patients predicted life expectancy for most scenarios, preferring surgery for patients with life expectancies of >5 years and PET for patients with life expectancies of <2 years, which is consistent with current guidelines [127]. There was more variation in opinion for the patients with life expectancies 2-5 years, with a preference for surgery in some scenarios and PET for others. In addition, opinion was more evenly divided for those scenarios in the medium life-expectancy category, for example scenario 7 (see table 7.3).

7.6. Discussion

7.6.1. Factors important in determining treatment preference

This DCE has confirmed the influence of several predictable factors on HCP decision-making in the management of older patients with operable breast cancer. To our knowledge, this is the first application of a DCE in this setting. The results must be interpreted with a note of caution due to the overall response rate of 40% which limits their generalizability, although we can still estimate the preference for different scenarios with a reasonable degree of precision as the study was adequately powered according to the *a priori* power calculation.

7.6.1.1. Impact of age on determining treatment

Recent national guidelines state that patients with operable breast cancer should be treated with surgery, and not PET, “irrespective of age” unless this is precluded by comorbidities [9]. However, age appears to be an independent factor that HCPs consider to be important when making a treatment decision in this population (see figure 7.2 and table 7.4). This is consistent with findings from several previous studies that have identified a reduction in surgery rates with increasing age for older patients with operable breast cancer [68, 89, 90, 398]. This is most likely due to chronological age often being used by clinicians as a surrogate marker for other factors that are more difficult to quantify, such as life expectancy and frailty [87].

7.6.1.2. Impact of comorbidity on determining treatment

Increasing rates of comorbidity with age may undermine the survival benefit of more aggressive breast cancer therapies [106] and in chapter 1.2 we can see that higher levels of comorbidity are associated with non-surgical treatment. Additionally, although current guidelines recommend that PET should only be offered to patients with “short estimated life expectancy (<2-3 years), who are considered unfit for surgery... or who refuse surgery” [127], they do not specify which comorbidities may preclude surgery or what constitutes being “unfit” and as such it is left to the treating clinician to determine which patients are considered unsuitable for surgery based on the clinical information available.

These results confirm that the degree of comorbidity is a significant factor for HCPs in determining treatment options for older patients with operable breast cancer (see figure 7.3 and table 7.4), thus

arguably reflecting why comorbidities are often presented as a reason for treating patients with PET [128, 362].

7.6.1.3. Impact of cognitive function on determining treatment

Dementia, predominantly affecting older age groups, represents a significant problem in this population, though there are currently no guidelines for the treatment of operable breast cancer in this group. Furthermore there appears to be a lack of consensus among HCPs regarding the optimal way to treat this group as can be seen in Chapters 2.1 and 2.2. Older patients with dementia are less likely to receive standard cancer therapies [449] and this is often stated as an explanation for selecting PET over surgery [69, 368]. These results confirm that HCPs are less likely to prefer surgery and more likely to opt for PET for patients with moderate and severe cognitive impairment. Interestingly, HCPs were more likely to prefer surgery for individuals with milder cognitive impairment compared to those with no cognitive impairment. This may be related to the fact that milder forms of cognitive impairment have less effect on life expectancy but clinicians may still feel they are less able to weigh up treatment options to make a choice.

7.6.1.4. Impact of tumour factors in determining treatment

Tumour factors were also shown to have an independent influence over the HCPs treatment preference. Larger tumours were associated with lower rates of preference for surgery. This may reflect the fact that larger tumours are more likely to require mastectomy rather than breast conservation surgery and clinicians may wish to avoid more major surgery. Interestingly, preference for surgery significantly increased with increasing ER status but preference for PET did not. This is contrary to what might be expected as response rates for PET are generally higher for patients with greater ER positivity [504]. Additionally, preference for surgery increased for HER2 negative tumours but there was no difference in preference for PET, despite the fact that HER2 positive cancers are less likely to respond to endocrine therapy [489]. However, the scenarios only contained limited information on the receptor status and combined ER and HER2 status, making the results slightly more difficult to interpret.

7.6.1.5. Impact of functional status on determining treatment

Although functional status was not included in the final model, on univariate analysis it was significantly associated with treatment preference, with worsening functional dependence associated with lower rates of preference for surgery and higher rates of preference for PET. These findings may be unsurprising given the impact of comorbidities, cognition and other more difficult to measure factors (such as obesity, mobility, etc.) on function which may in turn impact on a patient's fitness to undergo surgery and general anaesthesia. This in turn is likely to be the cause of the failure of the model to converge (i.e. collinearity).

7.6.1.6. Impact of life expectancy on determining treatment

The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) recommend that PET should only be offered to patients with “short estimated life expectancy (<2-3 years), who are considered unfit for surgery... or who refuse surgery” [127] and these data show that the majority of HCPs selected treatment in accordance with this for most scenarios, preferring surgery for patients with life expectancies of >5 years and PET for patients with life expectancies of <2 years. However, life expectancy is impossible to accurately assess with any certainty, with a recent study demonstrating that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [128].

7.6.2. Variability in treatment preference

Whilst a majority of HCPs within this study selected treatment in accordance with current guidelines relating to the presence of significant comorbidity and predicted life expectancy, this was not universal. Additionally, although just over three quarters of HCPs surveyed demonstrated a preference for operative treatment overall, the remainder exhibited a preference for PET (9%) or no preference (13%). This demonstrates a certain amount of variation in the way that HCP prefer to manage older breast cancer patients, suggesting this may be a contributing factor to the treatment variation seen in this population. There was no relationship between treatment preference and participant region identified, which may be due to the small numbers of participants from each region. Doctors were more likely to choose a specific treatment compared to nurses who were more likely to prefer choices ($p < 0.05$). This is perhaps unsurprising in view of their role in helping patients with decision-making.

7.6.3. Strengths and weaknesses of this analysis

The DCE design has enabled us to establish the relative importance of difference variables according to individuals HCPs [490] under experimental conditions using clinically realistic scenarios. This adds to the survey analysis where participants assess the importance of factors individually and allows assessment of these factors influence on decision-making and how they interact.

Again, a limitation of this study includes the low response rate to the questionnaire, although this is comparable with other similar studies [128, 474], but this limits the generalizability of the results.

In addition, not all relevant variables could be included in the DCE and so there may be other confounding factors contributing to treatment allocation that were not measured here. It was felt, based on previous research done in our unit, that HCPs could potentially review up to 25 scenarios with 5 factors (with up to five levels for some of the factors) before the questionnaire becomes unacceptably long for participants [474, 502]. The variables chosen for the DCE were deemed the most important by the study team based on review of the literature and interview findings.

7.7. Summary

In conclusion, the majority of HCPs within this study selected treatment in accordance with current guidelines relating to the presence of significant comorbidity and predicted life expectancy. However, in some scenarios, opinion was divided and age did appear to be an independent factor that HCPs considered when making treatment decisions in this population. This study demonstrates that HCP preferences for managing older breast cancer patients are not uniform, which may contribute to the treatment variation seen in this population.

Chapter 8: Review of Findings

8.1. Aim:

To examine the variability in the treatment of older women with operable breast cancer, after controlling for case mix, in relation to the views of specialist healthcare professionals.

This study investigated the variability in the treatment of older women with operable breast cancer, providing new insights and a fuller understanding of the mechanisms behind how clinicians determine what treatment options to offer to these patients.

Using a mixed methods approach, it has clearly been demonstrated that case mix alone does not account for the variation in treatment of older women with breast cancer and that some of this remaining variation is likely to be due to differences in how clinicians determine what treatment options to offer to patients and whether or not they present patients with a choice.

8.2. Objectives and findings

Objective: To determine the level of variance in the treatment of older women with operable breast cancer.

Finding: There is considerable variation in the rate of surgical treatment of older women with operable breast cancer in the UK and this is not accounted for by case mix.

The systematic review found that the rate of non-surgical treatment of older breast cancer patients in the UK varies between 14 and 50% in the published literature [68, 69, 73, 85, 89, 92, 374, 375, 378, 385, 391-393, 398].

Examining the retrospective registry data for 17 129 patients aged 70 years or more with assumed ER+ operable breast cancer, 9 955 were treated with surgery, giving an overall rate of 58.1%. Significant variation of surgery rates existed across the different hospitals examined and this persisted following adjustment for case mix, with 23.5% having a much higher rate of surgery than expected and 20.6% having a much lower rate than expected.

Results from surveying members of the UK Association of Breast Surgery (ABS) demonstrated variable use of PET, with 17/240 (7.1%) stating that more than 30% of women ≥ 70 were treated this way, 65/240 (27.1%) stating that 20-30% of women ≥ 70 were treated with PET, 67/240 (27.9%) stating that 10-20% of women ≥ 70 received PET and 91/240 (37.9%) stating that PET was used in less than 10% of women ≥ 70 years.

Responses from the 254 HCPs to the 17 discrete choice experiment scenarios varied, with 78% (199/254) of responders demonstrating a preference for operative treatment in the majority of the scenarios they rated, 9% (22/254) a preference for PET, and 13% (33/254) an equal preference for surgery and PET.

Objective: To explore the views of specialist healthcare professionals towards the management of older women (>70yrs) with operable breast cancer, particularly in terms of PET versus surgery.

Finding: Surgery was generally considered to be the gold standard treatment for any patient with operable breast cancer, including those aged over 70 years.

Qualitative methodology comprising semi-structured interviews highlighted that most HCPs viewed surgery as a safe and superior treatment option for most patients when compared to PET in view of the enhanced rate of local control. Some also viewed surgery as having a survival advantage over PET in selected older patients. In terms of the use of local anaesthetic surgery HCPs opinion varied, with some treating most patients in this way and others never utilising this option, instead treating their patients with PET.

A quantitative survey with members of the ABS showed that 60% (148/246) agreed with the statement "surgery is almost always possible for older women ≥ 70 with operable breast cancer under local or regional anaesthesia" and nearly all (98.4%; 241/245) HCPs stated that in their experience, surgery under GA was well tolerated in older women. However experience with the usage of local anaesthetic (LA) and regional techniques was more variable; as although nearly two-thirds (156/244; 63.9%) felt that surgery under LA was well tolerated in older women, only 43/244 (17.6%) had an anaesthetist who would happily perform regional blocks to allow surgical excision in patients where GA may carry an increased risk.

Finding: HCPs varied in their opinions on the use of PET as a treatment for older patients with operable breast cancer.

Semi-structured interviews with 34 HCPs from across the UK demonstrated a broad spectrum of beliefs, attitudes and behaviours in relation to the use of PET as a treatment for older patients with operable breast cancer. Some HCPs felt PET to be a valuable treatment option and others declaring they did not use it and did not consider it a treatment for operable breast cancer in patients of any age.

Opinions also varied regarding both response rates and duration of response, with HCPs from high PET units tending to think PET had a longer duration of response than HCPs from low PET units.

Analysing the responses from the quantitative survey, there was again variation regarding how long HCPs felt that PET was effective in maintaining local tumour control, with 64/238 (26.9%) stating 5 years or more; 74/238 (31.1%) stating 3 years, 70/238 (29.4%) stating 2 years and 30/238 (12.6%) stating 18 months or less.

Finding: HCPs varied in their opinions of whether older patients with operable breast cancer should be offered a choice of treatment options.

Qualitative interviews with HCPs revealed considerable variation in opinion regarding whether or not older patients with operable breast cancer should be offered a choice of treatments between surgery or PET. The majority, who tended to be from high PET units, felt that there were a sub-group of patients, who tended to be older, frailer and less fit, who were suitable to be offered a choice as it would not impact on their overall survival. However, a few HCPs from units with lower rates of PET, felt that as they considered it an inferior option, it was not appropriate to offer PET as a choice.

When quantitatively surveying a wider group of HCPs, over three quarters (199/249) of HCPs agreed with the statement "All women ≥ 70 with operable breast cancer should be offered an operation regardless of age", however only 65/244 (26.6%) agreed that PET may be offered to any older woman with ER positive disease as there is no proven survival disadvantage.

In addition patient preference was stated as one of the most important factors that HCPs take into account when deciding which treatment options to offer older patients with operable breast cancer, and there was a strong view that older women, if given the choice, would choose surgery over PET. This was

slightly incongruent with the interviews where it was clear that a significant number of HCPs steered their patients to their own preferred choice and in some cases did not offer choice when they felt it not in the patient's best interest.

Objective: To identify the factors underlying treatment decision-making by health care professionals relating to older women with breast cancer.

Finding: Patient age remains a factor underlying treatment decision-making by HCPs, despite many believing it should not influence treatment decision-making.

When interviewing HCPs, most said that age was not a factor when deciding treatment, however some, particularly those from high PET units, still talked about age-related cut-offs for discussing non-standard treatment and a couple implied subconscious age-related biases by comparing older patients to "normal" patients. There were a minority that openly acknowledged the importance of accounting for age due to its effect on tumour biology, patient physiology (senescence) and life expectancy.

Analysing the questionnaire data, age was considered as one of the least important factors considered by HCPs when making decisions about surgery vs PET, with only 4.9% (12/245) rating it as very important and 24.1% (59/245) rating it as important.

However, using DCE methodology, age was seen to be statistically associated with treatment preference on univariate ($p < 0.05$) and multivariate ($p < 0.001$) analysis, with HCPs being less likely to prefer surgery as age increases.

This can also be seen in the retrospective registry analysis, with rates of surgical treatment decreasing with increasing age, so that the proportion receiving surgery declines from 91.1% at age 70 to 38.5% at age 85 and less than 3% at age 95 and over.

Finding: Comorbidity is an important factor considered by HCPs when determining treatment for older women with operable breast cancer, and increasing comorbidity is associated with a reduction in rates of surgical treatment.

Around half of HCPs interviewed (18/34) felt that fitness for surgery equated to the comorbidity status of the patient. Although there was variability in which comorbidities HCPs felt caused a patient to be unfit for surgical treatment.

The questionnaire data showed the importance that HCPs placed on comorbidities when deciding treatment options for older women with operable breast cancer, with 100% (248/248) rating this as having at least some importance and 63.0% (155/246) agreeing with the statement “All women ≥ 70 with operable ER+ breast cancer, who have multiple comorbidities such that anaesthesia may carry an increased risk of morbidity and mortality, should be treated with PET”.

The effect of comorbidity on treatment preference was also seen on analysis of the DCE scenarios, where it significantly influenced HCPs treatment preference ($p < 0.05$). With increasingly severe comorbidity, HCPs were more likely to prefer PET (none vs. severe comorbidity; RRR 20.70, $p < 0.001$) and less likely to prefer surgery (none vs. severe comorbidity; RRR=0.05, $p < 0.001$).

This effect could also be seen in the retrospective registry data where increasing levels of comorbidity were again associated with decreasing rates of surgical treatment.

Finding: HCPs are divided in their opinion regarding the best way to treat older patients with operable breast cancer who have cognitive impairment, however increasing rates of cognitive impairment are associated with decreasing rates of operative treatment.

Analysis of 14 380 patients from the retrospective registry data with matched HES comorbidity data revealed that patients with a diagnosis of dementia were significantly less likely to receive surgery compared to those without (12.7% vs 58.8%; $p < 0.001$).

During qualitative interviews, HCPs were divided in their opinion regarding the best way to treat older patients with breast cancer and a diagnosis of dementia, with approximately half believing they should be surgically treated and the remainder expressing that they felt these patients should be treated with PET.

This division of opinion was mirrored in the quantitative questionnaire survey, with 41.1% (102/245) of HCPs agreeing with the statement “all women ≥ 70 with operable ER+ breast cancer, who have significant dementia (unable to give informed consent) should be treated with PET” and the remainder (146/248; 58.9%) disagreeing. What was clear is that nearly all (89.8%; 220/245) HCPs consider the presence of dementia as important in making treatment decisions in older breast cancer patients.

In the DCE scenarios, cognitive impairment was again seen to be significantly associated with treatment preference ($p < 0.05$), with increasingly severe cognitive impairment associated with a reduction in preference for surgery and an increase in preference for PET.

Finding: Frailty and functional status were considered by some HCPs to be inter-related and were factors considered important in determining treatment, with increased rates of functional dependence associated with a reduced preference for surgery.

Frailty was mentioned by around half ($n=16$) of the HCPs during semi-structured qualitative interviews as an important factor in determining treatment of older breast cancer patients, however it was difficult to define exactly what people meant by this term and for some it seemed to equate to their functional ability.

Functional status was a factor included in the quantitative survey of HCPs and was considered an important factor in deciding treatment in this population by 87.1% (217/249).

In the DCE section of the questionnaire, functional status showed the greatest association with treatment preference on univariate analysis ($p < 0.05$), with HCPs being less likely to prefer surgical treatment for patients with higher rates of functional dependence. However it could not be included in the multivariable analysis due to collinearity – that is the model could not distinguish between the effect due to functional status and that due to comorbidity and cognition which are intimately linked.

Finding: HCPs consider a variety of tumour factors important in the treatment decision-making process for older women with operable breast cancer.

Analysis of retrospective registry data demonstrated that tumour factors were associated with treatment type, with larger, node positive tumours being less likely to be treated surgically. Higher tumour grade was associated with increasing rates of surgery, possibly representing the assumption that more aggressive disease should be treated with more aggressive treatment.

During the semi-structured interviews, HCPs mentioned a variety of tumour factors that they took into account when determining treatment of older women with operable breast cancer, including the degree of ER-positivity, PR status, HER2 status, suitability for breast-conserving surgery and the histological subtype (specifically mucinous types).

The quantitative survey revealed that although tumour factors, such as stage and size of disease were important to HCPs in the clinical decision-making, with 87.4% (216/247) rating them as of at least some importance, they were viewed as less important than patient health and fitness measures. The presence of axillary disease was rated as slightly more important with 27.5% (68/247) rating it as very important. ER status was regarded as important or very important by most surgeons (87.1%; 216/248) but HER2 status much less so (50.2%; 123/245).

Tumour factors were assessed using DCE methodology with variables of tumour biology and tumour stage. Both tumour biology and tumour stage significantly influenced HCPs treatment preferences ($p < 0.001$). HCPs were more likely to prefer surgery for larger, node positive tumours compared to smaller node negative tumours and also interestingly, for HER2 negative tumours compare to HER2 positive tumours.

Finding: Patient preference was considered highly important to HCPs when determining treatment choices for older women with operable breast cancer.

Several HCPs (n=13) during semi-structured interviews state that patient preference was one of the most important factor in deciding treatment; even those who didn't offer a choice of treatment claimed they would use PET if a patient refused to undergo surgery, although this should not be surprising as they have little alternative in a patient who refuses consent to surgery. However, as mentioned above, and in contrast to this expressed opinion, many of the HCPs implied at interview that they often steer patients towards their own preferred treatment option. This may reflect a lack of insight or a desire to be politically correct during the interview.

Patient preference was also considered important by 94.8% (236/249) of HCPs answering the quantitative survey.

Objective: To quantitatively assess the above factors on a wide group of healthcare professionals to determine whether they account for variation in treatment.

Finding: The factors examined here account for some of the treatment variation seen in older women with operable breast cancer but not all.

Examining the goodness of fit of the multivariable model used to analyse the DCE scenario results, the variables of patient age, comorbidity level, cognitive function, tumour biology and tumour stage can be

seen to account for 31% of the treatment choice by HCPs (using the pseudo R2 value). This suggests that 69% of the treatment decision-making is affected by factors not included in this model. It was not possible to include all factors, which may also have been affected by specific comorbidities, educational level, perceived patient preference and also the innate opinion of the HCP themselves.

Using the retrospective registry data to account for patient age, comorbidity, tumour size, tumour grade, nodal status, method of presentation and deprivation quintile, there remained variability in surgery rates at hospital level, suggesting that factors other than those accounted for in the case mix analysis contribute towards the treatment variation seen.

8.3. Benefits of adopting a MM approach

8.3.1. Triangulation

As can be seen above, the results from each strand were compared and the major findings were corroborated by using the different methods.

8.3.2. Complementary

Using a mixed methods design has allowed the study of this complex problem from a variety of perspectives, with the richness of the qualitative findings enhancing those from the quantitative strands.

8.3.3. Development

The findings from the systematic review, meta-analysis and qualitative interviews informed the design of the quantitative survey, allowing the creation of a bespoke instrument to assess to specifically address the research question.

8.3.4. Sampling

Using different methodologies allowed us to take advantage of different sampling techniques. Purposive sampling could be used for the qualitative interviews to ensure opinions were gathered from HCPs in areas of high and low PET, as well as both surgeons and breast clinical nurse specialists. The questionnaire survey in combination with the DCE component enabled generalisation of the qualitative findings to a larger sample of the HCP population being studied. Finally, the registry population included *all* diagnoses of operable ER positive cancers treated over a consecutive 8 year period. As the findings are broadly concordant between sampling methods this suggests that they are generalizable more broadly.

8.3.5. Offsetting

Each method had its own strengths, and by combining methods, this helps to offset the weaknesses of any individual method. For example, the registry data provide information of the complete population

being studied, however because of limitations with accessing these data, they are a few years out of date. However the interviews and questionnaires studied a much smaller sample of the population but they provide a more current view of the issues being studied.

8.3.6. Expansion and comprehensiveness

Overall, use of this complex mixed methods design has extended both the breadth and range of investigation, allowing the research question to be addressed more fully.

Chapter 9: Discussion

Breast cancer is an increasingly common disease in older women and outcomes are inferior to those in younger women partly due to a lack of screening and awareness [101, 102], resulting in delayed diagnosis but also due to treatment variance from the recognised norms. One of the main areas in which treatment varies is the fact that a significant proportion of older women do not undergo surgery [68, 84, 89, 90]. Rates of surgery are highly variable across the UK [73] due to a lack of evidence based guidelines. This work has explored both the extent to which this variance occurs across the UK using registry data analysis corrected for case mix variation and has also examined some of the factors that influence health care professionals to make these treatment decisions using a mixed methods approach. The work has shown that the variability cannot be fully accounted for by patient variables and that variation in clinician opinion exists and likely accounts for a significant percentage of this treatment variability. This variation may be to the detriment of patient outcomes and indicates that there is a need for more structured guidelines for treatment decision making in this population.

9.1. Treatment variation according to age

As previously discussed, increasing age is associated with decreasing rates of surgery in patients with operable breast cancer [68, 78, 84, 90]. This study supports these findings, within the systematic literature review (Chapter 3), in the analysis of retrospective registry data (Chapter 4) and using the discrete choice experiment (DCE) methodology (Chapter 7).

Across the large population studies identified within the systematic review, women were less likely to receive standard treatment, including surgery, with increasing age [68, 78, 83, 84, 88-91, 374, 375, 377, 378, 385, 388, 389, 391, 398, 399].

Within the registry analysis, rates of surgical treatment also decreased as age increased, with the proportion receiving surgery declining from 91.1% at age 70 to 38.5% at age 85 and less than 3% at age 95 and over.

The DCE component of the study also confirmed that age of the patient statistically affected the treatment preference of HCPs ($p < 0.001$), being less likely to prefer surgery as age increases.

Non-standard treatment of breast cancer in older patients has been associated with poorer outcomes [78, 85, 371]. However a Cochrane review of seven randomised controlled trials comparing surgery with PET found no difference in overall survival [214, 215, 402] but did identify better local control in the surgery group. In this study, a review of the published non-randomised studies comparing surgery and

PET has suggested a difference in overall and breast cancer-specific survival in favour of surgery, however these results need to be interpreted with caution due to the evident selection-bias within the studies. They do however provide real-life evidence of the results of current clinical practice.

9.2. Regional variation in treatment of older breast cancer patients

There is considerable variation across the UK in the way older patients with operable breast cancer are treated, with regional rates of non-surgical treatment in this population varying between 12 and 40% [73]. This variation has also been reported by the Royal College of Surgeons and Age UK in their report “Access all ages 2” where they found a 37-fold difference between the highest (37 per 10 000) and lowest (1 per 10 000) rates of surgery for breast cancer in the over 65s depending on where they live [416]. This study has looked at the variability in treatment of older women with breast cancer across the UK and found similar variation exists.

The systematic review found that the rate of non-surgical treatment of older breast cancer patients in the UK varies between 14 and 50% in the published literature [68, 69, 73, 85, 89, 92, 374, 375, 378, 385, 391-393, 398].

Examining the retrospective registry data, significant variation of surgery rates existed across the different hospitals examined and this persisted following adjustment for case mix, with 23.5% having a much higher rate of surgery than expected and 20.6% having a much lower rate than expected.

The questionnaire survey also demonstrated variable use of PET amongst the membership of the UK Association of Breast Surgery (ABS), with 17/240 (7.1%) stating that more than 30% of women ≥ 70 were treated this way, 65/240 (27.1%) stating that 20-30% of women ≥ 70 were treated with PET, 67/240 (27.9%) stating that 10-20% of women ≥ 70 received PET and 91/240 (37.9%) stating that PET was used in less than 10% of women ≥ 70 years.

The variation in surgical treatment rates of cancer patients has been deemed a healthcare inequality by the National Cancer Equality Initiative (NCEI) [94], and the National Institute for Health and Care Excellence (NICE) have identified the rate of surgically treated older women with breast cancer as a quality indicator as part of their recently published quality standards report [505].

When looking at variation in treatment rates, it is vital to establish whether this “under treatment” is actually inappropriate since there are several acceptable and important grounds why some older

patients may not be treated according to standard protocols. These reasons include patient fitness measures which may render a patient “unfit” to undergo surgical management, as well as patient choice, when a patient may decide they do not wish to have operative management. According to published national and international guidelines on the management of older women with breast cancer, these factors, together with a short (2-3 years) predicted life-expectancy, are considered appropriate justifications to treat a patient with PET [9, 127].

As such, when examining the treatment variation in the eight years of retrospective registry data at hospital and clinician levels, a case mix adjustment was performed to account for variations in factors which might explain the treatment allocation, including patient age, deprivation quintile, level of comorbidity, method of diagnosis, cancer size, nodal status, tumour grade. However, as can be seen in Chapter 4, not all the treatment variation can be explained by case mix, particularly at hospital level where a significant proportion of units (44.1%) had surgery rates far outside the expected ranges.

In addition, the low pseudo R_2 value (0.31) of the HCP DCE questionnaire supports the case-mix adjustment findings that clinical factors available to clinicians do not account for patterns of treatment variation observed (Chapter 7). The clinical factors included as DCE variables (patient age, patient comorbidity level, patient cognition, tumour size and biology) all significantly influenced HCP treatment responses, however the pseudo R^2 value of 0.31 indicates that these variables only account for 31% of responses given. This in turn implies that there are other factors that influence HCP treatment decision-making, accounting for the remaining 69% of responses.

9.3. HCPs take a variety of factors into account when determining treatment

9.3.1. Fitness for surgery

One explanation for the persistent treatment variation seen in Chapters 4 and 7 may be that there are other factors which HCPs consider important when determining treatment options for older, operable breast cancer patients, such as fitness for surgery. There was no consistent definition of what HCPs considered as “fit” for surgery within the qualitative interviews and HCPs varied in what factors they considered when making this decision. This again is likely to be a source of some of the variation in treatment seen within the older breast cancer population.

Specific factors considered important by HCPs in both qualitative interviews and the quantitative survey questionnaire included age, life expectancy, comorbidities, cognitive function, frailty, functional status, tumour factors and patient preference. These are each discussed below.

9.3.2. Age and life expectancy

Although most HCPs interviewed in chapter 5 claimed that they did not consider age when deciding treatment for older women with operable breast cancer, some still mentioned age-related cut-offs for discussing non-standard treatment and there was the implication of subconscious age-related biases by some. Again, age was considered as one of the least important factors considered by HCPs when making decisions about surgery vs PET within the questionnaire survey, with only 4.9% (12/245) rating it as very important and 24.1% (59/245) rating it as important.

However, using DCE methodology, age was seen to be statistically associated with treatment preference on univariate ($p < 0.05$) and multivariate ($p < 0.001$) analysis, with HCPs being less likely to prefer surgery as age increases. This was also seen in the retrospective registry analysis, with rates of surgical treatment decreasing with increasing age.

As age increases so rates of comorbidities rise, in turn potentially reducing the survival advantage of more aggressive breast cancer therapies [106]. Short life-expectancy, also stated to be a reasonable justification for treating patients with PET [127], is also inextricably linked to age [334] and as a recent UK questionnaire study found that surgeons are poor at gauging life-expectancy of older patients [128], age may be commonly used as a surrogate marker for predicted life-expectancy.

9.3.3. Comorbidities, including dementia

Within the interviews, fitness for surgery was equated with comorbidity status for around half the HCPs interviewed, although variability remained over specifically which comorbidities were important. The questionnaire data confirmed the importance that HCPs place on comorbidities when deciding treatment options for older women with operable breast cancer, with all HCPs rating it as having at least some importance.

The effect of comorbidity on treatment preference was also seen within the DCE analysis, with HCPs less likely to prefer surgery and more likely to prefer PET as comorbidity increases ($p < 0.05$). A similar effect

could also be seen in the retrospective registry data where increasing levels of comorbidity were again associated with decreasing rates of surgical treatment.

Comorbidities are often stated as a reason for treating patients with PET [128, 362]. Increasing comorbidity burden impacts on life expectancy and in turn, may reduce the survival advantage of more aggressive breast cancer therapies such as surgery [106].

Dementia in particular has been suggested to influence treatment allocation of older breast cancer and studies examining the use of PET in small cohorts of older patients have suggested that the presence of dementia may have been a contributing factor in treatment decision-making in some patients [74, 224, 228, 339, 368].

Analysis of the registry data showed that patients with a diagnosis of dementia were significantly less likely to receive surgery compared to those without (12.7% vs 58.8%; $p < 0.001$) and in the DCE analysis, increasing cognitive impairment was seen to be significantly associated with a reduction in preference for surgery and an increase in preference for PET ($p < 0.05$).

Interestingly, during qualitative interviews, HCPs were divided in their opinion regarding the best way to treat older patients with breast cancer and a diagnosis of dementia, with approximately half believing they should be surgically treated and the remainder expressing that they felt these patients should be treated with PET. This division of opinion was mirrored in the questionnaire survey, however what was clear is that nearly all HCPs consider the presence of dementia as important in making treatment decisions in older breast cancer patients.

Cognitive impairment is an important comorbidity in this population, and to some degree affects up to 10% of people over the age of 65, being more prevalent in women, where the rate increases to 20% for women aged between 85-89 years of age [454].

There are several reasons why HCPs may be less inclined to operate on patients with dementia. Moderate to severe cognitive impairment may preclude surgery under local anaesthesia, and cognitive and functional ability may worsen following general anaesthesia [152]. Previous studies have also shown that patients with dementia may present with later stage disease [449], partly owing to poor symptom recognition and impaired communication among these patients [450, 451]. They are also unlikely to volunteer for screening which is associated with better disease stage [452] and so may require more

extensive surgical options. In addition, dementia is associated with a significantly reduced life-expectancy [506] which is one of the acceptable reasons for treating a patient with PET [127].

9.3.4. Frailty and functional status

Frailty can be defined as “the condition of being weak and delicate” or “a distinctive health state related to the ageing process in which multiple body systems gradually lose their built in reserves” [507] and contributors include diminished organ function, comorbidities, impaired physical function and geriatric syndromes. This makes it difficult to quantify. Frailty was mentioned by around half of HCPs during qualitative interviews, however it was again difficult to define exactly what people meant by this term and for some it seemed to equate to their functional ability.

There are a range of tests available for identifying frailty, many of which assess a person’s ability to function normally, but the accuracy of these is uncertain [507]. Functional status however is much easier to measure and was considered important by 87% of HCPs in the questionnaire survey. Additionally, within the DCE section of the questionnaire, functional status showed the greatest association with treatment preference on univariate analysis ($p < 0.05$), with HCPs being less likely to prefer surgical treatment for patients with higher rates of functional dependence. Unfortunately it could not be included in the multivariable analysis as the model was unable to distinguish between the effect due to functional status and that due to comorbidity and cognition.

A reduction in functional status is associated with a reduced life expectancy [508, 509], again one of the acceptable reasons for treating a patient with PET [127]. Both factors may impact on a patient’s fitness to undergo surgery and general anaesthesia, explaining why they were considered important by HCPs in determining treatment options for older breast cancer patients.

9.3.5. Tumour factors

Tumour factors considered important by HCPs in determining treatment options for older breast cancer patients included tumour size, nodal status and hormone receptor status. Within the registry analysis, larger node positive tumours were less likely and higher grade tumours more likely to be treated with surgery.

The quantitative survey revealed that although stage and size of disease were important to HCPs in the clinical decision-making, they were viewed as less important than patient health and fitness measures. The presence of axillary disease was rated as slightly more important and ER status was regarded as important or very important by most surgeons but HER2 status much less so.

Tumour factors were assessed using DCE methodology with variables of tumour biology and tumour stage. Both tumour biology and tumour stage significantly influenced HCPs treatment preferences ($p < 0.001$). HCPs were more likely to prefer surgery for larger, node positive tumours compared to smaller node negative tumours and also interestingly, for HER2 negative tumours compared to HER2 positive tumours.

Tumour size and nodal status may impact the type of surgery required, larger tumours are more likely to require mastectomy rather than breast conservation surgery and node positive disease requires surgery to clear the axilla, both of which may be considered more extensive procedures. Additionally, performing axillary clearance under local anaesthesia is not technically possible and would be precluded in women who were too frail to undergo GA. Mastectomy under general anaesthetic can be done but it is not easy or pleasant.

The degree of ER positivity impacts on whether the tumour will respond to endocrine therapy and PET is only considered an appropriate treatment for ER positive patients. In addition, HER2 positive cancers are known to be generally less likely to respond to endocrine therapy [489]. Higher tumour grade was also associated with increasing rates of surgery, possibly representing the assumption that more aggressive disease should be treated with more aggressive treatment.

9.4. HCPs vary in their opinion of which factors are important when determining treatment

Whilst current guidelines suggest PET is a suitable treatment option for patients who are “considered unfit for surgery” [127] or where “significant comorbidity that precludes surgery” [9], they do not specify what constitutes being “unfit” nor which comorbidities may “preclude” surgery [9, 127]. As such it is left to the treating clinician to determine treatment, potentially resulting in the wide variation in practice observed.

During qualitative semi-structured interviews, HCPs unanimously agreed that “fitness for surgery” was an important consideration in treatment decision-making for older patients. However there was

considerable variation among clinicians regarding key features that constituted being fit for surgery. This was specifically the case in older women with breast cancer and dementia. There are currently no guidelines pertaining to the treatment of cancer patients with dementia and this variation in opinion may reflect this. Another source of variability was the assessment process by which HCPs determined the fitness of their patients. This is unsurprising as the older population make up a very heterogeneous group and as SIOG points out, that although CGA may be useful, it is not clear which patients will benefit nor which method is best [127].

The data from the DCE suggest that there is considerable variance in the level of fitness that HCP consider significant in making these decisions and this implies that standardised guidelines would be helpful. Whilst the majority of HCPs had fairly similar treatment choices for most patients and selected treatment in accordance with the patients’ predicted life expectancy for most scenarios, as per current guidelines [127], there were some scenarios where opinion was divided, for example scenarios 3, 4 and 7 (see table 9.1). This demonstrates there may be personal preferences at play of a lack of understanding of the potential impact of the precise frailty and life expectancy impact of a particular set of personal patient attributes. Additionally, a recent study has shown that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [128].

	Age	Co-morbidity	Cognition	Function	Cancer size	Cancer biology	Predicted life expectancy	Prefer PET	Prefer surgery	Prefer both equally
3	70-74	Severe	Normal	Moderate dependence	Large, node negative	ER+, HER2+	<2 years	64 (25.3%)	111 (43.9%)	78 (30.8%)
4	80-84	None	Moderate impairment	Severe dependence	Small, node negative	ER+, HER2+	<2 years	63 (25.1%)	108 (43.0%)	80 (31.9%)
7	75-79	Moderate	Normal	Severe dependence	Large, node positive	ER++, HER2-	2-5 years	55 (22.0%)	100 (40.0%)	95 (38.0%)

Table 9.1: DCE scenarios showing a division in HCP opinion on the best way to treat older women with operable breast cancer.

9.5. HCPs vary in their opinion of whether patients should be offered treatment choice

In this study, HCPs varied in their opinions of whether older patients with operable breast cancer should be offered a choice of treatment, in particular surgery or PET. This was particularly evident within the qualitative interviews where the range of responses can be mapped more easily. There was also a suggestion that HCPs from high PET units tended to feel that offering a choice to some patients was

appropriate compared to a few HCPs from low PET units who considered it an inferior option and so did not consider PET a suitable treatment option to offer as a choice. Amongst the wider group of HCPs surveyed using the questionnaire around a quarter agreed that PET may be offered to any older woman with ER positive disease as there is no proven survival advantage. In addition patient preference was stated as one of the most important factors that HCPs take into account when deciding which treatment options to offer older patients with operable breast cancer.

Shared DM is increasingly considered to be relevant in preference sensitive health care decisions such as this, with patients and HCPs working together to make health care decisions that are based on clinical evidence and patients' informed preferences [268, 277, 456]. Shared Decision-Making (SDM) suggests that patients should be informed of their treatment options [277] and for some older women it may be appropriate to offer PET as an alternative to 'standard' surgical treatment and allow the patient to decide what is best for them. However this study found a considerable proportion of HCPs did not offer a choice of treatment options to their older breast cancer patients, despite the fact that evidence suggests that older patients may prioritise quality of life over quantity [415] and that patient choice is commonly stated as a reason for treating patients with PET [128, 369].

Hamaker and colleagues [373] suggested that variation in treatment may reflect underlying clinician preference influencing communication of treatment options. This seems a plausible explanation, especially in view of Schonberg and colleague's findings that the most influential factor affecting older women's breast cancer treatment decisions was the surgeon's recommendation [88]. Indeed, this study demonstrates multiple areas of variation in HCP opinion supporting this.

It is also important to recognise that not all older patients engage in SDM, with many preferring a more passive role [88, 278-280], and that encouraging a patient to take an active role in decision-making when they prefer a more passive role may increase anxiety and cause distress [295, 296], but may also reinforce the variation due to clinician preferences.

9.6. Impact of clinician preference on decision-making and treatment patterns

Treatment decision-making for older patients with operable breast cancer can be considered a complex process with many interacting components. These components can be divided into several categories:

- Patient clinical factors (such as comorbidity, age, cognition, functional status)

- Tumour factors (such as tumour size, nodal status, hormone receptor status)
- Patient intrinsic factors (also considered to be patient preference and previous experiences)
- Clinician factors (HCPs beliefs and opinions regarding the treatment of this population).

The first two, patient clinical factors and tumour factors, we can try and account for using case-mix adjustment as discussed above, but this does not appear to account for even half of the variation in treatment allocation of older breast cancer patients, as can be seen by the low pseudo R2 value of 0.31 within the DCE analysis, suggesting these factors account for only 31% of the treatment choice by HCPs. This is supported by the registry data, where there remained variability in surgery rates at hospital level despite adjusting for case mix.

Patient preference is difficult to assess, although a recent study has determined that lower rates of surgical treatment amongst older breast cancer patient are unlikely to be due to patient choice [375]. However patient preference and clinician factors are intricately linked. For instance, a patient presented with two treatment options may express a preference for one over the other; however a patient presented with only one treatment option may be unaware of the alternatives and therefore unable to express a preference. This differs from patient refusal to undergo surgery, which some HCPs in this study stated was the only circumstances under which PET was offered as a treatment alternative.

Additionally, as discussed above, patients rely heavily on the advice of their doctor which has been found to be the most influential factor affecting older women's breast cancer treatment decisions [88]. Therefore it is not just the options presented to a patient that may impact upon their choice, but the way in which the information surrounding treatment options are presented.

This study demonstrates that variations in clinician opinions are almost certainly contributing to the variation observed in the treatment of older women with operable breast cancer.

9.7. Limitations of the study

This study has a clear theoretical and methodology base but this approach is not without its challenges. The pragmatic grounding for the project has allowed the use of multiple methodologies best suited to answering the research question, the strengths and weaknesses of each of these methods have been discussed within the individual chapters. Limitations of the overall study are discussed here in broad terms.

9.7.1. Replication of findings

Every attempt has been made to demonstrate each phase in development of the project to allow other researchers to replicate the findings should they wish. Whilst we have not used validated instruments within some strands, in particular the questionnaire, the content was determined from multiple sources, including the prior qualitative interviews, literature review and feedback from experts within the field. In addition, this instrument was developed using recognised Likert style questions and assessed for psychometric rigour.

9.7.2. Population sampling

The use of different methodologies has allowed a variety of sampling methods within the study population. Although each sampling method has its weaknesses, these are offset by using multiple methods, each with their own benefits:

- **Registry analysis:** Cancer registry data allows analysis of large cohorts of women treated in everyday, normal clinical practice. Whilst data were only obtained from two of the UK's 11 cancer registration regions, all 23 960 new diagnoses of breast cancer in women over 70 years were analysed from an eight year period. However, it should be noted that these two regions have higher PET rates than other regions [73] which may potentially limit the generalisability of these results. Despite this, the population analysed represents a quarter of all breast cancer cases in the UK and the areas covered by these registries are demographically representative of the UK as a whole, making it reasonable to cautiously extrapolate these findings to the UK population generally.

- **Qualitative interviews:** Whilst the qualitative interview strand sampled only a small number of the target population, this provided a rich data source, enabling documentation of unique first-hand perspectives of HCPs that would be difficult to gather by any other method. In addition, purposive sampling of both surgeons and CNS's from units with high and low PET rates from right across the UK aimed to provide the broadest range of opinions. Findings from the interviews were then used to construct the questionnaire in order to better generalise the findings.
- **Questionnaire survey and DCE:** This strand was applied to all surgeon and nurse members of the Association of Breast Surgery, however the overall generalisability of the results is limited by the questionnaire response rate. HCPs, in particular doctors, are considered a problematic population from which to collect survey data [510] and response rates to questionnaire studies been shown to have fallen further in recent years due to increasing demands on HCPs to participate in research [511, 512] and the response rate of 40% is similar to other similar studies [128, 474].

9.7.3. Selection bias

Selection bias may be relevant within the study, particularly within the interview component where the participants were contacted via personal communication by the lead researcher (JM), however this was minimised by purposively selecting from units across the country and including individuals that were both known and not known to the researcher prior to the study.

In addition, research participants are a self-selected group and may potentially have different characteristics to those who did not take part [513]. Many of the behaviours and attitudes of interest to survey researchers correlate strongly with willingness to participate in research [514]. For instance, research participants are more likely to have an interest or be active in the area being studied [515-518] and may therefore have different practices from the rest of the non-sampled population.

9.7.4. Complexity of the problem

Decision-making in health care is a complex issue with many inter-related factors that need to be considered, and not all of them can be accurately measured or assessed. In this study, these factors have broadly been classified as:

- Patient clinical factors (such as comorbidity, age, cognition, functional status)
- Tumour factors (such as tumour size, nodal status, hormone receptor status)
- Patient intrinsic factors (also considered to be patient preference and previous experiences)
- Clinician factors (HCPs beliefs and opinions regarding the treatment of this population).

Although by using a variety of methods to approach the problem it can be examined more thoroughly, not all of these factors can be examined together. This is particularly relevant for the registry and DCE analysis where the results showed that factors other than those assessed in the case mix analysis are playing a part in treatment variation. Whilst variation in clinician preference is likely to account for some of this, there may be other factors involved that have not been identified or assessed, for example patient intrinsic factors, such as patient preference which is often cited as a reason for treating patient with PET [128, 369] and is one of the accepted reasons for doing so [127].

9.7.5. Improving the project

This study could have been further enriched by including a patient perspective on the decision-making process to better account for the patient intrinsic factors such as previous experience and preference. However this would have been difficult to account for within the current study components and would not have specifically improved the accuracy of the any of the results presented. Exploration of patient opinion on this subject forms another phase of work within the wider Bridging the Age Gap study which, together with this body of work, will bring us a step closer to understanding the complex relationship in the decision-making process between HCPs and older women with operable breast cancer.

9.8. Future work

This study has highlighted the need for more comprehensive guidelines for the treatment of older women with operable breast cancer. To this end, further research is required to determine the impact that patient factors (such as comorbidities, dementia, functional status) have on survival outcomes in both surgical and PET treatment groups. Ideally this would take the form of a randomised controlled trial (RCT) based on modern day practice using up-to-date surgical techniques and aromatase inhibitors. However a recent attempt at recruiting to such an RCT (the ESTEEM trial [342]) failed as patients wanted to be involved in their treatment choice and so were not happy to be randomised. The Bridging the Age Gap (BTAG) in Breast Cancer research project is a programme of study that includes a large, multi-centre non-randomised cohort study, collecting good quality patient, tumour and treatment data on women aged over 70 with primary operable breast cancer. To date the study has recruited over 1600 patients and will continue to collect prospective data for the next 2 years. This will allow the examination of the interaction between patient and tumour factors on survival outcomes in patients treated with both PET and surgery to hopefully address some of these questions. The aim of the BTAG study is to develop a decision-aid that will help both patients and clinicians tailor treatment towards the individual patient based on multiple factors.

In addition, it is important to examine the effect of patient opinion regarding both treatments themselves, and the provision of treatment choice in this situation. Further research is needed to identify whether patients would rather be offered a choice of treatments and be allowed to make their own decisions, even if their HCP deems one treatment may be inferior to another. It is also important to examine the impact of change in management and progressive disease on quality of life outcomes in patients treated with PET as there is little in the current literature pertaining to this. Importantly these studies would contain data on decision regret.

Finally, further research is needed to examine the influence of HCP opinion on patient decision-making. As variability in HCP opinion regarding the treatment of this patient population may be in-turn influencing patient decision-making by the level of information presented. Video recording of clinician-patient consultations at diagnosis would be the best way to monitor this interaction however would require substantial ethical consideration and would be difficult to determine whether the recorded practice was in line with true clinical practice.

Chapter 10: Conclusions

10.1. Conclusions

There are currently no definite answers about the best way to treat of older women with operable primary breast cancer. It is clear that this is a heterogeneous population, and older women presenting with a new diagnosis of breast cancer should be treated on an individual basis.

Surgical treatment does appear to be superior to PET in terms of local control and there is probably also a survival advantage favouring surgery for patients with a life expectancy more than 5 year. As such, fit and healthy older women should probably be treated according to standard practice, using the same strategies as are used in younger women, i.e. a choice of surgical treatment with the appropriate adjuvant therapies.

Very frail women at the extremes of age, or those with multiple significant co-morbidities, so that their predicted life-expectancy is significantly reduced, may benefit from treatment with PET. If PET is to be used, it should be reserved for patients with strongly ER positive cancers and an AI should be used in preference to tamoxifen where it is not contra-indicated. Letrozole appears to be the most effective of these in the literature to date. All women treated with PET should have regular clinical follow-up to assess the response of the primary tumour. If there are signs of disease progression then second-line hormone therapy or surgery under local or regional anaesthetic should be considered.

Currently, the exact guidelines regarding which patients may benefit from PET and which should have surgery are open to interpretation. UK healthcare professionals have a variety of opinions on which factors are important in determining who should be offered PET or surgery or both. The result is a wide variation in practice, resulting in a potential healthcare inequality. In view of the lack of definitive criteria, it may be appropriate to offer some patients a choice of treatments, in the process of shared decision-making, and allow the patient to consider the options and decided for them self. What is also clear, however, is that HCPs also vary as to whether they feel that patients should be offered PET as a treatment alternative and this is further compounding the variation of treatment across the UK.

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Appendices

Appendix 1: Abridged Bridging the Age Gap in Breast Cancer study protocol



Bridging the Age Gap in Breast Cancer:

Improving outcomes for older women.



Bridging the Age Gap in Breast Cancer: Improving outcomes for older women.

Study Protocol Version: 0.1

Date: 20th August 2012

MREC Number: Pending

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Section 3. Executive (Lay) Summary

The UK population is ageing with average life expectancy increasing from 50 years, 100 years ago to over 80 today. The level of fitness of older people is also increasing with many still healthy and fully independent in their 70s and 80s. Health technologies are also rapidly advancing with improvements in the survivability of health interventions such as surgery making them safe even for many people who would have been considered too frail 20 years ago.

Despite this, there is still a perception that once a person crosses the age threshold of 65 or 70 years they are classed as 'elderly' and often subjected to age bias in their medical care. These decisions are often non evidence based as little research has been done on older people to define optimal practice. In addition, research done in the fairly recent past may no longer be valid today due to the rapid changes in technology and the rapidly improving health status and life expectancy of our population.

In the field of breast cancer, age related practice variance is widespread. The gold standard of care for early breast cancer is surgical removal of the primary cancer, sentinel node biopsy of the axillary and adjuvant therapies which may include chemotherapy, trastuzumab, anti-oestrogens and radiotherapy. There is consistent evidence that older women are often denied surgery, chemotherapy, radiotherapy and trastuzumab based on the premise that there is no evidence of efficacy. It is known that cancer specific outcomes in older women with breast cancer are significantly worse than those in younger women and can no longer be simply attributed to competing causes of death.

In the case of surgery, up to 40% of older women do not get surgery for their breast cancer, with treatment being with anti-oestrogen tablets alone, known as primary endocrine therapy (PET). This type of treatment was shown to be effective in several trials in the 1980s, with the trials showing no survival disadvantage although rates of local control were sub-optimal. Life expectancy has moved on by almost 10 years since then and fitness levels have improved and surgical and anaesthetic techniques are much safer and yet many clinicians continue to use non surgical strategies in a significant proportion of women over 70.

Undoubtedly there are some older women for whom surgery is associated with significant risks and many older women have a preference for minimalist treatment for a variety of reasons. It is therefore appropriate to use anti-oestrogens in this way in some older women. The problem we have is that there is no guidance on the characteristics of older women which suggest they will do better with surgery or PET.

In a similar vein, chemotherapy is part of the gold standard of care for many women with aggressive, oestrogen receptor (ER) negative, breast cancer. However the rate of chemotherapy usage in older women is very low, with a lack of research evidence to support its use and concerns about its safety in older women. Older women with these more aggressive cancers are often denied this treatment. Clearly there will be some women for whom chemotherapy will be inappropriate and others for whom benefit may be gained.

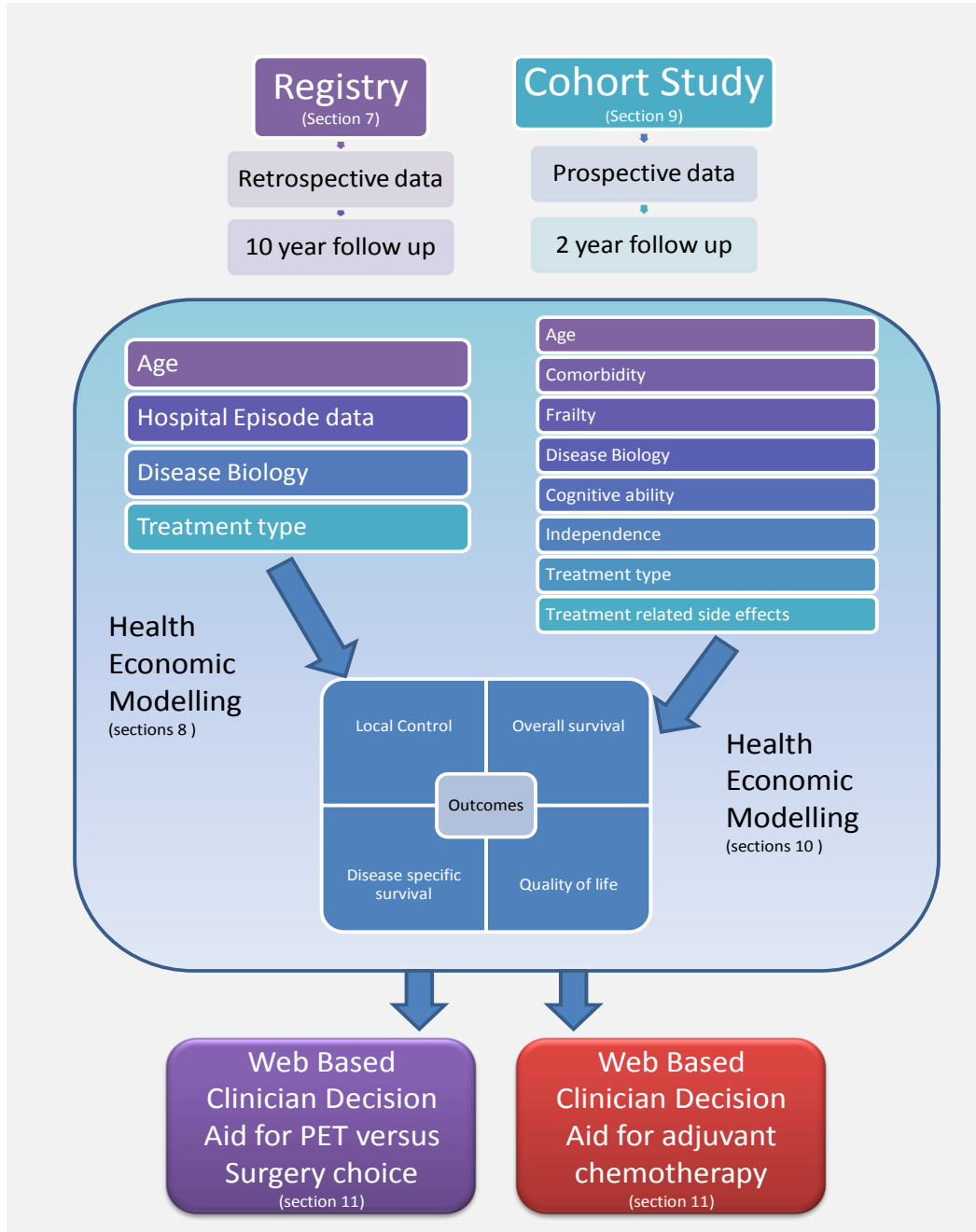
The Age Gap study will use state of the art statistical and modelling techniques to determine the age, comorbidity, frailty and disease characteristics of women over 70 with early breast cancer to provide guidance on 2 primary questions:

1. What are the personal and cancer characteristics of women who can be safely advised that surgery is unlikely to confer any advantage for them?
2. What are the personal and cancer characteristics of women who should be advised to have adjuvant chemotherapy after surgery?

A preliminary disease and outcome statistical model will be derived using pre-existing data from the UK primary breast cancer registry held by the West Midlands Cancer Intelligence Unit (WMCIU). These data have certain recognised areas of weakness, in particular relating to the completeness of and quality of comorbidity data (limited to the rather crude Hospital Episode Statistics (HES) data) and contain no data on frailty and independence measures which are an important determinant of life expectancy in older people. In addition, staging data may be less accurate in women treated non surgically as there will be no post-operative pathology data returns. To overcome these limitations a UK wide data collection exercise to gather detailed data on older women, their primary disease, health status and treatment details and medium term outcomes will be performed. These new data will be used to revise and validate the preliminary statistical model. The statistical models will also be used to develop a health economic model to estimate long-term health outcomes and costs for different intervention strategies.

The final stage of the project will be to use the model to develop a web-based algorithm to support clinicians in decision making related to older women with breast cancer which will be responsive to their personal and cancer characteristics.

Section 4. Study Algorithm



Section 5. Background to the study

5.1 An ageing population

The developed countries of the world are currently facing a growing crisis caused by their ageing populations. Life expectancy has increased by 30 years over the course of the 20th century, from 50 at the turn of the century, to 80 by the end of it and predictions are that children born today may have an average life expectancy of 100¹. Whilst much of the early gains in this trend were due to improvements in infant and child mortality rates, the age group where the gains are now being made are in the elderly, which represent the most rapidly increasing population group in developed nations². The quality of this increased life expectancy is also improving^{1,3} in part because of improved disease prevention, but also because many chronic diseases are now better controlled and diagnosed: the elderly therefore live longer even in the presence of chronic health problems.

This changing population age distribution means that determining best practice using trial data that are more than 20 years old may be inappropriate. The heterogeneity of the health status of this group is significant, with some 75 year olds running marathons, whilst some are too frail to live independently. It is therefore vitally important that our age limits for standard practice remain fluid and responsive to the changing demography of our population. This can only occur if chronological age and health status are decoupled and we continually research at the new boundaries of practice.

5.2 Breast cancer in the elderly

Breast cancer is the most common cancer to affect women with 44 000 diagnosed each year (UK Office for National Statistics) and some 12 000 die of the disease⁴. One third of all breast cancers occur in women over the age of 70, some 13 000 women in the UK. Breast cancer in older women tends to have a slightly different disease biology than in younger women, with higher rates of oestrogen sensitivity^{5,6}, lower rates of Her-2 receptor expression⁵ and a slower growth rate⁵. Balanced against these positive features, older patients more frequently present with more advanced disease⁷: the size of the primary tumour is larger^{8,5,7} with increased rates of locally advanced⁹ and metastatic disease^{10,11}. This may relate to the discontinuation of routine breast screening, reduced breast cancer awareness in older women¹²⁻¹³, and lower rates of regular self examination¹⁴.

The clinical significance of breast cancer is proportionately less in older women as breast cancer specific mortality is overtaken by other cause mortality once a woman is in her early 80s. So whereas breast cancer causes 73% of deaths in breast cancer patients in their early 50s, it is responsible for only 23% of deaths in women in their mid 80s⁵. This is not due to the innate features of the cancer itself, but to the rapidly rising mortality rates from other causes. Age, co-morbidity and most importantly frailty interact with the features of the breast cancer in a way which significantly affects disease outcome and treatment related problems. It is difficult to disentangle this interaction but there is convincing evidence that women over the age of 80 have a higher risk of dying of their breast cancer than women in their 70s, which may be due to sub-optimal treatment⁷. Clinician awareness of these interactions would enable treatment to be optimised to prevent over- or under-treatment.

Currently there are several tools to assess co-morbidity: some more complex than others. The Comprehensive Geriatric Assessment (CGA^{15,16,17}) is detailed but is time consuming and requires specialist training to administer. Simpler tools have also been evaluated such as the Activities of Daily Living Score (ADL), Instrumental Activities of Daily Living Score, (IADL) or the Charlson Index, which may have predictive value in terms of morbidity and mortality in the older cancer patient population^{15,18,19}. There is an urgent requirement for high quality studies which link simple, well validated co-morbidity assessments with disease biology, life expectancy and treatment type in this age group. Recently, web-based co-morbidity tools have started to appear but most are not geared to the complex interactions of age and multiple co-morbidities which affect the older patient, (Adjuvant On-Line²⁰ or the Prognostigram²¹).

5.3 Surgical treatment of breast cancer in the elderly

As has previously been stated, for some older women, the diagnosis of breast cancer poses little or no threat to life due to other, co-existent, disease processes. These same disease processes may also increase the morbidity and mortality associated with some of the treatments for breast cancer, altering the risk to benefit equation away from the therapy. The need for surgery for some older women is questionable as disease control may be achieved simply by use of anti-oestrogen drugs such as tamoxifen, (primary endocrine therapy, PET). Up to 90% of breast cancers in older women are oestrogen sensitive^{5, 6}, and therefore respond very well to anti-oestrogens. This has the advantage that the woman may avoid the need for anaesthesia with its risks of cardio-respiratory complications and the avoidance of the physical and psychological morbidity of surgery.

A Cochrane review of the randomised controlled trials (RCTs) evaluating the role of surgery versus endocrine therapy alone in older women with operable breast cancer has been undertaken²². Although the reviewed trials were flawed by modern standards, meta-analysis demonstrated no survival difference between the 2 treatment groups. Only one study demonstrated any survival benefit and this was only seen at long-term (12 year) follow up²³. There was however a clear benefit in terms of local disease control for those women who had surgery. An update of one of the earliest of these trials which compared surgery alone with Tamoxifen alone, showed no survival advantage to surgery after 28 years of follow up when all trial participants had died. This trial is flawed by modern standards however because no adjuvant Tamoxifen was given to the women in the surgical arm which would have given a potential survival advantage to the surgical arm patients and no Oestrogen Receptor (ER) testing was done on tumour tissue which is obligatory today²⁴.

Studies by our research group have demonstrated a high degree of satisfaction with treatment in older women treated by both surgery and PET²⁵. Factors cited in favour of PET are avoidance of hospitalisation and surgery, a desire to retain independence, fear of anaesthesia and a desire for minimal disruption to life²⁵.

Since these randomised trials were performed the practice of PET has moved on: all women are now tested to ensure they have oestrogen sensitive tumours and we now have a new range of anti-oestrogen drugs, the aromatase inhibitors, which are more potent than tamoxifen in all treatment settings^{26 27 28 29}. PET may therefore be more efficacious if potential candidates are selected appropriately.

There has been a wide variation in practice in the UK where some regions have up to 40% non-operative treatment rates for older women with breast cancer compared to other areas where the rate is only 10%³⁰. Clearly some women in the low surgery rate regions will be inappropriately denied surgery and run into problems later requiring a change of management. In contrast, in the high surgery rate regions many women may have been subject to the morbidity or even mortality of surgery for no benefit.

The ESTEEM trial set out to provide clear guidance regarding selection criteria for either surgery or PET, but closed early due to patients expressing a treatment preference rather than accepting randomisation³¹. It is unlikely therefore that the data we need to provide guidance on selection criteria for PET versus surgery will ever be acquired via an RCT. The present study will therefore gather data via cancer registries and a cohort study of UK older women treated with either surgery or PET, adjust for selection bias between groups and use statistical and modelling techniques to determine the variables which predict an optimal outcome from PET or surgery.

5.5 Choice of a Cohort Study Design

The pre-eminence of the RCT in the hierarchy of research evidence was called into question recently by Professor Sir Michael Rawlins, Chairman of NICE³⁶. He suggested that there should be acceptance of data from more diverse evidence sources, including observational and cohort studies to reflect the fact that the RCT may be inappropriate to answer all types of research questions.

There are precedents for such studies and the high quality data they can generate: The Adjuvant on Line system³⁷²⁰ and the Nottingham Prognostic Index³⁸ were not based on RCT data but cohort data from large data sets. This study will obtain high quality, contemporary, population specific data from National Cancer Registry sources to develop a preliminary disease model, and then test and validate this model using data from a UK wide, prospectively collected, cohort study. The cohort study will also allow us to collect Quality of Life (QoL) data and more detailed health economic data to validate the model. The current management of these patients across the UK creates very large subgroups or cohorts which can be compared (PET versus surgery, chemotherapy versus no chemotherapy). Comorbidity indices can be calculated from HES data which is available via the cancer registries and also supplemented by more detailed data from the cohort study. Unlike an RCT where follow-up for 5 or even 10 years is needed to determine outcomes in a disease like breast cancer where events may occur over many years, this technique of meshing together recent retrospective data with data from relatively short term follow-up from a cohort study will allow us to predict outcomes, make data available more quickly and keep costs to a minimum. This approach has recently been used comparing the Adjuvant-on-line outcome prediction tool with a large Dutch Cohort study and a high level of correlation was found³⁹. Therefore by use of an accurate model based on UK population based outcome data we can use surrogate end points to predict longer term outcomes from our cohort study data. In effect, the study plans to conduct a 'virtual RCT'.

Section 6. Aims and Objectives

6.1 Primary Endocrine Therapy

1. To determine the patient and cancer characteristics which predict whether Primary Endocrine Therapy (PET) is a safe and effective breast cancer treatment in older women with ER+ breast cancer by means of statistical modelling based on both retrospective registry data and prospective cohort study data.
2. To develop a simple scoring system, based on co-morbidity, dependency, age and tumour characteristics, which will enable prediction of those women best treated with PET or surgery.
3. To develop a web-based algorithm based on the developed model to aid clinician decision making.

6.3 Secondary Objectives

1. To determine post-operative surgical outcomes in older women undergoing surgery for breast cancer and correlate outcomes with age and co-morbidity.
2. To determine chemotherapy adverse events in older women undergoing adjuvant chemotherapy for breast cancer and correlate these with patient age, comorbidity and frailty.
3. To determine QoL outcomes in older women undergoing surgery, chemotherapy or PET for breast cancer and correlate outcomes with age, comorbidity and frailty.
4. To determine the factors underlying treatment decision making in health care professionals relating to older women with breast cancer.

6.4 Further Objectives

1. Data from this study will be made available to collaborators developing a patient Decision Support Instrument (DSI) to facilitate patient decision making by enabling detailed, patient specific outcomes to be predicted. (This will be part of a separate ethics application).
2. The study will request ethics approval for long-term access to the cancer registry data and outcomes of all women enrolled in the cohort study to permit further longer term analysis of outcomes and add value to the project.

6.5 Translational studies

Patients enrolled in the cohort study will also be asked to provide permission for future access to archived tumour samples by study researchers. It is intended that once medium and long-term disease outcomes and treatment responses are collected for this cohort of patients, the project team will apply for further funding to permit analysis of more detailed tumour biological markers to determine how these correlate with outcomes.

Section 7. Registry Data Collection

7.1. The West Midlands Cancer Intelligence Unit

The West Midlands Cancer Intelligence Unit (WMCIU) is the National Cancer Intelligence Network (NCIN) lead registry for breast cancer. It provides data on 4,000 cases per year for the West Midlands region (population 5.3 million) and undertakes annual collation of all UK registry data on breast cancer through the NHS Breast Screening Programme and the Breast Cancer Clinical Outcomes Measures Project (BCCOM Audit). The WMCIU data quality is excellent. Data back to the 1980's includes date of birth, ethnic origin, cancer stage (NPI), grade of tumour, laterality, ER status (from 2002), Her2 status (from 2004) method of diagnosis, treatment type (surgery, radiotherapy, chemotherapy, hormone therapy, other), date of diagnosis, recurrence rates and mortality including date and cause of death.

In addition the registry collects linked Hospital Episode Statistics (HES) Data (NHS information about inpatient and outpatient activity) for each patient with cancer. HES data can act as a surrogate indicator of co-morbidity levels⁴⁰, permitting derivation of a proxy Charlson Index¹⁹ based on the International Classification of Diseases (ICD) codes for each individual's admissions to hospital. In the first stage of model development HES data will be used as a proxy for co-morbidity. The quality of the HES data will also later be compared with actual comorbidity data derived from the cohort study (see section 9).

7.2. Data items

The WMCIU database will be interrogated for the following data items between 2004 and 2011 on all UK women with breast cancer diagnosed after 70 years of age:

Cancer Characteristics	Patient Characteristics	Treatment
Primary Size (mm)	Age at diagnosis	Surgery type
Nodal status	Means of diagnosis	Timing of surgery
Number of positive nodes	In Patient HES Proxy Charlson Index	Primary endocrine therapy
Metastatic disease	Other HES co-morbidities	Chemotherapy

Grade (1,2 or 3)	Survival (overall)	Radiotherapy
ER status	Cause of Death	Trastuzumab
Her-status	Disease free survival	Death or 30 day readmission due to treatment
Derived NPI	Recurrence/progression	Treatment for recurrence
UICC stage	Out-patient HES data	

A more comprehensive list is provided in Appendix 6.

It is expected that data for patients whose cancers were detected through screening will have more complete data, as will cases whose data has been checked as part of the BCCOM audit. In particular, the data from the recent recurrence and metastatic disease audit will be closely examined to estimate missing or inaccurate data in previous time periods.

Data will be checked for completeness and compared with published data series to validate them.

In addition, data will also be collected, from women with breast cancer in the 50-70 age range. This will serve as a comparator for chemotherapy usage rates in the non-elderly population, the complications, indications and types used.

The data will then be used to develop a model of breast cancer outcomes according to patient, disease and treatment characteristics in older women.

7.3. The Cognitive Function and Ageing Dataset (CFAS)

The model will incorporate the MRC Cognitive Function and Ageing (CFAS) Dataset⁴¹. The CFAS study investigated long-term cognitive decline, co-morbidity and mortality in a sample of over 18 000 people in the UK aged over 65 years. The project has approved access to this dataset. This dataset recorded co-morbidity using a number of different measures and this will enable the model to estimate how these co-morbidity measures affect life expectancy. As well as demographics, the dataset has longitudinal information on cognitive and functional ability. The comorbidities collected in the CFAS data-set include assessment of the extent of suffering from angina, peripheral vascular disease (intermittent claudication), the extended mental state exam (EMSE), the Cambridge Cognitive Examination, Activities of Daily Living (ADL)⁴², Instrumental Activities of Daily Living (IADL) scores⁴³, the Modified Townsend Disability Scale, the Blessed Dementia Scale, the Hachinski Ischaemic Score, and a Mini-Mental State Examination (MMSE)⁴⁴, as well as social class/employment, the Townsend Deprivation Index and other demographic data. Together these data provide information on clinical, cognitive and functional health status. Recent work by the CFAS collaboration has included modelling of life expectancy with and without specific diseases⁴⁵ and modelling trends in long-term population size and structure⁴⁶.

Merging the retrospective data from WMCIU and CFAS and our planned prospective cohort study, we will have access to a comprehensive dataset which will be used to predict survival and other cancer outcomes in older women.

Section 8. Statistical Model Development

8.1 Model design

We will fit various risk models to the time to breast cancer recurrence, breast cancer and non-breast cancer death, employing relevant covariates, including treatment modality, from the two datasets. The cancer registry data sets provide the data to model time to breast cancer recurrence and time to breast cancer mortality. The CFAS dataset

will separately provide models of all-cause mortality with covariate adjustment for co-morbidities. The central aim is to produce models which will enable detailed analysis of the competing risks of breast cancer and other causes of mortality.

Observational data typically suffer from selection bias and do not directly provide unbiased estimates of treatment effect. Patients are not allocated to treatments at random and their actual treatment received depends on other factors. In the case of breast cancer, older women or those with higher levels of co-morbidities may be less likely to want to undergo surgery or receive chemotherapy. Therefore, the observed and unobserved baseline characteristics of the patients will not be balanced between the PET and surgery treatment groups or the chemo or no-chemotherapy groups. Another factor affecting treatment allocation is the treating physician and/or centre at which the patients present themselves. This is known to vary significantly.

Statistical methods for dealing with selection bias in the analysis of observational data include matching, stratification, and/or covariate adjustment based on patient characteristics known before assessments were taken. The aim of the analysis is to obtain an unbiased estimate of the treatment effect that might have been observed if patients had been randomised to treatments.

The statistical model will be built to adjust for the imbalances in patient characteristics and the non-random allocation to treatment. This will be done by modelling allocation based on observed covariates using propensity scoring methods as well as adjusting for the effects of other covariates directly in the model. We will explore the use of propensity score methods by including as many baseline characteristics in the model as possible.

The recognition that treatment effects are biased leads to a subjective judgement about the extent of the bias that might not be fully captured with available covariates using the propensity score approach. In the first stage, we will have addressed the availability of baseline characteristics in relation to known prognostic effects.

8.2 Model Analysis

We will employ a Bayesian approach building on the models proposed by Basu and colleagues⁴⁷ to undertake statistical modeling to predict cancer outcomes and how these interact with frailty, age and co-morbidity. The survival curves will provide both mathematical and visual descriptions for an individual woman with specified covariates. Most importantly, we will also compute competing risk probabilities over time e.g. the probability that by 2 years post-treatment she is either recurrence-free, has local or metastatic recurrence or has died from breast cancer or non-breast cancer causes. Depending on the form of the survival curves these computations may be achieved analytically or via Monte Carlo sampling from randomly generated event histories for the woman concerned given the competing risk curves. Thus, we will examine co-morbidity and frailty thresholds for women beyond which surgery may be of little or no benefit in women with ER+ cancers or in whom chemotherapy may confer no benefit in women with ER- cancers. This will provide the statistical input to the web-based clinical decision algorithm.

8.3. Modelling Software

The statistical package 'R' will be the primary tool used for the analysis of the retrospective cohort data and for the modelling of breast cancer and health economic outcomes. The package OpenBUGS will be used for any Bayesian analyses which require Monte Carlo Markov Chain (MCMC) procedures. Other packages may be used for specific analyses where appropriate.

Section 9. Cohort Study

9.1 Research Governance

9.1.a. Ethics

Research Ethics Committee approval will be obtained for all sites registered for the study. A Mental Capacity Act (MCA) compliant ethics committee will be used for the study.

9.1.b. NHS Research and Development Approval

R & D site specific approval will be obtained for each site registered for the study.

9.2 Trial Design

A non-randomised, pragmatic, cohort study.

9.3 Sample Size

9.3.a. PET versus surgery analysis

The study aims to recruit from multiple UK centres. For this analysis women over the age of 75, who might be deemed suitable for either PET or surgery by their clinician, regardless of the treatment they ultimately receive will be eligible if they have ER+ cancers. Women over 75 make up 25% of the breast cancer population so each centre will see 75 per year, of which 85% will have ER+ cancers (64 per year). Over 2 years, if we have a minimum of 20 recruiting centres, this will give us a potential population of 2560 patients.

As the study is very low risk, with no change of management and a simple (and optional) requirement to complete QoL questionnaires, we anticipate that recruitment rates will be high.

9.4 Recruitment

Centres and patients may **choose** one of 3 levels of participation (none of which involve any change of management or intervention other than completion of questionnaires):

9.4.a. Full participation

9.4.b. Partial participation

Women will be asked permission for data collection, including a research nurse completed baseline health questionnaire which may be derived from the case notes, but will not be asked to complete any of the above questionnaires.

9.4.c. Data collection only

For women with significant cognitive impairment in the opinion of their treating clinician (usually formally classified as a MMSE of less than 18, although this will not be formally measured in these individuals), next of kin or carers will be asked to assent to data collection only, including collection of baseline health status data from case notes, proxy completion of some of the health questionnaires (IADL, ADL, Charleson), long-term survival outcomes from the cancer registry and archival tissue access. A specially adapted relative or carer assent form and modified Patient Information Sheet (PIS) will be used for this purpose (PIS in Appendix 8 and assent for in appendix 10).

Data items to be routinely collected for all 3 groups of patients will include: cancer type, grade, nodal status, tumour size, oestrogen, progesterone and Her-2 receptor status, treatments and outcomes (overall and disease specific survival, disease free and progression free survival, whether a change of management was required). In addition, in women on PET the treating clinician will assess the primary tumour response based on the RECIST Criteria⁵⁶.

All levels of participation will involve requesting permission for access to stored tumour tissue (archival only: no new biopsies will be required).

The study also request ethics approval for long-term access the linked records held by the cancer registries for long-term follow up purposes of all participating patients.

A summary of visits and the data items to be collected for each level of participation and at each time point is shown (in section 9.18), the Visit Schedule.

9.5 Participating UK Breast Units

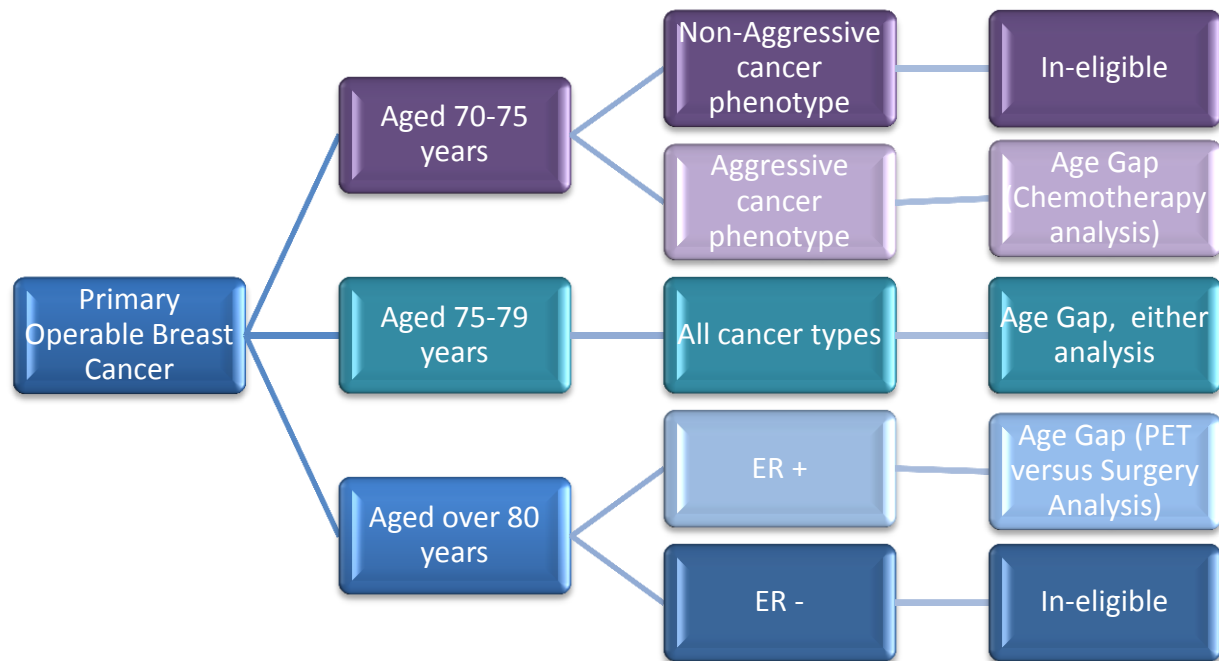
The following centres have agreed to participate in the study:

No.	Town	Hospital	Local PI	Annual no. breast cancers cases
1	Sheffield	Royal Hallamshire Hospital	Ms Lynda Wyld	500
2	Leicester	Glenfield Hospital	Ms Anne Stotter	800
3	Nottingham	City Hospital	Ellie Gutteridge?	
4	Nuneaton	George Eliot Hospital	Mr Medy Tsalic	
5	Whiston	St Helen's and Knowsley NHS Trust	Professor Riccardo Audisio	
6	Hull	Castle Hill Hospital	Mr Peter Kneeshaw	
7	Dartford	Darent Valley Hospital	Ms Seema Seetharam	
8	Newcastle	Royal Victoria Infirmary	Mr Richard Bliss and Mr Andy Griffiths and Professor Tom Lennard	
9	Weston Super Mare	Weston General Hospital	Mr Nick Gallegos	
10	Chesterfield	Chesterfield Royal Infirmary	Mr Steve Holt	
11	Coventry	University Hospital	Mr Martin Lee	
12	Cardiff	University Hospital of Wales	Professor Robert Mansel	
13	Bristol	Frenchay Hospital	Mr Mike Shere	
14	Milton Keynes	Milton Keynes NHS Trust	Ms Amanda Taylor	
15	Dundee	Ninewells Hospital	Professor Alistair Thompson	?include as need sep ethics
16	Southend	Southend Breast Unit	Mr Neil Rothnie	
17	Plymouth	Derriford Hospital	Mr Roger Watkins	
18	Liverpool	Liverpool University Hospital	Mr Chris Holcombe	
19	Derby	Derby Royal Infirmary	Mr KL Cheung	500
20	Grantham	Grantham and District	Mr AK Modi	
21	Scarborough	Scarborough Hospital	Sister Alison Ames, (Oncology)	

			Research Nurse)	
22	Wakefield	Pinderfields Hospital	Mr Jit Parmar	
23	Reading	Royal Berkshire Hospital	Mr Stephen Courtney	
24	Doncaster	Doncaster Royal Infirmary	Ms Clare Rogers	450
25	York	York Royal Infirmary	Ms Rana Nasr	
26	London	Guy's Hospital	Mr Michael Douek	
27	Dudley	Russells Hall Hospital	Mr Paul Stonelake	
28	Birmingham	Queen Elizabeth Hospital	Ms Adele Francis	
29	Walsall	Manor Hospital	Ms Marlies Heitmann	
30	Stoke on Trent	University Hospitals of North Stafford	Mr Robert Kirby	
31	London	King's College Hospital	Professor Arnie Purushotham	
32	Leeds	St James Hospital	Mr Kieran Horgan	
33	Oxford	Radcliffe Royal Infirmary	??	
34	Bristol	University Hospitals Bristol	Ms Zoe Winters	
35	London	St Bartholomew's Hospital	Professor Andrew Baildam	
36	Rhyl, North Wales	Glan Clwyd District General Hospital	Mr Tibor Kovacs	
37	Rotherham	Rotherham District General	Mr Inder Kumar	150
38	Barnsley	Barnsley District General Hospital	Ms Julia Dicks	150
39	Truro	Royal Cornwall Hospital	Professor Philip Drew	
40	Southampton	University Hospital	Mr David Rew	

9.6 Eligibility Criteria

The algorithm below is a simplified schematic of the broad eligibility criteria for the different components of the cohort study.



9.6.a Inclusion Criteria

- (1) Female
- (2) Aged over 70 years of age at the time of diagnosis of cancer
- (3) Primary operable (TNM categories: T1, T2, T3, N0, N1, M0; please refer to appendix 3 for further details) invasive breast cancer (core biopsy or diagnostic incision biopsy)
- (4) Tumour ER and Her-2 status available and categorised according to accepted scoring systems e.g. H score⁶ or Allred score⁵⁷ for ER and for Her-2, IHC score 1-3 plus FISH testing if IHC equivocal.
- (5) Ability to give informed consent if considering full or partial trial participation (see below).
- (6) Willing to complete the questionnaires for the additional trial evaluations if considering full trial participation.
- (7) If suitable for data collection only, the patient does not need to give consent but participation in the data collection exercise should be agreed and assented to by their next of kin, friend or carer. (Appendix 10 for Assent form).
- (8) Women aged 70-75 are only eligible for the chemotherapy analysis and therefore will be recruited post operatively once they are known to have breast cancer which fulfils any of the following 3 criteria (based on those of the ACTION Trial) suggesting a high risk of relapse (~30% at 10 years).
 - Her-2 positive disease (IHC 3+ or IHC 2+ with +ve FISH testing) or
 - ER- disease, (Allred score of 0-2, H score of <50/300) or

- High risk ER+ disease (grade 3 with 4+ positive nodes).

(9) Women aged over 80 are only eligible for the PET versus surgery comparison (rates of chemotherapy use in this age group are negligible, Alistair Ring, personal communication). They are only therefore eligible if they have ER+ tumours (Allred score ≥ 3 or H score $>50/300$).

(10) Women aged 75-79 are eligible for either arm of the study and may be invited to participate regardless of tumour biology and will be included in the analysis depending on their treatment pathway.

9.6.b. Exclusion Criteria

- (1) Disease unsuitable for surgery e.g. inoperable or metastatic disease.
- (2) Multifocal or bilateral invasive breast cancer.
- (3) Previous invasive breast cancer.
- (4) There is no restriction for people who are unable to speak English. Translation of study documents and translators will be undertaken by recruiting centres if required.
- (5) For patients considered for the PET versus surgery comparison, use of concurrent Hormone Replacement Therapy (HRT) or therapy with any other oestrogen containing preparation is an exclusion criteria, unless treatment is discontinued for 4 weeks before the study starts.
- (6) There is no restriction for any co-morbidity or frailty as the study aims to capture data on management and outcomes in these cases.
- (7) Patient without capacity being considered for the data collection only arm of the study but for whom there is no consultee available.

9.7. Policy relating to non-English speaking participants

Data from the 2001 UK Census show that UK wide ethnic minorities make up 7.6% of the total population. However, unlike the majority white population where 16% are over the age of 65, this percentage is much less in minority ethnic groups with less than 5% of the population being in the over 65 age group. By these figures, the percentage of over 65s of ethnic minority origin will be approximately $1/3^{\text{rd}}$ of the percentage in the white population, equating to about 2%. This figure drops still further in the over 70 age group. This lack of ethnic diversity in the older age groups is partly a result of the timing of the main migrations from different international areas and is highly variable between areas of the UK. For those areas with significant ethnic minority population groups we will offer to provide specific translations of PISs and consent forms and support the cost of 'Language Line' telephone translation services for research consultations. The policy of the Trial Management Group (TMG) is to be inclusive of minority ethnic groups at a level representative of population norms. However the small numbers will inevitably mean that sub-group analysis by ethnicity is unlikely to be possible and will not be part of the statistical analysis plan.

9.8. Policy related to women with reduced cognitive capacity

One of the key reasons for undertaking this research is to ensure that all older women are given access to optimal treatment for their breast cancer which takes into account their age, health status, tumour characteristic and

personal preferences. One of the major disease states that affects older people is cognitive impairment, which will affect a significant percentage of women in this age group. Severe cognitive decline is a major determinant of life expectancy and therefore is a critical factor to take into account when assessing optimal treatments. Moderate degrees of cognitive impairment may influence perceived ability to give informed consent to research but is still compatible with a reasonable life expectancy and therefore treatment optimisation is of great importance. There has been very little research to study cancer of any sort in people with cognitive decline due to the perceived difficulty of obtaining consent. This group of people are therefore excluded from research and we have little or no idea how they should be best treated.

The study will try to ensure that older women with cognitive impairment are offered access to this research. The 2005 MCA⁵⁸ sets out clear guidelines for when and how researchers should approach this issue. There are 3 tests to apply to determine if it would be appropriate to include people lacking capacity in the research. The criterion relevant to this research is:

‘That the research will serve to increase knowledge of the cause, treatment or care of people with the same or similar condition and that the risks to participants will be negligible, with no significant interference with their privacy of freedom of action’.

For women in whom there is doubt about capacity, as mandated by the MCA, we will take steps to ensure that participants are given the opportunity to comprehend the study and if it is then established that they do not have capacity to do so we will identify a personal consultee (a family member or friend) who is prepared to act on their behalf. This project will not use nominated consultees if there is no available personal consultee.

These are defined as followed for the purpose of this study⁵⁸⁻⁵⁹:

- **Personal consultee:** someone who knows the person who lacks capacity in a personal capacity who is able to advise the researcher about the person who lacks capacity’s wishes and feelings in relation to the project and whether they should join the research (section 32(2)). They may be either of the following:
 - a family member, carer or friend
 - an attorney acting under a Lasting Power of Attorney (LPA)
 - a court appointed deputy, provided that they had a relationship with, or personal knowledge of, the person lacking capacity before their appointment as deputy (for example, a deputy could be a family member).

The personal consultee must not be someone who is caring for the person who lacks capacity or is interested in their welfare in a professional capacity or for remuneration. Remuneration does not cover family members receiving some of the person’s pension or other benefits as a payment towards their share of the household expenses.

In accordance with the general principles of the Act, the researcher must make every effort to take into account the wishes of the person who lacks capacity about whom to consult (e.g. their partner, or a particular friend or carer) and to act in accordance with any relevant previous statement or wishes, however made, including non-verbal forms of communication. Depending on the nature of the research, it may be possible to establish a person’s general wishes and feelings, for example if they experience diminishing or fluctuating capacity.

A number of people may be capable of acting as a personal consultee, but they should be someone whom the person who lacks capacity would trust with important decisions about their welfare. Usually it will be someone with a close personal relationship with the potential subject, for example their next of kin, spouse or partner (including same-sex partners), adult child or parent. Other relatives or a close friend or past carer may be considered. If a potential consultee does not feel able to take on the role, they may suggest that someone else takes on the role.

The personal consultee may withdraw the patient's participation at any time and if, at any future date the participant expresses a wish or indicates by showing distress that they do not wish to be involved, their participation will be terminated.

The study will involve the completion of a few simple questionnaires by women who are cognitively able to complete them but for women without such ability, the study will be purely an observational/data collection exercise which will expose them to no risks. The treatment offered in the cohort study will be normal care. It is likely that most of the women with severe cognitive decline will be offered PET and whilst this will be a source of bias, this group's outcomes with PET have never been studied to determine whether this approach is satisfactory. We will be able to undertake a planned subgroup analysis of women with cognitive decline as a result of this data which will be a unique and very valuable resource.

Given the low risk and burden of this study to participants, consultee agreement is reasonable in those who do not have the capacity to give consent. It is also necessary to include the non-statutory carers of these patient participants as carer participants. Figure 2 shows the recruitment algorithm to be used depending upon the presence or absence of capacity to consent to the study, and the presence or absence of a carer.

The researcher will have primary responsibility for assessing the capacity of the individual to participate in research, according to the 2005 MCA and under the direct supervision of the local investigators and the overall supervision of the Chief Investigator of the project. The researchers will have a health professional background and will be fully trained in assessing older people, and compliant with ICH Good Clinical Practice (GCP) recommendations. The researcher will be informed by the clinical teams of all necessary and appropriate issues and information regarding the participant.

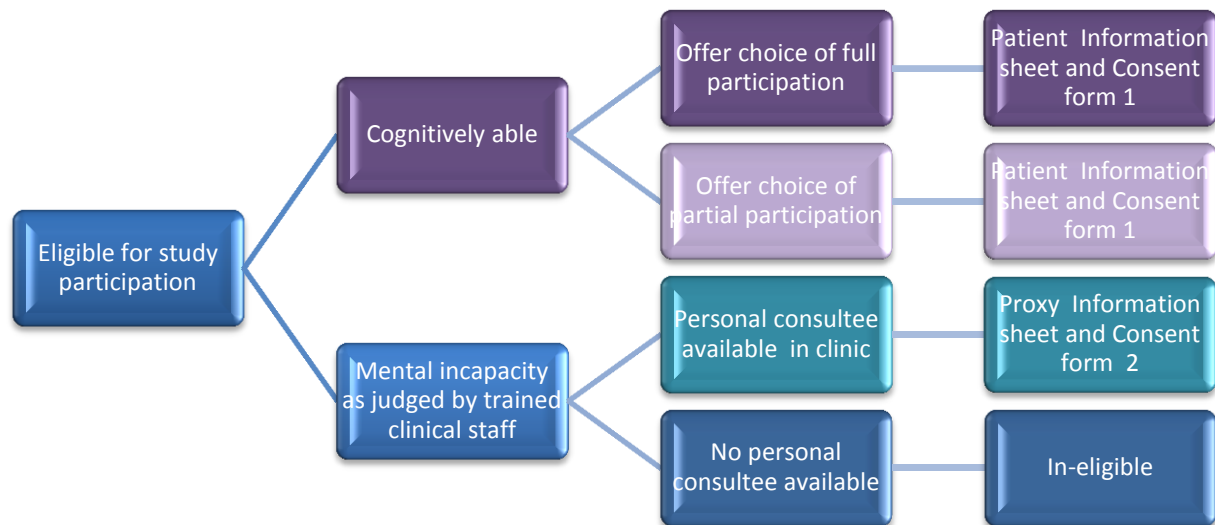
Patients who do not have capacity to give consent and have no consultee present will be excluded.

All participants will be given study information material, including those recruited using the consultee procedures; copies will be provided to consultees or next of kin as appropriate.

9.9 Loss of capacity during the research project

Because of the age group under study for this project, it is possible that some study participants may lose capacity during the follow up period. The following arrangements will be made once it becomes known that the person has lost capacity. Schedule 2 of the Regulations (MCA: Loss of capacity during a research project, 2007) sets out the requirements to identify a consultee for the patient (as above). That person should be provided with information about the project and with information on the nature of the consent given by the participant when they consented to participate.

The role of the consultee is similar to that in normal research situations. They must advise on whether the research subject would want to allow samples or data collected before loss of capacity to continue to be used in the study. The fact that the person who lacks capacity had originally consented to join the research project, and the extent to which future incapacity was considered at that time, will be important aspects to draw to the attention of the consultee. However, the researcher must take due heed of any advice from the consultee that continued involvement in the study would be contrary to the wishes of the person who lost capacity.



The versions of the PISs and consent forms are contained in appendices 8 and 10. Differentiation between full and partial participation will be achieved by means of a tick box on the consent form agreeing to complete the questionnaires, which is clearly noted to be optional for all participants.

9.10. Screening

Prior to study entry, each patient's inclusion and exclusion criteria must be checked.

The ER status of the tumour must also be known before study entry is considered to ensure they meet the criteria for either the PET or the chemotherapy options. Patients considered for the chemotherapy comparison may be considered after definitive surgery when full histology is available.

Staging investigations are not required as part of the study protocol, but if indicated clinically, patients should not be considered for trial entry until staging investigations show them to be free of metastatic disease.

9.11. Patient Invitation

Patients will be invited to participate by the Consultant Breast Surgeon or Consultant Oncologist or an appropriate delegated individual. A full verbal explanation of the trial and Patient Information Sheet will be provided by a

member of the trial team at site (medical staff and research nurses with up to date GCP training) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the study.

In order to reduce the burden of visits for these older women, and in view of the low impact of the trial which involves no change of management and simple completion of optional questionnaires and follow up data collection, a minimum of 15 minutes (but longer if wished) is permissible for patients to decide if they wish to enter the trial. In practice they will be given written information after a verbal explanation and if they are interested, offered a quiet room with a drink where they may chat with relatives, friends and/or a breast care nurse. They will be given the opportunity to discuss the trial with their healthcare professional or research nurse before they are asked whether they would be willing to take part in the trial. The rationale for this short time period is to remove the need for an additional visit for consenting for the frailer older women who are considering PET. For these women a trip to hospital may involve a lengthy ambulance ride, a lot of waiting around in the ambulance bays and is very tiring. In normal practice they would simply be given their PET tablets at their diagnostic visit and not seen again in clinic until their first follow up visit at 6-12 weeks. The study does not wish to burden them with the additional requirement for an extra visit to discuss the trial.

For patients who will be re-attending (those who want more time to consider treatment options or who are having surgery for example), re-discussion prior to consent will be after a longer interval if wished.

9.12. Informed Consent

Assenting patients will then be formally assessed for eligibility and invited to provide written informed consent if for full or partial participation. Those who are considered for limited participation who are cognitively impaired will have participation agreed with their personal consultee who will assent to the study. Formal assessment of eligibility and informed consent discussion will be undertaken by the Principal Investigator at each individual centre or by appropriate personnel who are authorised to do so by the Principal Investigator responsible for that site. This may include appropriately qualified medical and nursing staff. The consent process will be documented in the patient's medical notes. Written informed consent (or consultee assent) for entry into the trial must be obtained prior to participation. All staff involved in the consent process will be trained in the assessment of mental capacity and in cases where this is lacking, efforts will be made to first assess the patient's own wishes (both directly or via any documented advanced directives) before discussion with a personal consultee.

The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. A copy of the consent form will be given to the patient (or personal consultee), a further filed in the hospital notes and a third will be held in the site file.

9.13 Safety endpoints

There are no pre-defined safety end-points for this study. However, any adverse events which occur as a result of normal care will be reported to the TMG.

The bulk of the research will involve completion of simple and well validated questionnaires, so there will be no physical pain, discomfort or distress. Questionnaires, however, take time to complete and so can be perceived as an inconvenience. Some of the questions refer to personal care (IADL, ADL) and mental health (MMSE), so they can also be perceived as being intrusive and it is possible in some participants the mere asking of these questions could give rise to a sense of distress, or could unmask distress about these issues.

Recruitment burdens will be minimised by the following approaches:

- The recruitment process has been designed to avoid being overly onerous or time consuming.
- We have chosen assessments which are widely used and validated and have been found to be generally acceptable in use.
- Experienced research nursing staff, used to dealing with patients with cancer, will be involved.
- Women with cognitive incapacity or significant frailty will not be expected to undertake these questionnaires which will be administered by proxy (carer or relative) as much as possible, or omitted altogether.
- In some cases women will be offered telephone/remote questionnaire completion to reduce time spent in clinics.

9.14. Stopping rules and discontinuation

There are no planned early stopping rules for this trial other than failure to recruit at a viable rate.

9.15 Study Treatments

The study is a pragmatic data collection only cohort study with no change to normal planned treatment for participating patients.

9.15.a. Primary Endocrine Therapy versus Surgery plus Adjuvant Endocrine Therapy

PET Alone

The standard therapeutic dose of Anastrozole (1mg orally, once daily), Tamoxifen (20mg orally, once daily) or Letrozole (2.5mg orally, once daily) will be given until disease progression or side effects mandate a change of management or death occurs. Treatment is continued indefinitely whilst there is evidence of continued clinical benefit. Monitoring is undertaken at the discretion of the Unit according to their normal protocol but must be undertaken at least once every 6 months during the study follow up period.

On the development of progressive disease management will be changed as per local protocol, patient preference and clinical indications and may include: surgery, change to an alternate anti-oestrogen or radiotherapy (chemotherapy is less unlikely in this cohort but will be documented if used). Change of management, its indication, type and timing will be recorded by the study staff.

New primary breast cancer or metastatic disease will be treated in accordance with the MDT decision and patient's tolerances and wishes.

9.15.b. Surgery plus adjuvant endocrine therapy (+/- radiotherapy)

Surgery to the breast

Women who are to be treated by surgery will be offered a choice of surgery appropriate to their preferences, the extent of their disease and their fitness for anaesthesia according to local Unit Protocols. The post-surgical specimen will be examined by the local pathologist and the final pathology report copied for the study site file.

Axillary surgery

Axillary surgery should be offered according to local Unit protocols and patient tolerances and wishes.

Radiotherapy (post-surgery)

Post-operative radiotherapy should be offered to women according to local and national guidelines and tailored to the woman's wishes and tolerances.

Adjuvant endocrine therapy following surgery

The standard therapeutic dose of Anastrozole (1mg orally, once daily), Tamoxifen (20mg orally once daily) or Letrozole (2.5 mg orally once daily) will be offered to women with ER+ve cancers for 5 years post-operatively according to unit protocols and her wishes and tolerance or until local/regional disease recurrence, new primary breast cancer, metastatic disease or drug intolerance develops.

Disease recurrence, new primary breast tumour and metastatic disease

Second and subsequent endocrine therapy and radiotherapy for local or regional disease recurrence will be at MDT discretion and tailored to the wishes and tolerances of the individual patient.

New primary breast cancer or metastatic disease will be treated in accordance with the MDT decision and patient's tolerances and wishes.

Concomitant Therapies

The following concomitant medications are prohibited for both the PET and surgery arms: Hormone replacement therapy (HRT) or therapy with any other oestrogen containing preparation.

9.16. Withdrawal from Treatment

There are 3 levels of patient withdrawal:

- Patients withdrawing from the study treatment but still willing to be followed up according to the visit schedule.
- Patients withdrawing from the study treatment and the visit schedule but still willing to be followed up at their standard visits.
- Patients withdrawing consent for the study. In this case data up until the point of withdrawal for these patients will be used unless patients request removal of their data from the trial database under the provisions of the Data Protection Act 1998.

9.17. Patients lost to follow-up

One or two attempts will be made by the local clinician to contact the patient either in writing or by phone if a patient does not attend follow-up assessments in clinic. If this proves unsuccessful patients who no longer attend follow-up assessments in clinic will be considered lost to follow-up and no more clinic appointment reminders will be sent. However attempts will still be made by the local clinician to obtain survival data by contacting the patient's GP or care home etc. The only exception to this is patients who withdraw consent for the trial and collection of follow-up data.

9.18. Visit Schedule.

Full Participation	Baseline	6 weeks	6 months	12 months	18 months	24 months	Long-term
IADL	*						
ADL	*						
MMSE	*						
ECOG perf. status	*						
Subjective Global Assessment	*						
Co-morbidity	*						
EQ5D	*	*	*	*	*	*	
QoL	*	*	*	*	*	*	
Decision style	*						
RECIST if PET	*	*	*	*	*	*	
Registry data access							*
Tissue Access							*
Tumour details	*						
Treatment details	*	*	*	*	*	*	
Adverse events	*	*	*	*	*	*	

Partial Participation	Baseline	6 weeks	6 months	12 months	18 months	24 months	Long-term
IADL	*						
ADL	*						
MMSE	*						
ECOG perf. status	*						
Subjective Global Assessment	*						
Co-morbidity	*					*	
RECIST if PET	*	*	*	*	*	*	
Cancer Registry permission							*
Tissue Access							*
Tumour details	*						
Treatment details	*	*	*	*	*	*	
Adverse events	*	*	*	*	*	*	

Data collection only	Baseline	6 weeks	6 months	12 months	18 months	24 months	Long-term
IADL (proxy)	*						
ADL (proxy)	*						
MMSE (proxy)	*						
ECOG perf. status (proxy)	*						
Co-morbidity (proxy)	*					*	
RECIST if PET	*	*	*	*	*	*	
Cancer Registry Access							*
Tissue Access							*
Tumour details	*						
Treatment details	*	*	*	*	*	*	
Adverse events (proxy)	*	*	*	*	*	*	

9.19.b. Follow-up Assessments

The follow-up assessments detailed should be undertaken at the time-points specified in the visit schedule.

Clinical Follow-up Assessments

Patients on PET

The Consultant Breast Surgeon, Consultant Oncologist or an appropriate delegated individual will measure the size of the primary tumour and the largest of the diseased axillary lymph nodes (if present) as detailed in appendix 4. The presence or absence of non-target lesions will also be recorded. Response will be assessed based on the RECIST Response criteria⁵⁶ below. Response will be graded as either complete response, partial response, static disease or progressive disease.

RECIST Response Criteria

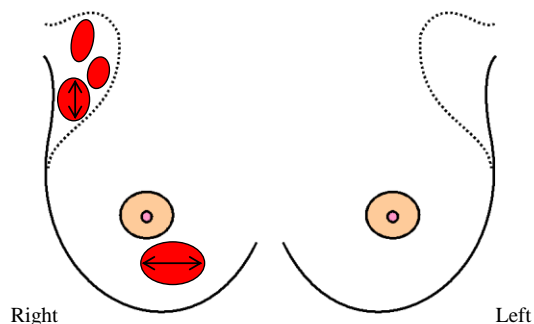
Using the sum of the longest diameter of the target lesions (primary tumour and the largest diseased axillary lymph node, if present):

Complete response (CR): Complete disappearance of disease.

Partial response (PR): At least a 30% decrease in the size of the target lesions relative to baseline.

Progressive disease (PD): At least a 20% increase in the size of the target lesions relative to the smallest measurement since start of treatment or an increase in the total number of palpable lesions or the development of metastatic disease.

Static disease (SD): Neither sufficient shrinkage for PR, nor sufficient increase for PD.



All Patients

Appropriate clinicians as delegated by the Principal Investigator will carry out the following assessments:

- Failure-Free Survival
Patients who attend follow up visits free of local or regional disease (or without progressive disease for patients on PET alone arm), and free of metastatic disease, will be classed as being failure free. Patients with either local or regional disease recurrence (those who have had surgery), PD (patients on the PET arm), or metastatic disease at follow-up will be categorised as having an ‘event’.
- Physical examination according to local practice
- Treatment details e.g. radiotherapy, surgery, chemotherapy, trastuzumab, endocrine therapy
- Treatment related adverse events
- Management of local/regional recurrence, progressive disease, metastatic disease or new primary breast tumour (if applicable)

Quality of Life Assessment

The QoL questionnaires will be completed again at follow up visits every 6 months.

Health Economics Assessment

The EQ5D questionnaire will be completed again at each follow up visit.

9.20 Statistical Considerations

9.20.a. Statistical team members

Statistical analysis is the responsibility of the study statistical team led by Professor Stephen Walters (Senior Study Statistician) with support from Dr Neil Shephard (Study Statistician). The analysis plan outlined in this section will be reviewed and a final statistical analysis plan (SAP) written before any analysis is undertaken. All analyses will be performed by the same statistician (Neil Shephard) under the supervision of Professor Walters.

9.20.b. Trial Design

The trial is a pragmatic cohort study designed to observe normal UK clinical practice. Data will be reported and presented according to the revised CONSORT guidelines for pragmatic trials⁶⁰.

9.20.c. Sample size

We propose to recruit and follow-up eligible women from at least 22 UK Breast Units. Each Unit sees between 200 and 700 breast cancers per year, of which 30% will be over age 70. Assuming an uptake rate of 50% this will allow us to collect data on over 3 500 subjects over 3 years. We expect a high uptake rate from this simple, questionnaire-based study. With 2 years follow-up this integrated dataset will provide an evidence base for the medium term post primary treatment. Longer-term follow-up via registry data will maximise the project’s long-term value. We will ask all women to consent for the study team to have access to their registry data and also to give consent for subsequent access to their stored tissue samples (which will form the basis of future research).

9.20.d. Baseline Characteristic Data Analysis

Baseline sociodemographic (age, ethnicity) and individualised baseline scores (EORTC QoL scores, EQ-5D, ADL, IADL, MMSE, Charlson Index, ECOG performance status) will be summarised and assessed for comparability between the different treatment groups (surgery versus PET and chemotherapy versus no chemotherapy). For continuous variables means and standard deviations or medians and interquartile ranges will be calculated depending on the distribution of the data. The number of observations will be presented alongside the summaries. For categorical variables such as age sub-group and ethnicity, the number and percentage of participants in each of the categories will be presented.

All baseline summaries will be presented and reported for each treatment group (surgery; PET; chemotherapy; no chemotherapy) and in total. Baseline imbalances in these characteristics will be descriptively reported and adjusted for in the statistical model.

9.20.e. Interim Analysis and Data Monitoring and Ethics Committee.

There are no statistical criteria for stopping the study early as the study is simply observing normal UK practice and therefore very low risk. The study may be stopped after interim analysis after 12 months if the study is not meeting recruitment targets. This decision will be made by the TMG on the basis of advice from the DMEC.

9.20.f. Data Sources

Data used in this study will come from data entered into the following sources:

- The CRFs
- Study Questionnaires
- Cancer Registry Outcome Data (longer term outcomes and patients lost to follow-up).

The data will be stored on a bespoke database, constructed by the Study Data Manager, (Dr Tim Chater). Data will be monitored by the study data monitor periodically to check accuracy.

9.20.g. Statistical Analyses

Since the study is a cohort it is likely that the baseline demographic, clinical and QoL characteristics of the women on the different treatment regimens (surgery versus PET, and chemotherapy versus no chemotherapy) are different and this may influence future outcomes. In order to make sure that we are comparing like with like and allow for differences in case-mix between the different treatment regimens we shall use a variety of statistical methods. The two main statistical approaches that will be used to adjust for baseline imbalances in patient characteristics will be:

1. Propensity score methods and
2. Analysis of covariance

However with sufficiently large numbers of patients an analysis of covariance model alone is often sufficient. Analysis of covariance can produce biased estimates of treatment effect if there is extreme imbalance in baseline characteristics or if the treatment effect is not constant with respect to the baseline characteristics. We will therefore also use propensity score methods which are based on determining an individual patient's probability of being treated, with a particular therapy/regimen, conditional on their baseline characteristics (e.g. age, ethnicity, EORTC QoL scores, EQ-5D, ADL, IADL, MMSE, Charlson Index, ECOG performance status, treating centre). A propensity score for each patient or the probability of having a particular treatment regimen (for example surgery

or PET) will be derived from a binary logistic regression model using baseline characteristics as covariates. A second propensity score for each patient or probability of being treated with chemotherapy or no chemotherapy will also be derived from a binary logistic regression model.

We will then use matching, stratification or analysis of covariance using the calculated propensity scores (for each individual patient) to balance patient characteristics between treatments and allow the estimation of an unbiased estimate of treatment effect of firstly PET versus surgery and secondly chemotherapy versus no chemotherapy on QoL outcomes.

9.20.i. Patient and Clinician Decision Making Preferences and Styles

Patients are recognised to possess different preferences for involvement in healthcare decision-making. Decision Making Preferences (DMP) and Decision Making Styles (DMS) are terms most commonly adopted regarding this. Three main categories are described in the literature; active, collaborative and passive; representing those wanting to take control, share decisions with others or defer decision making to others. Most published international studies utilise a validated tool comprising a simple five-point scale, to capture patient's DMP and DMS⁶⁴. This tool will be used in the study to determine the decision making preferences and styles of the patients. This is shown in Appendix 12.1. In addition, for each patient recruited the treating clinician (surgeon or oncologist with primary responsibility for care) will be asked to state whether each patient is best treated with either PET or surgery or chemotherapy or no chemotherapy, regardless of the final treatment choice. This will give us some insight into the relative importance of patient and clinician opinion on ultimate treatment preference.

9.20.K. Data Completeness

Reporting data completeness is an integral part of trial reporting. Hence a CONSORT style flow diagram will be used to display data completeness and patient throughput from eligibility screening, invitation, study acceptance and final follow-up visit. This information will be made available to the TMG and DMEC on request and as regular reports. The statistical team will also report the number of:

- Patients screened per month
- Patients recruited per month
- The number and percentage of patients who complete each follow up or are lost to follow up
- The number of patients who have complete data for each key variable.

To allow time for data entry, items will only be considered incomplete if they have not been entered within 30 days of the expected date.

9.20.I. Primary Endpoint

The study is unusual in that the primary outcome will be a statistical model of outcomes for older women and the determination of the complex and interacting set of characteristics that determine optimal treatment for older women. It is fully expected that a direct comparison of the typical outcome measures such as overall and disease specific survival rates between women treated with both surgery or PET or chemotherapy or no chemotherapy will be different. This is because clinicians will select frailer, older women for non-surgical treatment and for no chemotherapy. These 2 groups will therefore be expected to have higher overall mortality rates and, as these treatment arms are less effective, they may also have higher rates of disease related mortality and disease recurrence. It would therefore not be appropriate to directly compare these standard outcomes as if this were an RCT. The following outcomes will however be described and reported for the study by treatment type:

- Overall survival
- Breast cancer specific survival
- Other cause mortality
- Cause of death.

Kaplan Meier curves will be derived for each treatment type, by age, disease characteristics, co-morbidity and frailty subgroup to illustrate how these factors interact with treatment type and disease stage.

Overall survival (OS) curves will be calculated using the Kaplan Meier method. Overall survival will primarily be compared between the treatment groups using multivariate modelling, Cox's Proportional Hazards model if appropriate, to adjust for minimisation factors. Overall survival will also be compared using multivariate modelling adjusting for the minimisation factors and other important prognostic factors. Hazard ratios (HR) and corresponding 95% CIs will be presented. The upper limit of the 95% CI around the HR for the treatment effect will be compared with the HR non-inferiority margin of 1.245. Yearly OS, median survival, and corresponding 95% CIs will be presented for each treatment type

9.20.m. Secondary Endpoints

As for the primary outcomes, it is expected that there will be systematic bias between the baseline characteristics of the different treatments groups which will impact on outcomes making direct, unadjusted statistical comparisons difficult. However the following secondary outcome measures will be described for each of the following:

- Failure free survival
- Time to local recurrence (disease progression in PET)
- Time to local recurrence
- Time to metastatic recurrence
- Date of change of management for PET patients (delayed surgery, change of anti-oestrogen or radiotherapy)
- Time to change of management.

Kaplan Meier curves for the above will be derived for women in different age, disease characteristic, co morbidity and frailty subgroups. Failure Free Survival and cumulative incidence functions for local disease control will be calculated and compared using multivariate modelling, Cox's Proportional Hazards model if appropriate, to adjust primarily for the minimisation factors only, and also to adjust for the minimisation factors and other important prognostic factors. HRs and corresponding 95% CIs will be presented. Yearly survival/local disease control, median survival/local disease control, and corresponding 95% CIs will be presented for each treatment group.

Sensitivity analyses will be conducted to account for missing data for Failure Free Survival, breast cancer specific survival and local disease control.

Time to local progression or recurrence and its treatment will be summarised descriptively.

Treatment related adverse events and reasons for stopped treatment will be summarised descriptively for each treatment group. The maximum grade of toxicity (AEs) per patient and the overall rate of toxicities will be summarised (according to standard Common Terminology Criteria for Adverse Events, CTCAE)

9.20.n. Subgroup analyses

Age subgroup analysis (75-79, 80-84, 85-89 and 90+ years), Barthel Index subgroup analysis (mild, moderate or severe), Charlson score and degree of dementia (mild, moderate or severe) will also be carried out on the primary and secondary outcome measures.

9.20.o. HES data analysis.

HES data from the WMCIU will be collected for all patients in the cohort study and once the cohort study is complete the quality of the HES data will be compared with the actual comorbidity data, to assess whether its use as a proxy for comorbidity is valid or accurate. Similarly the accuracy of the HES data derived Charlson index will be compared with the cohort study derived index.

9.21. Data Management

Trial data will be recorded by hospital staff (predominantly the NCRN funded locality research nurses) in the electronic or paper-based CRFs and signed off by appropriate trial personnel as detailed in the authorised signatories log completed for each participating site. It is anticipated that the majority of CRF completions will be electronic using a specially designed electronic web-based CRF designed for the study by the study Data Manager, (Tim Chater) and Chris Murray (EpiGenesys). The Study Manager, Study Monitor and Data Manager will collate all data from all study sites and will be responsible for verifying and checking the data.

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Quality control will be maintained through adherence to departmental standard operating procedures (SOPs), and by following the principles of GCP according to the EU Directive 2005/28/EC (GCP Directive), which was implemented in The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the Study team. It is the responsibility of each centre to retain copies of all completed CRFs for the trial and their study file on site or at their designated archive facility for a minimum of 15 years after study completion.

All centres will be asked to complete a log of all patients who are screened for eligibility who do not subsequently take part and the reason for non-participation.

9.22. Data Monitoring

Data will be monitored for quality and completeness by the Study Team. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis.

The Study Team will conduct source data verification (SDV) on a minimum of 10% of patients.

9.22.a. Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be established to review the safety and ethics of the trial. Detailed reports will be prepared by the Study Manager for these committees on an annual basis, and for the interim and final analyses. The committee will meet every 12 months and will produce a report on trial viability and safety.

The DMEC will be composed of the following independent members: a geriatrician, a medical oncologist and a breast surgeon.

9.22.b. Trial Management Group (TMG)

A TMG will be established to provide overall supervision of the trial, in particular: trial progress, adherence to protocol, patient safety and consideration of new information. The committee will meet every 6 months during recruitment and annually thereafter for the duration of the trial.

Membership of the TMG:

Lynda Wyld: Chair

Malcolm Reed: Co-Chair

Sue Ward: Lead Modeller

Stephen Walters: Senior Trial Statistician

Rosie Cooper: Trial Manager

Chantelle Morris: Clerical officer and study monitor (will take minutes)

A minimum of 2 Consumer representatives

Jenna Morgan: Clinician variation project lead

Karen Collins: Quality of life lead

Paul Richards: Trial modeller

Alistair Ring: Oncology Advisor

Tom Robinson: Geriatrics advisor

Gill Lawrence and Catherine Lagord: Representatives of the WMCIU

9.23. Ethics and Good Clinical Practice

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent (or consultee assent) will be obtained from the patients prior to participation in the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing her further treatment. The study will be submitted to and approved by a National Research Ethics Committee (MCA Approved) and the appropriate locality site specific R&D approval prior to entering patients into the study. The Study will provide the main Research Ethics Committee with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation. The trial will be conducted in accordance with the principles of GCP according to the EU Directive 2005/28/EC (GCP Directive), which was implemented in The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

9.24. Confidentiality

The Study Team will collect patient data that includes some patient identifiers. The latter are required to allow back-identification of patients for the purpose of data clarification and clinical safety monitoring. The Study Team will comply with all aspects of the Data Protection Act, 1998. Any information that would allow patients and clinicians to be identified will not be released into the public domain. If a patient withdraws consent from further study participation but not from collection of data, their data will remain on file and will be included in the final study analysis.

9.25. Archiving

At the end of the trial, data and the Trial Master File will be securely archived at the Academic Unit of Surgical Oncology and participating centres for a minimum of 15 years. Following authorisation from the sponsors arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed.

9.26 Indemnity

This study is sponsored by the Sheffield Teaching Hospitals NHS Foundation Trust (STHNHSFT) which will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is a clinician-led study there are no arrangements for no-fault compensation.

9.27. Trial Sponsorship

The trial will be sponsored by the Sheffield Teaching Hospitals NHS Foundation Trust (STHNHSFT). This organisation will therefore be responsible for the initiation and management of the trial as defined in the principles of GCP according to the EU Directive 2005/28/EC (GCP Directive), which was implemented in The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

9.28. Study Organisational Structure

9.28.a. Chief Investigator (CI)

The Chief Investigator is involved in the design, conduct, co-ordination and management of the trial.

9.28.b. Trial Management Group (TMG)

The TMG (membership detailed above) will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (v) appointing and facilitating the TSC and DMEC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (viii) auditing consent procedures, data collection, trial end-point validation and database development.

9.28.c. Data Monitoring and Ethics Committee (DMEC)

The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet or communicate via teleconference 12-monthly.

9.29. Funding

The study is funded by a Programme Grant from the National Institute for Health Research.

9.30. Publication Policy

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship.

Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigators will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publications, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigators. In addition, individual collaborators must not publish data concerning their patients which is directly relevant to the questions posed in the trial until the main results of the trial have been published.

Section 10.0. Revision and validation of model based on cohort study data

The initial statistical model using merged retrospective data from the WMCIU and CFAS will be revised and refined using data from the cohort study.

It is proposed that the data from the Cohort study will be used to test and revise the initial statistical model as follows:

1. We will use the baseline integrated data set to analyse patterns of allocation to Surgery or PET or surgery alone versus surgery + chemotherapy and the relationship with breast cancer specific and co-morbidity covariates.
2. We will repeat the time to event modelling from the initial statistical model using the (up to three years' worth of) longitudinal data from the cohort study alone as the data source. This will enable us to examine whether evidence is emerging of differences in model coefficients.
3. We will undertake comparison using the original statistical models to predict probabilities of early outcomes for the cohort and examine them against observed outcomes.
4. Finally, we will develop Bayesian evidence synthesis approaches to provide a new set of statistical models for time to recurrence, time to breast cancer and non-breast cancer death linking the longer-term data from separate cancer registry and MRC CFAS data with the short to medium term outcomes data from the prospective cohort study.

The end product will be a revised statistical model incorporating retrospective and prospective collected data. Of note, the statistical model will be further updatable if the cohort is followed longer-term through the routine cancer registry data collection process.

In addition to the development of a statistical model that can be used to predict individual outcomes, we are proposing to construct an economic model to inform National Guidelines on treatment choice for older women with breast cancer.

The economic model is likely to take an individual level modelling approach, incorporating the revised statistical model (using both retrospective and prospective data) that allows the impact of different strategies for treatment selection to be compared.

We will use standard approaches to incorporate evidence on costs and QoL of health states including using routine sources, literature and the combined data from the retrospective sources and the cohort study. This will enable both healthcare costs and expected QALYs lived for different treatment options to be calculated for the individual and for subgroups. Discounting of longer term costs and benefits will be undertaken in line with standard UK practice.

Estimates from the model will be used to assess the comparative cost-effectiveness of different intervention strategies. The effects of structural and parameter uncertainties on the model estimates will be assessed using sensitivity analyses as recommended in the NICE guide to the methods of technology appraisal. Results of probabilistic sensitivity analyses will be plotted on the cost-effectiveness plane along with associated acceptability curves⁶⁷.

Section 11. Development of software to support interactive web pages for decision support

The web-based treatment algorithm will be based on the computer model of predicted outcomes and the variance caused by patient and disease parameters. The University of Sheffield web design service, EpiGenesys, will develop the 'front end' of the algorithm. Using a similar format to Adjuvant On-Line³⁷, with facility to specify patient parameters (age, health status, frailty, tumour characteristics), it will present the user with an output suggesting outcomes from either surgery or PET (survival, recurrence or progression free survival, death from non-breast cancer causes, QoL) or surgery alone or surgery plus or minus chemotherapy. These will be presented in a range of graphic formats depending on the expected user groups (clinicians or patients).

Section 12. Piloting of interactive web tool and refinement prior to National launch

The web treatment decision algorithm will then be tested for ease of use, practicality and intention to use long-term in the 22 participating centres using individual interviews, questionnaires and focus groups of 6 to 8 professionals (Surgeons, Oncologists, Breast Care Nurses, Consumers). Feedback will be collated and built into the algorithm before a final version is made available for general use. **This phase of the project is not detailed in the present protocol and will be developed for a separate ethics application in future.**

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Appendix 2: Research Ethics Committee approvals for Bridging the Age Gap in Breast Cancer study



NRES Committee London - South East

HRA Ground Floor
Skipton House
80 London Road
London
SE1 6LH

30 November 2012
Ms Lynda Wyld
Senior Lecturer in Surgical Oncology and Honorary Consultant Surgeon
University of Sheffield
Room EU 36, Academic Unit of Surgical Oncology
E Floor, Royal Hallamshire Hospital
Beech Hill Road, Sheffield
S10 2JF

Dear Ms Wyld

Study title: **Bridging the Age Gap in Breast Cancer: Improving Outcomes for Older Women.**

REC reference: **12/LO/1808**

Protocol number: **STH17086**

The Research Ethics Committee reviewed the above application at the meeting held on 14 November 2012. Thank you for attending to discuss the study.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mr Jay McGregor, nrescommittee.london-southeast@nhs.net.

Ethical opinion

Q) The Committee was concerned that a follow-up phone call to the home of a participant who has died could cause distress to the family. How will this be accounted for and what measures are in places to help/prevent distress?

A) Ms Wyld explained that her team see the participants regularly in clinic and she will be aware of who has or hasn't died. The follow-up visits are linked with clinic appointments and if the participant doesn't turn up, and doesn't reply to correspondence, then she will contact the participant's GP to find out further information.

Q) The Committee wanted to know why the participants are recruited into the study on the day of their diagnosis. There was a concern that participants will be distressed by the news that they have breast cancer and will not want to take part in a research study.

A) Ms Wyld explained that it would be burdensome to ask elderly women to come back to clinic more than once. Also, most of the women will have already been told that they may have cancer by their GP. For some of the patients, Ms Wyld argued, taking part in the study will be a welcome distraction from the distress of being diagnosed with breast cancer.

Q) The Committee were keen to know what clinicians will say to potential participants to recruit them into the study. There was a concern that participants could feel coerced to take part in the study depending on what the clinician says to them.

A) Ms Wyld acknowledged that this was a possibility. She agreed to create an information pack for recruiting clinicians. She said this will be as sensitive as possible and she agreed to share it with the Committee.

She said this will be as sensitive as possible and she agreed to share it with the Committee.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		22 October 2012
Investigator CV		
Letter from Sponsor		
Other: Summary of PPI Feedback		
Other: Data protection register entry university of Sheffield		
Other: Section 251 approval request		
Other: Computer system security	2	21 October 2011
Other: Computer system validation	1	21 October 2011
Other: Computer system disaster mitigation and recovery	2	21 October 2011
Other: HES data application outpatient		
Other: HES data application inpatient		

Other: Funding agreement from NIHR		
Other: Permission from the trusts caldicott guardian		
Other: Thank you letter	1	20 October 2012
Other: STH Data protection registration		

Other: Information security policy for the STH trust	5	15 August 2012
Participant Consent Form: Patients	1	20 October 2012
Participant Consent Form: Assent form, for relatives, carers and friends	1	20 October 2012
Participant Information Sheet: patient	1	20 October 2012
Participant Information Sheet: carer	1	20 October 2012
Protocol	1	20 October 2012
REC application		25 October 2012
Referees or other scientific critique report		
GP letter	1	20 October 2012
Other: Dataset requirements	1	22 October 2012
Other: Data protection register renewal: STH Trust		15 January 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

There were no declarations of interest.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
 - Adding new sites and investigators
 - Notification of serious breaches of the protocol
 - Progress and safety reports
-
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/LO/1808

Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

Handwritten initials 'PP' and a signature.

Professor David Caplin
Chair

Email: nrescommittee.london-southeast@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments “After ethical review – guidance for researchers”

Copy to: Erica Wallis, Sheffield Teaching Hospitals NHS Foundation Trust Erica Wallis, Sheffield Teaching Hospitals NHS Foundation Trust NIGB Ethics & Confidentiality Committee Secretariat

**NRES Committee London -
South East**

**Attendance at Committee meeting on 14
November 2012**

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Ashok Bhiman	Consultant Psychiatrist	No	
Professor David Caplin	Physicist	Yes	
Mr Ron Driver	University	Yes	
Professor John Eastwood	Consultant Renal	Yes	
Dr Alan Fishtal	GP	Yes	
Dr Ann Gallagher	Reader in Nursing Ethics	Yes	
Mr Guy Gardener	Retired Assistant Chief	Yes	
Mrs Vera Hughes	Training Consultant	Yes	
Dr Robin MacKenzie	Director Medical Law & Ethics	No	
Professor Liz Meerabeau	University Professor	Yes	
Professor Liz Meerabeau	University Professor	Yes	
Mr Roy Sinclair	Pharmacist	Yes	



Health Research Authority

Confidentiality Advisory Group

Ms Lynda Wyld
The Medical School
University of Sheffield
Beech Hill Road Sheffield
S10 2JF

Skipton House
80 London Road
London SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net

Date: 12 April 2013

Dear Ms Wyld

Study title: Bridging the Age Gap in Breast Cancer: Improving
Outcomes for
Older Women
Project CAG reference: ECC 8-04 (g)/2013

Thank you for your research application, submitted for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered by the Confidentiality Advisory Group's predecessor, the Ethics and Confidentiality Committee at its meeting on the 6 February 2013.

Secretary of State approval decision

The Secretary of State provided provisional approval for this amendment which was confirmed in the outcome letter dated 20 February 2013 and agreed that final approval could be given once the conditions had been met.

As these conditions have been met, final approval can be confirmed.

This letter should be read in conjunction with the outcome letter dated 20 February 2013.

Context

This research application from the University of Sheffield detailed a study which aimed to determine the age, co-morbidity, frailty and disease characteristics of women over 70 with early breast cancer in order to provide guidance on 2 primary questions:

1. What are the personal and cancer characteristics of women who can be safely advised that surgery is unlikely to confer any advantage to them?
2. What are the personal and cancer characteristics of women who should be advised to have adjuvant chemotherapy after surgery?

Support was requested in order to access linked HES and cancer registry data which included date of death.

Specific conditions of support

1. Confirmation of a favourable REC opinion. **Received**
2. Confirmation of satisfactory security arrangements. **Confirmed 11/04/2013**
3. Reasonable efforts should be made to inform the cohort of the processing to ensure that the requirements of the DPA are met.

As the above conditions have been accepted and/or met, this letter provides confirmation of final approval. I will arrange for the register of approved applications on the HRA website to be updated with this information.

Annual review

Please note that this approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report 6 weeks prior to the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements.

Please do not hesitate to contact me if you have any further queries in relation to this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
Deputy Confidentiality Advice Manager

Email: HRA.CAG@nhs.net

Enclosures: Standard conditions of approval

Copy to: *London - South East, nrescommittee.london-southeast@nhs.net*

Standard conditions of approval

The approval provided by the Health Research Authority is subject to the following standard conditions. The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent is facilitated and supported.
8. The wishes of patients who have withheld or withdrawn their consent are respected.
9. The Confidentiality Advice Team is notified of any significant changes (purpose, data flows, data items, security arrangements) prior to the change occurring.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter.
11. Any breaches of confidentiality / security around this particular flow of data should be reported to
CAG within 10 working days, along with remedial actions taken / to be taken.

Appendix 3: Signed Funding Agreement

AGREEMENT

SECRETARY OF STATE FOR HEALTH

AND

SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST

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SECTION 1:

FORM OF AGREEMENT

THIS Agreement is made between:

The Secretary of State for Health ("The Authority")
of Richmond House, 79 Whitehall, London SW1A 2NS

and

Sheffield Teaching Hospitals NHS Foundation Trust ("the Provider")

of

Northern General Hospital, Herries Road, Sheffield, South Yorkshire, S5 7AU

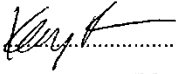
(the Authority and the Provider being together referred to as "the Parties")

Whereas it is agreed that:

1. The Provider shall use the funding provided under this Agreement as specified in Section 3.
2. This Form of Agreement (Section 1) together with the attached Sections 2, 3, 4 and 5 inclusive are the documents which collectively form "the Agreement" (as defined in Section 2).
3. The Agreement effected by the signing of this Form of Agreement constitutes the entire agreement between the Parties relating to the subject matter of the Agreement and supersedes all prior negotiation, representations or understandings.
4. Where the Provider is a health service body within the meaning of Section 9 of the National Health Service Act 2006 then this Agreement is an NHS Contract within the meaning of that Act.

SIGNED on behalf of the Parties:

For the Authority:

By 


DR. KAY PATTISON

Full Name: Section Head, RDD - DH

Position held on behalf of the Authority:

Date: 20 MAR 2012

For the Provider:

By 

Full Name Professor Mike Richmond

Position held on behalf of the Provider MEDICAL DIRECTOR

Date 6/3/12

SECTION 2:

CONDITIONS OF AGREEMENT

1. DEFINITIONS AND INTERPRETATIONS
2. ENTIRE AGREEMENT
3. TERM
4. ADMINISTRATION AND DIRECTION OF RESEARCH
5. ACCOUNTING AND PAYMENTS
6. VARIATION
7. CONFIDENTIALITY
8. CONFIDENTIALITY OF PERSONAL DATA
9. ANONYMISING OF BASIC FACTUAL DATA
10. RIGHTS TO DATA
11. ETHICS AND RESEARCH GOVERNANCE
12. MONITORING AND REPORTING
13. INTELLECTUAL PROPERTY RIGHTS
14. PUBLICITY
15. PUBLICATION
16. EQUIPMENT
17. NIHR FACULTY
18. TERMINATION
19. CORRUPT GIFTS AND PAYMENTS
20. INDEMNITY AND INSURANCE
21. ASSIGNMENT
22. WAIVER
23. DISPUTE RESOLUTION
24. NOTICES
25. FORCE MAJEURE
26. RELATIONSHIPS
27. SEVERABILITY
28. DISCRIMINATION AND HUMAN RIGHTS
29. FREEDOM OF INFORMATION
30. CONTRACTS (RIGHTS OF THIRD PARTIES) ACT 1999
31. INTERPRETATION

1.1 In the Agreement unless the context otherwise requires:

"Agreement"	means the agreement concluded between the Authority and the Provider comprising: Section 1: Form of Agreement Section 2: Conditions of Agreement Section 3: Purpose and use of NIHR Programme Grants for Applied Research Funding Section 4: Financial Arrangements Section 5: Administration Instructions, which in the event of ambiguity or contradiction between Sections shall be given precedence
"Background Intellectual Property"	means Intellectual Property owned or controlled by either of the Parties at the date of the Agreement or which shall at any time thereafter become so owned or controlled otherwise than as a result of the research under the Agreement.
"Break Date"	means 30th June 2015
"Commencement Date"	means 1st July 2012
"Completion Date"	means 30th June 2017
"Confidential Information"	means information that falls within the types of information which has been designated as confidential by either Party or that ought to be considered as confidential (however it is conveyed or on whatever media it is stored) including information which relates to the business, affairs, properties, assets, trading practices, Goods/Services, developments, trade secrets, Intellectual Property rights, know-how, personnel, customers and suppliers of either Party, all personal data and sensitive personal data within the meaning of the Data Protection Act 1998 and the commercially sensitive information.
"Copyright"	has the meaning assigned to it in the Copyright Designs and Patent Act 1988
"Data"	means information processed or recorded for the purpose of the research in the Agreement whether manually, electronically or by other means.
"Full Economic Costs"	means the total ("full economic") costs of undertaking a research project, as calculated by the TRAC (Transparent Approach to Costing) methodology.

"Intellectual Property"	means patents, trade marks and service marks, rights in semiconductor chip topographies, present and future copyrights, design rights and database rights, whether or not any of them are registered and including applications for registration of any of them, trade secrets and rights of confidence, and all rights or forms of protection of a similar nature which have an equivalent effect to any of them which may exist anywhere in the world.
"National Institute for Health Research (NIHR)"	means a co-ordinated set of research funding schemes, research infrastructure and research management systems established by the Authority.
"NIHR Programme Grant for Applied Research Funding"	means the amount to be paid by the Authority to the Provider for the purposes set out in section 3
"Personal Data"	means information relating to an individual who can be identified from it or from it and other information which is likely to come into the possession of the person who determines the purpose for which and the manner in which any personal data are or are to be processed.
"Programme of Work"	means the Programme of Work specified in Appendix 1 to Section 3.
"R&D"	means research and development.
"Variation"	means a variation to the Agreement agreed by the Parties in accordance with Condition 6 of Section 2

1.2 The interpretation and construction of the Agreement shall be subject to the following provisions:

- (i) any reference to a condition shall be interpreted as a reference to the condition bearing that number in the Agreement;
- (ii) a reference to any statute, enactment, order, regulation or other similar instrument shall be construed as a reference to the statute, enactment, order, regulation or instrument as subsequently amended or re-enacted;
- (iii) unless the context otherwise requires, words importing the singular shall include the plural and vice versa, and words importing the masculine gender shall import the feminine gender and vice versa; and
- (iv) condition headings are for ease of reference only and shall not affect the interpretation or construction.

- 2.1 The Agreement constitutes the entire agreement between the Parties in connection with its subject matter and supersedes all prior communications, negotiations and understandings, whether written or oral, concerning the subject matter of the Agreement except that this Condition shall not exclude liability in respect of any fraudulent misrepresentation.

3. TERM

- 3.1 The Agreement shall take effect on the Commencement Date and shall terminate on the Completion Date unless it is terminated under these Conditions, or otherwise lawfully terminated or extended in accordance with the provisions of Conditions 3.3.

- 3.2 The Authority shall carry out a review of the Provider's work on the Programme of Work in year 2 of the Agreement. As a result of the findings of this review, the Authority shall either:

3.2.1 confirm the continuation of the Agreement for the remaining term; or

3.2.2 give notice of termination with effect on the Break Date in accordance with Condition 4.2 hereof.

- 3.3 The Provider shall be given at least 3 (three) months notice of the Authority's intention to terminate the Agreement under the preceding provisions of this Condition.

4. ADMINISTRATION AND DIRECTION OF RESEARCH

- 4.1 The Provider shall comply with guidance and advice from the Authority on the conduct and administration of research which may be issued from time to time.

- 4.2 The Authority reserves the right to terminate this Agreement forthwith should the Provider be unable or unwilling for any reason to continue with the Programme of Work or if in the reasonable opinion of the Authority the Provider is consistently failing to achieve an acceptable standard in relation to the Programme of Work in which case no financial compensation shall be payable to the Provider.

5. ACCOUNTING AND PAYMENTS

- 5.1 The total NIHR Programme Grants for Applied Research Funding shall not exceed the amounts detailed in Section 4. Subject to the conditions set out in Section 3, the Provider is free to administer the funds without further reference to the Authority. Payments to third parties remain the responsibility of the Provider who shall ensure such payments are made promptly.

- 5.2 Payments will be made by the Authority on the basis of the dates and amounts specified in Section 4. The Authority may suspend this payment schedule at any time if in its opinion reasonable progress on the activities is not being maintained, or the reports specified at Condition 12 of Section 2 and paragraph 2 of section 4 are not submitted. The Authority may request at any time such evidence as may reasonably be required that the Provider has spent the amounts paid. To facilitate this the Provider shall maintain its financial records relating to the Agreement for a

period not less than two years after the end of the Completion Date.

- 5.3 The Provider grants to the Authority and to any statutory or regulatory auditors of the Authority and to their authorised agents the right of reasonable access to (and if necessary to copy) the relevant financial records during normal business hours.
- 5.4 The Provider shall provide all reasonable assistance at all times during the currency of the Agreement and during the period of two years after termination or expiry of this Agreement for the purposes of allowing the Authority to obtain such information as is necessary to fulfil the Authority's obligations to supply information for Parliamentary, Governmental, Judicial or other administrative purposes and/or to carry out an audit of the Provider's compliance with this Agreement including all activities, performance, security and integrity in connection therewith.
- 5.5 If at any time an overpayment has been made to the Provider for any reason whatsoever, the amount of such overpayment shall be taken into account in assessing any further payments, or shall be recoverable from the Provider.

- 6.1 If, at any time, any provision of the Agreement needs to be varied, the Authority may issue a Variation to this Agreement or give notice of termination.
- 6.2 The Provider must notify the Authority, within ten working days, if any of the following changes are made:
- (i) Change of Lead Applicant for the Programme Grant for Applied Research
 - (ii) Significant changes to the agreed programme of work

7. CONFIDENTIALITY

- 7.1 In respect of any Confidential Information it may receive from the other Party and subject always to the remainder of this Clause 7, the receiving Party undertakes to keep secret and strictly confidential and shall not disclose any such Confidential Information to any third party, without the disclosing Party's prior written consent provided that:
- (i) the receiving Party shall not be prevented from using any general knowledge, experience or skills which were in its possession prior to the commencement of the Agreement;
 - (ii) nothing herein shall be so construed as to prevent either party from using data processing techniques, ideas, know-how and the like gained during the performance of the Contract in the furtherance of its normal business, to the extent that this does not result in a disclosure of confidential information or infringement of any valid Intellectual Property Rights of either Party or the unauthorised processing of any Personal Data."
- 7.2 Condition 7.1 shall not apply to any Confidential Information received by one Party from the other:
- (i) which is or becomes public knowledge (otherwise than by breach of this Condition);
 - (ii) which was in the possession of the receiving Party, without restriction as to its disclosure, before receiving it from the disclosing Party;
 - (iii) which is received from a third party who lawfully acquired it and who is under no obligation restricting its disclosure;
 - (iv) is independently developed without access to the Confidential Information; or
 - (v) which must be disclosed pursuant to a statutory, legal or parliamentary obligation placed upon the Party making the disclosure, including any requirements for disclosure under the FOIA, or the Environmental Information Regulations pursuant to Condition 29 (Freedom of Information).
- 7.3 The obligations of each of the Parties contained in Condition 7.1 above shall continue without limit in point of time. In the event that the Provider fails to comply with this Condition 7.3 the Authority reserves the right to terminate the Agreement by notice in writing with immediate effect.

8. CONFIDENTIALITY OF PERSONAL DATA

- 8.1 The Provider shall ensure that the collection, handling and use of Data related to individuals shall be treated as confidential at all times, in particular:
- (i) medical information for research shall be used in accordance with:
 - a) the Medical Research Council's "Personal Information in Medical Research", January 2003; available at www.mrc.ac.uk; and
 - b) "The NHS Confidentiality Code of Practice", guidelines on the use and protection of patient information, November 2003; available on the Authority's website (www.dh.gov.uk).
 - (ii) non-medical information shall be used with such guidance as may be issued by the professional body concerned or in accordance with advice as may from time-to-time be issued by the Authority.
- 8.2 The Provider shall at all times be responsible for ensuring that all Data (including Data in any electronic format) is stored securely. The Provider shall take appropriate measures to ensure the integrity of security of such Data and guard against unauthorised access thereto or disclosure thereof or its loss or destruction while in its custody.
- 8.3 The Provider shall fully indemnify and hold harmless the Authority, its employees and agents against all liabilities, losses, costs, charges and expenses incurred as a result of any claims, demands, actions and proceedings made or brought against the Authority by any person in respect of any loss or distress to that person by the loss, unauthorised disclosure of Personal Data or medical records by the Provider, or any sub-contractor, servant or agent of the Provider or any person within the control of the Provider.
- 8.4 The Provider shall at its own expense conduct any litigation arising from any such claims, demands, actions or proceedings and all the negotiations for the settlement of the same and the Authority hereby agrees to grant the Provider exclusive control of any such litigation or the negotiations for the settlement of the same.
- 8.5 No information which could lead to the identification of an individual shall be included in any publication without the prior agreement in writing of the individual concerned. No mention shall be made of individual officers of the Authority, nor shall information be included which might lead to their identification.
- 8.6 The Provider shall comply with the provisions of the Data Protection Act 1998.

9. ANONYMISING OF BASIC FACTUAL DATA

- 9.1 The Provider shall safeguard the confidentiality of the research and any personal data provided for the research. The Authority shall be deemed irrevocably to have waived its rights and entitlement to demand sight or production of any specific basic factual (or "raw") Data from the research other than in an anonymised form. Accordingly, the Provider shall ensure that all basic factual Data is anonymised as and when it is received and that the key to personal identities of persons involved in the research is kept in a separate and secure place.
- 9.2 On termination of the research, for whatever reason, the Provider shall arrange to keep Personal Data securely for at least ten years after the Completion date or destroy it in accordance with the directions of the Authority

10. RIGHTS TO DATA

- 10.1 Subject to the provision of Condition 9, the Authority reserves the right to have access to and to use Data compiled during the course of the research and will respect existing guidance on confidentiality of any Data which it obtains.

11. ETHICS AND RESEARCH GOVERNANCE

- 11.1 The Provider will ensure that research in any way connected with this Agreement is conducted in accordance with the Department of Health guidance "Research Governance Framework For Health and Social Care" and, if relevant, in accordance with the Department of Health guidance "Governance Arrangements for NHS Research Ethics Committees" or such other guidelines as may be issued from time to time by the Authority and made available on its website (www.dh.gov.uk).
- 11.2 The Provider shall comply with all relevant legislation including but not limited to:
- (i) The Medicines for Human Use (Clinical Trials) Regulations (SI2004/1031)
 - (ii) The Human Tissue Act 2004

12. MONITORING AND REPORTING

- 12.1 The Provider is required to provide reports to the Authority at intervals specified by the Authority and in a format and containing information specified by the Authority.
- 12.2 The Authority has the right to call upon the Provider for further interim reports or information at any time on any aspect of the Agreement.
- 12.3 The Provider shall provide project based information on the research and development undertaken by the Provider under the Agreement in accordance with the latest guidance to data providers provided by the Authority on its website (<http://www.nihr.ac.uk>).

13. INTELLECTUAL PROPERTY RIGHTS

- 13.1 All Intellectual Property (other than Background Intellectual Property) arising from research and development carried out by the Provider in connection with the Agreement shall belong to and vest in the Provider.
- 13.2 The Provider shall manage Intellectual Property arising from the funding provided under this Agreement in line with the guidance published by the Authority and available on its website, currently *The NHS as an Innovative Organisation: A Framework and Guidance on the Management of Intellectual Property in the NHS*.
- 13.3 The Provider shall permit the Authority to monitor the operation and effectiveness of the Provider's procedures for the management of Intellectual Property in such a way as the Authority considers reasonably necessary.

14 PUBLICITY

- 14.1 During the Term of the Agreement, and prior to the publication of the Research Results or Data, or of matters arising from such Results or Data, in accordance with Condition 15, the Provider shall, not without the prior written consent of the Authority, release, or otherwise make available to third parties, information relating to the Agreement or the approved Programme of Work by means of any public statement, in particular any press announcement or displays or oral presentations to meetings.
- 14.2 In the event that the Provider fails to comply with this Condition 14, the Authority reserves the right to terminate the Agreement by notice in writing with immediate effect.

15. PUBLICATION

- 15.1 The Provider acknowledges the Authority's statement on Open Access to research (<http://www.nihr.ac.uk/files/pdfs/OpenAccessPolicyStatement.pdf>), in which the Authority encourages free access to information both on research being conducted, and on the findings of research, once these have been subjected to critical review through the accepted scientific and professional channels.
- 15.2 All publications arising out of work in connection with the activities funded through this Agreement shall acknowledge the Authority's financial support from the NIHR Programme Grants for Applied Research funding scheme.
- 15.3 The Authority's Representative must be notified prior to any publication (whether in oral, written or other form) of Data or the Results of the Programme Grant. One draft copy of the proposed publication shall be sent to the Authority's Representative at the same time as submission for publication, or at least 28 days before the date intended for publication, whichever is earlier.

16. EQUIPMENT

- 16.1 The Provider shall take all practical steps to purchase all materials and equipment at a fair and reasonable price. The Authority may inspect the original quotations and invoices issued to the Provider for equipment purchased in connection with this Agreement and recover any funds provided for the purchase if the Provider does not provide this documentation on request.
- 16.2 Following the submission of all information and reports required by the Authority, such equipment purchased shall become the property of the Provider.

17. NIHR FACULTY

- 17.1 The Provider shall ensure that any individuals employed by or having a contract for services with the Provider relating to this Agreement shall comply with the rules and regulations of the NIHR Faculty as set out on the NIHR website (<http://www.nihr.ac.uk/faculty.aspx>).
- 17.2 The Provider shall inform the Authority immediately of any suspension or termination of such employment.

18. TERMINATION

- 18.1 Without prejudice to the provisions of Condition 18.3, the Agreement may be terminated by either Party giving three months notice in writing to the other. Should the option to terminate be exercised by the Authority it shall indemnify the Provider for and against all and any actual loss unavoidably incurred by reason of or in consequence of the termination provided that the Provider takes all immediate and reasonable steps to minimise the loss.
- 18.2 Under Condition 18.1, the Authority will not pay any sum which, when taken together with any sums paid or due or becoming due to the Provider under the Agreement will exceed the total sum payable under the Agreement.
- 18.3 The Authority may terminate the Agreement, without liability for any damage, loss or expenses arising as a result of or in connection with such termination if:
- (i) the Provider is in material breach of any of the terms and conditions of the Agreement, and in the case of breach capable of remedy fails to remedy that breach within 30 days of the service of a written notice by the Authority specifying the breach; or
 - (ii) the Provider shall be subject to the exercise of any power conferred on the regulator by:
 - (a) sections 52 to 55 (failing NHS Foundation Trusts), or
 - (b) sections 56 and 57 (mergers)
- of the National Health Service Act 2006, provided that, in respect of the exercise of powers conferred on the regulator by sections 56 and 57 of that Act, such exercise impacts adversely and materially on the performance of the Agreement and the Authority exercises its right to terminate within six months of the date of any authorisation made in accordance with those sections.
- 18.4 Termination of the Agreement however caused shall not release the Provider from any duty or obligation of confidence which falls on it, its servants, agents or employees or sub-contractors or under general law governing confidential information nor shall it prejudice or affect any right or remedy which shall have accrued before termination or shall accrue thereafter.

19. CORRUPT GIFTS OR PAYMENTS

- 19.1 The Provider shall not do (and warrants that in entering the Agreement he has not) any of the following (referred to in this condition as "Prohibited Acts");
- (i) offer, give or agree to give to any person in the employment of the Authority any gift or consideration as an inducement or reward for doing or refraining from doing any act in relation to the obtaining or performance of this or any other Agreement with the Authority or for showing or refraining from showing favour or disfavour to any person in relation to this or any other Agreement with the Authority; nor
 - (ii) enter into this or any other Agreement with the Authority if any commission has been paid or agreed to be paid to any person in the employment of the Authority by or on behalf of the Provider or to this knowledge, unless particulars of such commission and the terms of any agreement for the payment of it have been disclosed to the Authority in writing before the Agreement is made.
- 19.2 If the Provider or any of his employees, agents or sub-contractors, or any person acting on his or their behalf, does any of the Prohibited Acts or commits any offence under the Prevention of Corruption Acts 1889 to 1916, with or without the knowledge of the Provider, in relation to this or any other Agreement with the Crown, the Authority shall be entitled:
- (i) to terminate the Agreement and recover from the Provider the amount of any loss resulting from the termination;
 - (ii) to recover from the Provider the amount or value of any such gift, consideration or commission; and
 - (iii) to recover from the Provider any other loss sustained in consequence of any breach of this condition, whether or not the Agreement has been terminated.
- 19.3 In exercising its rights of remedies under Condition 19.2, the Authority shall:
- (i) act proportionately in the light of the gravity and circumstances of the particular breach; and
 - (ii) give all due consideration, where appropriate, to action other than termination of the Agreement.

20. INDEMNITY AND INSURANCE

- 20.1 The Provider shall indemnify the Authority against any liability, loss, claim or proceedings howsoever arising in respect of:
- (i) any damage to property real or personal including any infringement of third party patents, copyright and Intellectual Property; and
 - (ii) any injury to persons including injury resulting in death arising out of, or in the course of, or in connection with this Agreement, excepting in so far as such damage or injury shall be demonstrated by the Provider to be due to any act or neglect of the Authority, or their officers, servants or agents.
- 20.2 Nothing in this Condition 20 shall operate so as to restrict or exclude the liability of any party in relation to death or personal injury caused by the negligence of that party or its servants, agents or employees or to restrict or exclude any other liability of either party which cannot be so restricted or excluded in law.
- 20.3 In no circumstances shall either party be liable to the other party in contract, tort (including negligence or breach of statutory duty) or otherwise howsoever arising or whatever the cause thereof, for any loss of profit, business, reputation, contracts, revenues or anticipated savings for any special, indirect or consequential damage of any nature, which arises directly or indirectly from any default on the part of any other party.
- 20.4 Subject to Condition 20.2, the Provider's liability to the Authority arising out of or in connection with any breach of this Agreement or any act or omission of the Provider in connection with the performance of the Agreement shall in no event exceed the amount of the Programme Grants for Applied Research Funding payable by the Authority to the Provider under this Agreement.
- 20.5 Without prejudice to Condition 20.1, the Provider shall, if requested by the Authority, throughout the duration of this Agreement effect and maintain with a reputable insurance company a policy or policies of insurance providing an adequate level of cover in respect of all risks which may be incurred by the Provider arising out of the Provider's performance of the Agreement.
- 20.6 The Provider shall produce on demand by the Authority documentary evidence that any insurance policies required by Condition 20.5 are in force.
- 20.7 Should the Provider fail to obtain or maintain insurance as provided in Condition 20.5, the Authority may without prejudice to any other right or remedy itself insure against any risk in respect of which such insurance is required, charge the cost of such insurance, together with an administration charge equal to 5% of the cost of such insurance, to the Provider and deduct such charges from any sums due from the Authority to the Provider under Section 4.
- 20.8 The terms or the amount of cover of any insurance shall not relieve the Provider of any liabilities under the Agreement. It shall be the responsibility of the Provider to determine the amount of insurance that will be adequate to enable the Provider to satisfy any liability referred to in Condition 20.1.

- 21.1 Except as set out in Section 3, the Provider shall not sub-contract, transfer or assign the whole or any part of the Agreement without the prior written consent of the Authority, which consent may be subject to such terms and conditions as the Authority may specify. Approval of a sub-contractor shall be signified by the inclusion of the name in the paragraph in Section 3 entitled "Approved Sub-Contractors".
- 21.2 The Provider shall be responsible for the acts and omissions of its sub-contractors as though they are its own.

22. WAIVER

- 22.1 The failure of the Authority to insist upon strict performance of the Agreement, or the failure of the Authority to exercise any right or remedy to which it is entitled hereunder shall not constitute a waiver thereof and shall not cause a diminution of the obligations established by the Agreement.
- 22.2 A waiver of any default shall not constitute a waiver of any subsequent default.
- 22.3 No waiver of any of the provisions of the Agreement shall be effective unless it is expressly stated to be a waiver and communicated to the other party in writing in accordance with the provisions of Condition 24.

23. DISPUTE RESOLUTION

- 23.1 All negotiations and proceedings connected with any dispute, claim or settlement arising out of or relating to this Agreement ("dispute") shall be conducted in confidence. The performance of obligations under this Agreement shall not cease or be delayed by the application of any procedure to resolve a dispute.
- 23.2 The Parties will attempt in good faith to resolve any dispute promptly through negotiation between their authorised representatives.
- 23.3 If the matter cannot be resolved through negotiation, either Party may, where applicable, refer the matter to the Secretary of State for determination in accordance with section 9 of the National Health Service Act 2006.
- 23.4 Where not so applicable the Parties will, at the request of either of them, attempt in good faith to resolve the dispute through an agreed Alternative Dispute Resolution ("ADR") procedure. If the matter has not been resolved by an agreed ADR procedure within one month of the initiation of such procedure, the dispute shall be referred to a single arbitrator to be agreed upon by the Parties or in default of agreement within 14 days to be nominated by the President for the time being of the Chartered Institute of Arbitrators in accordance with the Arbitration Act 1996. The arbitration shall take place in London and shall be in accordance with the Arbitration Act 1996 and such arbitration rules as the Parties may agree or, in default of agreement, in accordance with the Rules of the London Court of International Arbitration which Rules are deemed to be incorporated by reference into this Clause.
- 23.5 The decision of the Arbitrator shall be final and binding on the Parties.

24. NOTICES

24.1 Any notice or other communication which is to be given by either Party to the other shall be given by letter (sent by hand, post, registered post or by the recorded delivery service), by facsimile transmission or electronic mail (confirmed in either case by letter). Such letters shall be addressed to the other Party in the manner referred to in Section 5. Provided the relevant communication is not returned as undelivered, the notice or communication shall be deemed to have been given two working days after the day on which the letter was posted, or four hours, in the case of electronic mail or facsimile transmission or sooner where the other Party acknowledges receipt of such letters, facsimile transmission or item of electronic mail.

25. FORCE MAJEURE

25.1 For the purposes of the Agreement the expression "Force Majeure" shall mean any cause affecting the performance by a party of its obligations arising from acts, events, omissions, happenings or non-happenings beyond its reasonable control including (but without limiting the generality thereof) governmental regulations, fire, flood, interruption to electricity supply or any disaster or an industrial dispute affecting a third party for which a substitute third party is not reasonably available. Such cause shall only be considered Force Majeure if it is not attributable to the wilful act, neglect or failure to take reasonable precautions of the party claiming Force Majeure or its servants, agents or employees.

25.2 Neither of the parties shall in any circumstances be liable to the others for any loss of any kind whatsoever including but not limited to any damages or abatement of charges whether directly or indirectly caused to or incurred by any of the other parties by reason of any failure or delay in the performance of its obligations hereunder which is due to Force Majeure.

25.3 If either of the parties shall become aware of circumstances of Force Majeure which give rise to or which are likely to give rise to any such failure or delay on its part it shall forthwith notify the others by the most expeditious method then available and shall inform the others of the period which it is estimated that such failure or delay shall continue.

25.4 Any failure by the Provider to perform or any delay by either of the parties in performing its obligations under the Agreement which results from any failure or delay in the performance of its obligations by any person, firm or company with which the Provider shall have entered into any contract, supply arrangement or sub-contract or otherwise, shall be regarded as a failure or delay due to Force Majeure only in the event that the said person firm or company shall itself be prevented from or delayed in complying with its obligations under such contract, supply arrangements or sub-contract or otherwise as a result of circumstances of Force Majeure.

26. RELATIONSHIPS

- 26.1 The Agreement does not make any Party the employee, agent, partner or legal representative of the other Party for any purpose whatsoever. No Party is granted any right or authority to assume or create any obligation or responsibility, expressed or implied, on behalf of or in the name of the other Party. In fulfilling its obligations pursuant to the Agreement the Provider shall be acting as an independent contractor.

27. SEVERABILITY

- 27.1 If any provision of the Agreement is held invalid, illegal or unenforceable for any reason by any court of competent jurisdiction, such provision shall be severed and the remainder of the provisions hereof shall continue in full force and effect as if the Agreement had been executed with the invalid conditions eliminated. In the event of a holding of invalidity so fundamental as to prevent the accomplishment of the purpose of the Agreement, the Authority and the Provider shall immediately commence good faith negotiations to remedy such invalidity.

28. DISCRIMINATION AND HUMAN RIGHTS

- 28.1 The Provider shall not discriminate unlawfully within the meaning and scope of any law, enactment, order, regulation or other similar instrument relating to discrimination (whether in relation to race, gender, disability, religion, age or otherwise) in employment. The Provider shall take all reasonable steps to ensure the observance of the provisions of this Condition by all members of the Provider's personnel and by all sub-contractors of the Provider.
- 28.2 The Provider acknowledges that in relation to the work carried out pursuant to this Agreement it is subject to the Human Rights Act 1998 ("the Act"). The Provider agrees it will:
- (i) at all times act in accordance with the relevant requirements of the Act in relation to matters within the scope of this Agreement;
 - (ii) take such action as the Authority may reasonably require for the purpose of ensuring compliance with such requirements of the Act.

29. FREEDOM OF INFORMATION

- 29.1 The Parties acknowledge that, except for any information which is exempt from disclosure in accordance with the provisions of the FOIA, the content of this Agreement is not Confidential Information. The Authority shall be responsible for determining in its absolute discretion whether any of the content of the Agreement is exempt from disclosure in accordance with the provisions of the FOIA. Notwithstanding any other term of this Agreement, the Contractor hereby gives his consent for the Authority to publish the Agreement in its entirety (but with any information which is exempt from disclosure in accordance with the provisions of the FOIA redacted), including from time to time agreed changes to the Agreement, to the general public.
- 29.2 The Contractor's attention is drawn to the FOIA and the Environmental Information Regulations ("EIRs"). The Department of Health ("DH") has a publication scheme which sets out the type of information publicly available on its website or published as documents. In addition, the Authority has an obligation to respond to specific requests and may be required to disclose information about or provided by the Contractor. In some cases the Authority may consult the Contractor before deciding whether to disclose information requested under FOIA, but it is not obliged to do so. If a Contractor considers that any information it provides to the Authority would be subject to an exemption under FOIA or the EIRs it should clearly identify such information and explain why it considers the information exempt. The Authority will consider such explanation. For the avoidance of doubt, notwithstanding the previous sentence, whether or not information will be disclosed shall be at the Authority's sole discretion.
- 29.3 Where the Authority considers that the Contractor or its collaborator, employee, agent or sub-contractor, is holding information that it requires in order to comply with its obligations under FOIA or the EIRs, the Contractor undertakes to (and shall procure that its collaborators, employees, agents and sub-contractors shall) provide access to such information as soon as reasonably practicable, at its own expense and at no charge to the Authority, on the request of the Authority and in any case within five (5) working days.

30. CONTRACTS (RIGHTS OF THIRD PARTIES) ACT 1999

- 30.1 A person who is not a Party to this Agreement shall have no right to enforce any terms of it which confer a benefit on him.

31. INTERPRETATION

- 31.1 The Agreement will be governed by and interpreted in all respects with the laws of England and Wales.

**PURPOSE AND USE OF NIHR PROGRAMME GRANTS
FOR APPLIED RESEARCH FUNDING**

- 1.1 Funding provided by the Authority under the NIHR Programme Grants for Applied Research scheme is to be used to support work whose emphasis is on delivering research findings that will have practical application for the benefit of patients, typically through improved health care or better health care delivery. The funding provided under this Agreement will be used to meet the recurrent costs of the programme of applied health research approved by the Programme Grants for Applied Research Selection Panel.
 - 1.2 The funding should be used to support a discrete programme of applied health research which is not otherwise supported by the Authority or other funding bodies.
 - 1.3 This funding will be separate from, and additional to, any other NIHR Funding received by the Provider.
- 2. Costs which may normally be met by NIHR Programme Grants for Applied Research Funding**
- 2.1 Eligible costs include those relating to:
 - (i) research staff engaged by the Provider on the approved programme of applied health research
 - (ii) research support staff engaged by the Provider and supporting the approved programme of applied health research.
 - (iii) research training, leading to a higher degree by research (e.g. MPhil, MD, PhD), for staff, of all disciplines, engaged by the Provider on the approved programme of applied health research.
 - (iv) other recurrent, direct research costs associated with the approved programme of applied health research, including infrastructure, essential to deliver the programme, including consumables, consultancy fees, software licences and equipment costing less than £5,000.
 - (v) a reasonable programme overhead to cover indirect costs incurred in the NHS, e.g. costs of accommodation, payroll, HR, and finance associated with this Agreement
 - 2.2 It is normally expected that the staff providing services under this Agreement will be employed by the Provider. However, where there is a local agreement for staff to be employed by the university or other third party, and where this does not attract additional costs over and above the normal costs of employment, this will be allowed (i.e. the cost of employer's contributions will be met, but the posts will not attract Full Economic Costs in the university).
 - 2.3 It is permissible to reimburse, with funding provided under this Agreement, the university partner for the cost of the time devoted to the approved work programme by university employed and funded staff, provided that this does not attract additional costs over and above the normal costs of employment.

- 2.4 Funding under this Agreement may be used to support university research facilities (including laboratories) which are located in NHS premises and are essential for the conduct of applied health research in support of the approved programme of applied health research.
- 2.5 The Provider's costs of supporting UKCRC/MMC Integrated Academic Training awards may be met, where the individual will be providing services under this Agreement.
- 2.6 The Provider's costs of research training (e.g. for higher degrees) associated with the work of an individual providing services under this Agreement can be funded. This can include fees for higher degrees (for NHS staff), and the costs of academic supervision by NHS staff and the use of NHS facilities, when the direct costs of the training are incurred by the university partner. The cost to the University of Academic Supervision of NHS research students working within the approved programme of applied health research may also be met.
- 2.7 Standard NHS accounting policy and guidance (as set out in the NHS Finance Manual) shall be followed in determining the appropriate costs to be charged
- 3. Costs which shall not normally be met by NIHR Programme Grants for Applied Research Funding**
- 3.1 The Provider shall not normally use the funding provided under the Agreement for any of the following costs:
- (i) costs of animal research, or other work which is not applied health research
 - (ii) costs relating to activities undertaken outside the approved programme of applied health research, including infrastructure and support costs of related research supported by other funding bodies
 - (iii) costs of university laboratories or infrastructure which are located in the university
 - (iv) Full Economic Costs of the time of university employed and funded staff devoted to the approved programme of applied health research
 - (v) costs associated with R&D activity which does not have a clear written protocol, and which has not been subjected to appropriate independent peer review
 - (vi) costs of patient care services (i.e. treatment costs as defined in HSG(97)32 dated 29 May 1997), staff training, undergraduate or postgraduate education, not covered above)
 - (vii) costs that are, or should be, in the opinion of the Authority, met by another body, for example a commercial organisation.

PROGRAMME OF WORK

- 1.1 The NIHR Programme Grant for Applied Research Funding will support a programme of applied health research approved by the NIHR Programme Grants for Applied Research Selection Panel entitled:

RP-PG-1209-10071 Bridging the age gap in breast cancer. Improving outcomes for older women dated 18th October 2010 and as amended by email correspondence, dated 5th March 2012, with the abstract as described below:

Breast cancer affects 13000 UK women over age 70 annually. Patients >70 have seen less than half of the reduction in cancer mortality compared to younger women. This is due, in part, to sub-optimal treatment due to concerns about poor treatment tolerance. Older women have not benefitted from the advances in chemotherapy (and trastuzumab) & many do not undergo surgery

There is little research to guide best practice in older patients. National, evidence based guidance is needed to optimise treatment for older women. This programme includes workstreams to provide data to guide best practice & aid older women make informed choices about their care.

Workstreams 1:

Treatment Optimisation.

A) Optimisation of surgery.

Surgery should be offered to all women with breast cancer who are fit enough to tolerate it. Patients who are unfit for surgery may be offered PET as an alternative. However rates of PET vary 4 fold between UK regions suggesting variation in the attitudes of clinicians to treatment in this patient group & the need for guidelines. Modelling, based on retrospective & prospective UK data will be used to develop an accessible web-based clinical management algorithm.

B). Optimisation of Chemotherapy.

Younger women with ER-ve breast cancer may be offered chemotherapy/trastuzumab as an adjuvant to surgery which has significantly enhanced survival. In older women, there is little trial data to guide practice, although evidence suggests chemotherapy may have a relatively smaller benefit & increased risks with increasing age. At present in the UK use of chemotherapy/trastuzumab in women over 70 with ER-ve cancers is infrequent and variable. Fitter women in the 70-75 age range with poor prognosis, ER negative cancers may be offered chemotherapy in some centres. This study will use modelling, based on retrospective & prospective UK data to develop an accessible web-based clinical management algorithm to facilitate individualised decision making.

Workstream 2:

Treatment Decision Support.

Little is known about the information needs of older women with cancer. The programme will develop & evaluate a series of decision support instruments, tailored to older women, to support them in deciding between surgery or PET for those women where both options are likely to give good outcomes. We will also examine clinician attitudes to these treatment options

1.2 Approved sub-contractors

The following sub-contractors are approved by the Authority:

- Cardiff University
- Sheffield Hallam University
- St Helens and Knowsley Hospitals NHS Trust
- University of Birmingham
- University of Bristol
- University of Leicester
- University of Liverpool
- University of Oxford
- University of Sheffield
- University Hospitals of Leicester NHS Trust

FINANCIAL ARRANGEMENTS

1. Payment Arrangements

- 1.1 The total NIHR Programme Grants for Applied Research Funding to be paid by the Authority to the Provider for the period of the Agreement is shown in the payment schedule at Appendix 1 to this Section.

2. Financial Monitoring Arrangements

- 2.1 The Provider is required to provide an annual report to the Authority in a format and containing information specified by the Authority and which will include a statement of expenditure in a format specified by the Authority.
- 2.2 If the total expenditure is less than the funding received by the Provider, the funding for the subsequent financial year shall be reduced by this amount unless the Provider demonstrates its requirement for the original funding in future years.
- 2.3 At the termination of the Agreement the Authority will request a final expenditure statement. If the total expenditure is less than the funding received by the Provider, this amount shall be recovered by the Authority.
- 2.4 If, in the opinion of the Authority, satisfactory progress has not been made against the research objectives in Section 3 at any point during the period of the Agreement payments may be withheld pending satisfactory resolution.

Appendix 1 to Section 4

PAYMENT SCHEDULE

This payment schedule is for Programme Grants for Applied Research award:
(Reference No: RP-PG-1209-10071 Bridging the age gap in breast cancer. Improving outcomes for older women)

It is intended that the indicated amounts will be paid by the Authority to the Provider within 30 days of the dates listed.

Date	Amount (£)
15th July 2012	£89,500
15th October 2012	£89,500
15th January 2013	£89,500
Financial Year 2012 - 2013 sub-total	£268,500
15th April 2013	£89,500
15th July 2013	£89,500
15th October 2013	£89,500
15th January 2014	£89,500
Financial Year 2013 - 2014 sub-total	£358,000
15th April 2014	£89,500
15th July 2014	£89,500
15th October 2014	£89,500
15th January 2015	£89,500
Financial Year 2014 - 2015 sub-total	£358,000
30th June 2015	£89,501
Financial Year 2015 - 2016 sub-total	£89,501
Phase 1 Total	£1,074,001
Release of remaining funding subject to Section 2 clause 3.2	
15th July 2015	£86,105
15th October 2015	£86,105
15th January 2016	£86,105
Financial Year 2015- 2016 sub-total	£258,315
15th April 2016	£86,105
15th July 2016	£86,105
15th October 2016	£86,105
15th January 2017	£86,105
Financial Year 2016 - 2017 sub-total	£344,420
30th June 2017	£86,112
Financial Year 2017 - 2018 sub-total	£86,112
Phase 2 Total	£688,847
GRAND TOTAL	£1,762,848

An appropriate inflation uplift may be added to these payments.

ADMINISTRATIVE INSTRUCTIONS

1. Authorisation

- 1.1 The following person is authorised to act as the Authority's representative on all matters relating to the Agreement:

Mr Raj Flora,
Assistant Director, NIHR Central Commissioning Facility

- 1.2 The Authority's representative may authorise in writing other officers to exercise on his behalf such powers as are contained in the Agreement that he defines.

2. Provider's Representative

- 2.1 The Provider's representative under the Agreement will be:

Professor Malcolm Reed
Professor of Surgical Oncology

3. Correspondence

- 3.1 All correspondence to the Authority shall quote the Agreement reference and be sent to the following address:

NIHR Central Commissioning Facility
Grange House
15 Church Street
Twickenham
TW1 3NL

- 3.2 All correspondence to the Provider shall be appropriately referenced and sent to the following address:

Professor Malcolm Reed
Academic Unit of Surgical Oncology, University of Sheffield
Glossop Road
Sheffield
South Yorkshire
S10 2JF

Appendix 4: Systematic review and Cochrane search strategies

MEDLINE (Cochrane)

▲ Searches

- 1 randomised controlled trial.pt.
- 2 randomized controlled trial.pt.
- 3 controlled clinical trial.pt.
- 4 randomized.ab.
- 5 randomised.ab.
- 6 placebo.ab.
- 7 randomly.ab.
- 8 trial.ab.
- 9 groups.ab.
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 early breast cancer.mp.
- 12 early breast carcinoma.mp.
- 13 early breast tumor.mp.
- 14 early breast tumour.mp.
- 15 early breast neoplasm.mp.
- 16 locally advanced breast cancer.mp.
- 17 locally advanced breast carcinoma.mp.
- 18 locally advanced breast neoplasm.mp.
- 19 locally advanced tumor.mp.
- 20 locally advanced tumour.mp.
- 21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
- 22 exp Mastectomy/
- 23 mastectom\$.mp.
- 24 surger\$.mp.
- 25 wide local excision.mp.
- 26 axillary surger\$.mp.
- 27 22 or 23 or 24 or 25 or 26
- 28 endocrine therapy.mp.
- 29 primary endocrine therapy.mp.
- 30 exp Tamoxifen/
- 31 tamoxifen.mp.
- 32 29 or 30 or 31

- 33 10 and 21 and 27
- 34 10 and 21 and 27 and 28
- 35 10 and 21 and 32
- 36 33 or 34 or 35

37 limit 36 to (humans and yr="2008 -Current")

EMBASE (Cochrane)

- #41: #40 AND [humans]/lim AND [embase]/lim AND [2008-2013]/py
- #40: #37 OR #38 OR #39
- #39: #9 AND #27 AND #36
- #38: #9 AND #27 AND #32 AND #33
- #37: #9 AND #27 AND #32
- #36: #34 OR #35
- #35: 'tamoxifen'/exp OR tamoxifen
- #34: 'primary endocrine therapy'
- #33: 'endocrine therapy'/exp OR 'endocrine therapy'
- #32: #28 OR #29 OR #30 OR #31
- #31: 'axillary surgery'
- #30: 'wide local excision'/exp OR 'wide local excision'
- #29: 'surgery'/exp OR surgery
- #28: 'mastectomy'/exp OR mastectomy
- #27: #15 AND #26
- #26: #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
- #25: 'locally advanced breast tumor'
- #24: 'locally advanced breast tumour'
- #23: 'locally advanced breast carcinoma'
- #22: 'locally advanced breast neoplasm'
- #21: 'locally advanced breast cancer'
- #20: 'early breast tumor'
- #19: 'early breast tumour'
- #18: 'early breast carcinoma'
- #17: 'early breast cancer'
- #16: 'early breast neoplasm'
- #15: #10 OR #11 OR #12 OR #13 OR #14
- #14: 'breast tumor'/exp OR 'breast tumor'
- #13: 'breast tumour'
- #12: 'breast carcinoma'/exp OR 'breast carcinoma'
- #11: 'breast cancer'/exp OR 'breast cancer'
- #10: 'breast neoplasm'
- #9: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
- #8: groups:ab
- #7: trial:ab
- #6: randomly:ab

- #5: placebo:ab
- #4: randomi*ed:ab
- #3: controlled AND clinical AND trial
- #2: randomized AND controlled AND trial
- #1: randomised AND controlled AND trial

WHO ICTRP (Cochrane)

Basic Searches:

1. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)
2. (Surgery AND endocrine therapy) AND breast cancer
3. (mastectomy AND endocrine therapy) AND breast cancer
4. Primary endocrine therapy AND breast cancer

Advanced Searches:

1. Title: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Recruitment: All
2. Condition: early breast cancer. Intervention: surgery AND endocrine therapy. Recruitment Status: All
3. Condition: locally advanced breast cancer. Intervention: surgery AND endocrine therapy. Recruitment Status: All
4. Condition: early breast cancer. Intervention: surgery OR endocrine therapy. Recruitment Status: All
5. Condition: locally advanced breast cancer. Intervention: surgery OR endocrine therapy. Recruitment Status: All
6. Condition: early breast cancer. Intervention: primary endocrine therapy OR Tamoxifen. Recruitment Status: All
7. Condition: locally advanced breast cancer. Intervention: primary endocrine therapy OR Tamoxifen. Recruitment Status: All

ClinicalTrials.gov (Cochrane)

Basic Searches:

1. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)
2. (Surgery AND endocrine therapy) AND breast cancer

3. (mastectomy AND endocrine therapy) AND breast cancer
4. Primary endocrine therapy AND breast cancer

Advanced Searches:

1. Title Acronym/Titles: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Recruitment: All Studies. Study Results: All Studies. Study Type: All Studies. Gender: All Studies
2. Condition: early breast cancer OR locally advanced breast cancer. Intervention: surgery AND endocrine therapy. Recruitment: All Studies. Study Results: All Studies. Study Type: All Studies. Gender: All Studies
3. Condition: early breast cancer OR locally advanced breast cancer. Intervention: surgery OR endocrine therapy. Recruitment: All Studies. Study Results: All Studies. Study Type: All Studies. Gender: All Studies
4. Condition: early breast cancer OR locally advanced breast cancer. Intervention: primary endocrine therapy OR Tamoxifen. Recruitment: All Studies. Study Results: All Studies. Study Type: All Studies. Gender: All Studies

CENTRAL (Cochrane)

- #1 MeSH descriptor: [Breast Neoplasms] explode all trees
- #2 early breast cancer* or early breast neoplas* or early breast tumour* or early breast tumor*
- #3 locally advanced breast cancer* or locally advanced breast neoplas* or locally advanced breast tumour* or locally advanced breast tumor*
- #4 #2 or #3
- #5 #1 and #4
- #6 MeSH descriptor: [Mastectomy] explode all trees
- #7 mastecom* or surger* or wide local excision or axillary surger*
- #8 #6 or #7
- #9 endocrine therap*
- #10 primary endocrine therapy or tamoxifen
- #11 MeSH descriptor: [Tamoxifen] explode all trees
- #12 #10 or #11
- #13 #5 and #8
- #14 #5 and #8 and #9

#15 #5 and #8 and #12

#16 #13 or #14 or #15

Re-run Search EMBASE, MEDLINE, PsycINFO, CINAHL (JM #1):

1. "Primary endocrine therapy".ti,ab; 156 results.
2. "breast cancer".ti,ab; 372631 results.
3. tamoxifen.ti,ab; 39543 results.
5. letrozole.ti,ab; 3840 results.
6. anastrozole.ti,ab; 171 results.
7. Exemestane.ti,ab; 1905 results.
8. Arimidex.ti,ab; 586 results.
9. Femara.ti,ab; 206 results.
10. Aromasin.ti,ab; 80 results.
12. "aromatase inhibitor".ti,ab; 5542 results.
13. 1 OR 3 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 12; 45314 results.
14. "breast carcinoma".ti,ab; 41713 results.
15. 2 OR 14; 397757 results.
16. ("elderly women" OR "older women" OR "over 70 years" OR "over 65 years" OR "over 80 years").ti,ab; 53112 results.
17. 13 AND 15 AND 16; 556 results.
18. (adjuvant OR neoadjuvant).ti,ab; 218474 results.
19. 17 NOT 18; 231 results.
20. Duplicate filtered: [17 NOT 18]; 231 results.
21. (cohort OR longitudinal OR population).ti,ab; 2635192 results.
22. 17 AND 21; 149 results.
23. Duplicate filtered: [17 AND 21]; 149 results.
24. 19 OR 22; 321 results.
25. ("randomised control trial" OR "RCT" OR "randomized control trial").ti,ab; 24301 results.
26. 17 AND 25; 1 results.
27. 24 OR 26; 299 results.
28. Duplicate filtered: [24 OR 26]; 299 results.

Re-run Search EMBASE, MEDLINE, PsycINFO, CINAHL (JM #2):

1. breast.ti,ab; 620918 results.
2. mammary.ti,ab; 116787 results.
3. 1 OR 2; 703410 results.
4. carcinoma.ti,ab; 865262 results.
5. tumour.ti,ab; 327512 results.

6. tumor.ti,ab; 1534028 results.
7. cancer.ti,ab; 2198338 results.
8. malignant.ti,ab; 580370 results.
9. malignancy.ti,ab; 191631 results.
10. 4 OR 5 OR 6 OR 7 OR 8 OR 9; 4121836 results.
11. elderly.ti,ab; 434690 results.
12. older.ti,ab; 661946 results.
13. (age AND 65).ti,ab; 207197 results.
14. (over AND 65).ti,ab; 100427 results.
15. (age AND 70).ti,ab; 193387 results.
16. (over AND 70).ti,ab; 117974 results.
17. (age AND 75).ti,ab; 177202 results.
18. (over AND 75).ti,ab; 100641 results.
19. (age AND 80).ti,ab; 179242 results.
20. (over AND 80).ti,ab; 125010 results.
21. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 1754791 results.
22. 3 AND 10 AND 21; 34122 results.
23. "primary endocrine therapy".ti,ab; 156 results.
24. 3 AND 10 AND 23; 137 results.
25. Duplicate filtered: [3 AND 10 AND 23]; 137 results.

Appendix 5: NIGB approvals for registry study

NIGB

Ethics and Confidentiality Committee

Ms Lynda Wyld
The Medical School
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*5th Floor, Skipton House,
80 London Road
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SE1 6LH
Tel: (020) 7004 1539
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20 February 2013

Dear Ms Wyld

ECC 8-04 (g)/2013 Bridging the Age Gap in Breast Cancer: Improving Outcomes for Older Women

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions. This application was considered on 06 February 2013.

Secretary of State decision

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined that the application should be provisionally approved.

Context

This research application from the University of Sheffield detailed a study which aimed to determine the age, co-morbidity, frailty and disease characteristics of women over 70 with early breast cancer in order to provide guidance on 2 primary questions:

1. What are the personal and cancer characteristics of women who can be safely advised that surgery is unlikely to confer any advantage to them?
2. What are the personal and cancer characteristics of women who should be advised to have adjuvant chemotherapy after surgery?

Support was requested in order to access linked HES and cancer registry data which included date of death.

ECC advice

Members considered the application at their meeting on the 06 February 2013, the advice provided to the SofS is reproduced below.

Members discussed that the questions posed by the study were important and were supportive of the activity taking place.

Practicable alternatives

Members considered whether there was a practicable alternative to the use of identifiable data in this instance and noted that the argument for requiring full date of death had been discussed at length and approved in relation to previous cancer studies.

Compliance with the DPA principles

One of the requirements of the Regulations is that applications should not be inconsistent with the Data Protection Act 1998 (DPA), with this in mind members noted that the application did not detail any fair processing activities in relation to the activity. Members advised that reasonable efforts should be made to ensure that the cohort is informed about the processing of data for the specified purposes.

ECC conclusion

In line with the comments above, members agreed that the minimum requirements of the Regulations appeared to have been met and agreed to provide a recommendation of approval for this activity, subject to the following conditions.

Conditions of support

1. Confirmation of a favourable REC opinion. **Received**
2. Confirmation of satisfactory security arrangements. Please note there has been a change to the security review process. Please review the following link (<http://www.nigb.nhs.uk/s251/forms>) which sets out the change, and please follow the guidance given. If you have any queries over this, please contact the Exeter Helpdesk. You can contact the Exeter helpdesk on 01392 251289 or exeter.helpdesk@nhs.net
3. Reasonable efforts should be made to inform the cohort of the processing to ensure that the requirements of the DPA are met.

Further actions

Once the conditions of approval have been accepted or met final confirmation of approval can be provided.

Important changes

Please note that the current administration of applications made under these Regulations by the NIGB Ethics and Confidentiality Committee is due to transfer to the Health Research Authority by 01 April 2013. Such arrangements will be communicated to applicants once confirmed.

Please do not hesitate to contact me if you have any queries following this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
NIGB Deputy Approvals Manager

Cc. London - South East, nrescommittee.london-southeast@nhs.net

Standard conditions

The approval provided by the Secretary of State for Health is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and that there is no disclosure of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.

4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent of the Secretary of State is facilitated and supported.
8. The wishes of patients who have withheld or withdrawn their consent are respected.
9. The NIGB Office is notified of any significant changes (purpose, data flows, security arrangements) to the application.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter. Details are available on the NIGB website.
11. Any breaches of security around this particular flow of data should be reported to the NIGB within 10 working days, along with remedial actions taken.

Appendix 6: Variation in Clinician Preference study protocol



The
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Of
Sheffield.

Sheffield Teaching Hospitals **NHS**
NHS Foundation Trust
Excellence as standard

Variation in Clinician Preferences for Treatment in Older Women with Operable Breast Cancer.

Protocol Version 1.0

24th October 2012



Study Protocol version:1.0

Date: 24th October 2012
Study Start Date: 1st October 2012
Funder: National Institute for Health Research
Funding Type: Programme Grant
Award Number: RP-PG-1209-10071
Sponsoring Body: Sheffield Teaching Hospitals NHS Foundation Trust

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Study Team.

Research Fellow:

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Specialist Advisors:

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Qualitative and Mixed Methodology Advisors:

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Name here, Breast Care Nurse, Royal Hallamshire Hospital, Seffield, E-mail: . Tel. .

STH NHS Foundation Trust Administrator:

Erica Wallis, Senior Research Coordinator, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield. E-mail: Erica.Wallis@sth.nhs.uk. Tel. 0114 2265931.

MD Supervision:

The project will form the basis of a higher degree for Jenna Morgan.

Primary Supervisor:

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Secondary supervisor:

Dr Karen Collins, Principal Research Fellow. Centre for Health and Social Care Research, Sheffield Hallam University, Faculty of Health and Wellbeing, 32 Collegiate Crescent, Sheffield, S10 2BP. E-Mail: k.Collins@shu.ac.uk.

Executive Summary.

Breast cancer is now the most common cancer in the UK, with 48,000 cases diagnosed in the UK each year [Cancer Research UK, 2009]. A third of these occur in women over the age of 70 years [Reed MWR, 2009]. Recent reports demonstrate that patients aged over 70 years are the only group of cancer patients in the UK where the mortality from cancer is not falling and may even be rising [Bastiaannet E, 2011]. This is thought to be due, in part, to under-treatment.

One area of practice where treatment in older women differs from that in younger women is the omission of surgery in women with oestrogen receptor positive cancer. Surgery is the mainstay of treatment for younger women, but in frailer, older women, surgery may be avoided and disease control achieved with anti-oestrogens alone. This is called primary endocrine therapy (PET). This may be a perfectly appropriate treatment option in frailer older women, for whom operative intervention may be associated with increased risks of complications because of pre-existing co-morbidities or frailty. However practice in the UK is highly varied with some health regions operating on almost 90% of older women, others on only 60%. This suggests that guidelines on best practice are urgently needed to standardise care. Much of the data on the use of PET was derived from studies which are now 30 years old. In this time life expectancy has risen, with many people still healthy and fully independent in their 70s and 80s. The resulting effect is that some older women may be under-treated, whilst others are over-treated.

Currently, there are no treatment guidelines to determine which patients should be offered PET as opposed to surgery. The decision is a complex one with many factors that may influence how a particular patient is managed, for example: co-morbidities, cognitive function, frailty and dependence, patient preference and clinician preference.

This proposed mixed methodology study has 3 stages:

1. Systematic review of the current published literature on clinician preferences for surgery versus primary endocrine therapy in older women with operable breast cancer.
2. Elicit the views and preferences of specialist health care professionals regarding the benefits and risks of surgery and primary endocrine therapy through semi-structured, purposively selected interviews.
3. Use of a bespoke questionnaire to quantify the strength of each theme identified in stages 1 and 2. This will permit the study team to determine levels of clinician practice variance and the key factors that underpin this.

Background.

An Ageing Population.

The population of the UK is aging and the average life expectancy has increased by 30 years during the last century, with most people now expected to live into their 80s [Christensen K, 2009]. The elderly are the most rapidly increasing population group [Olshansky SJ, 2001] and the overall health status of this group is also improving [Christensen K, 2008; Christensen K, 2009]. Improved disease prevention with better control of chronic diseases, mean the elderly are living longer even in the presence of chronic health problems. Despite this, there is wide variation in the health status of this age group, with some 75 year olds who are fit and healthy, living an active lifestyle, whilst others are frail, with multiple co-morbidities, necessitating assisted living. Determining best practice in this group is therefore complicated and treatment requires tailoring to individual patients, not to their chronological age.

Breast Cancer in Older Women.

A third of the 48,000 breast cancers diagnosed in the UK each year occur in women over the age of 70 years [Reed MWR, 2009]. Recent reports demonstrate that patients aged over 70 years are the only group of cancer patients in the UK where the mortality from cancer is not falling and may even be rising [Bastiaannet E, 2011]. This inequality is a major priority for the NHS [Department of Health, 2012].

Breast cancer in older women tends to have a slightly different disease biology than in younger women, with higher rates of oestrogen sensitivity [McCarty KS, 1983; Diab SG, 2000], lower rates of HER-2 receptor expression [Diab SG, 2000] and a slower growth rate [Diab SG, 2000]. However, older women tend to present with more advanced breast cancer [Schonberg MA, 2010]. The size of the primary tumour is larger [Diab SG, 2000; Golledge J, 2000; Maidone MG, 2003; Monfardini S, 2009] and there are increased rates of locally advanced [Eaker S, 2006] and metastatic disease [Yancik R, 1989; Wyld L, 2004].

Breast cancer outcomes have been shown to be inferior in older women compared to those in younger women [Bastiaannet E, 2009; Wishart GC, 2010; van de Water W, 2012]. Despite this, however, the clinical significance of breast cancer is proportionally less in older women as breast cancer specific mortality is overtaken by other cause mortality once a woman is in her early 80s. This translates to breast cancer causing only approximately 23% of deaths in women with breast cancer in their mid-80s, compared to 73% of deaths in patients in their early 50s [Diab SG, 2000]. However the interactions of age, co-morbidity and frailty in older patients with breast cancer has a significant impact on disease outcomes and there is convincing evidence that women over the age of 80 have a higher risk of dying of their breast cancer than women in their 70s [van der Water W, 2012]. It is thought that this may be due, in part to sub-optimal treatment [Schonberg MA, 2010]. Clinician awareness of these interactions would enable treatment to be optimised to prevent over- or under-treatment.

Treatment of Breast Cancer in the Elderly: Surgery versus PET

The mainstay of treatment for breast cancer in most women is surgery, and whilst fitter older women should ideally be offered the same treatments as younger women, less aggressive strategies may be justified for frailer patients where surgery may carry increased risks. Primary endocrine therapy (PET) is an example of a modified treatment strategy that is suitable for this group of patients, and uses only medical therapy in the form of anti-oestrogen drugs, such as Tamoxifen. Up to 90% of breast cancers in older women express the oestrogen receptor (ER) [McCarty KS, 1983; Diab SG, 2000] which, when stimulated, promotes tumour growth. Anti-oestrogen therapies block the ER, causing tumour regression. PET is an effective means of breast cancer control in the short to medium term in frailer older women [Hind D, 2007] and has the advantage of avoiding anaesthesia with its risks of cardio-respiratory complications, as well as avoiding the physical and psychological morbidity of surgery.

Primary Endocrine Therapy was first described in the late 70s and early 80s and rapidly became popular [Preece PE, 1982; Bradbeer JW, 1983], with early response rates of 75% or better [Preece PE, 1982; Bradbeer JW, 1983]. Whilst initially effective, well-tolerated and associated with a low complication rate, tumour re-growth occurs within a median of around 24 months [Fentiman IS, 2003; Mustacchi G, 2003] and second line therapy is required.

Randomised controlled trials comparing PET with surgery have shown PET to have inferior local disease control rates [Robertson JF, 1988; Gazet JC, 1994; Mustacchi G, 1998; Fentiman IS, 2003; Mustacchi G, 2003]. Despite this, there is no mortality disadvantage on meta-analysis of all trials, although there is a trend in favour of surgery [Hind D, 2006]. In addition, since these trials were carried out, a new, more potent class of anti-oestrogen drugs (the aromatase inhibitors) have become available [Eiermann W, 2001; Ellis MJ, 2001; Mouridsen H, 2003; Howell A, 2005], meaning that PET may now be more efficacious if candidates are selected appropriately.

Patients themselves have demonstrated a high degree of satisfaction with both surgery and PET [Husain LS, 2008]. Factors in favour of PET include: avoidance of hospitalisation and surgery, a desire to retain independence, fear of anaesthesia and a desire for minimal disruption to life and independence [Husain LS, 2008].

Variation in Practice.

In the UK there is wide variation in practice relating to the treatment of older women with breast cancer, with some areas demonstrating a 40% rate of PET, whilst in other areas the rate is only 10% [BCCOM Audit, 2007]. The concern is that women in centres with low

surgery rates will be inappropriately denied operative intervention, with the long-term consequences of local recurrence, necessitating a change in management. Conversely, in regions with high rates of surgery, women may be inappropriately subjected to the morbidity or even mortality of surgery with no benefit.

Regionally, variance may be explained in part by deprivation levels. The low PET rate regions are in southern England (Oxford and Thames), where rates of deprivation are low. The higher PET rate areas are in northern England (Yorkshire and Humber, North East) where levels of deprivation are higher. It is widely accepted that deprivation levels are linked to higher burdens of other diseases, rates of smoking, lower levels of educational attainment and lower screening uptake rates. These factors may contribute to women presenting at a later stage in their disease and being less able to undergo safe surgery. This is speculation as no study has looked at this issue and it is unlikely to account for a 4 fold variation in practice.

Clinician preference may also form a substantial cause of practice variance. Anecdotal evidence indicates that some surgeons have a very strong preference for surgery and others feel that PET is appropriate for the majority of older women. The causes of this varying opinion are not known but may include person experience, interpretation of the literature or unit protocols. It may also be affected by the anaesthetic staffs' attitudes to anaesthesia in older women and the availability of regional and local anaesthesia techniques.

This study will examine the variance in practice by two means. Initially, a series of interviews with health care professionals will be undertaken in units with high, intermediate and low rates of non-surgical treatment. This will establish the factors taken into account when assessing older women for treatment and the personal weights that clinicians place on these. Following this a bespoke questionnaire will be used to quantify these factors and correlate them with the different health regions. This will incorporate a number of scenarios relating to hypothetical older women with varying levels of health, fitness, cognition etc. This will enable us to explore the contribution of physician opinion in treatment decisions and how this varies by health region. A separate study which is not included in this protocol (and is part of a separate ethics application) will study regional PET rates and case mix adjustment (for issues such as stage at diagnosis, deprivation levels, screening etc).

Summary

Consistently research has reported that older women (>70 years) have huge variation in their breast cancer treatment pathways compared to younger women and that this variance is, in part, determined by locality.

Given than most breast cancers occur in older age it is important that this group receive appropriate treatment options based on their personal health status and treatment preferences rather than their chronological age. There is a need for more standardised assessment of patient fitness, taking into account individual co-morbid status and frailty.

This study will give an insight into the factors that are taken into account when clinicians are deciding on treatment plans for older women. It is part of a larger programme of research which will also determine the factors the older women themselves take into account when they decide on how they wish to be treated and the outcomes of different treatments in this age group. It is hoped that the research will enable the development of guidelines for optimised, individualised care of older women with breast cancer.

Aims of the study.

1. To explore the views of specialist healthcare professionals towards to management of older women (>70yrs) with operable breast cancer, particularly in terms of PET versus surgery.
2. To determine the factors underlying treatment decision making in health care professionals relating to older women with breast cancer.
3. By means of a bespoke questionnaire, to quantitatively assess the above factors on a wide group of healthcare professionals and correlate these findings with local social and demographic factors.

Study Outcomes.

Primary Outcome:

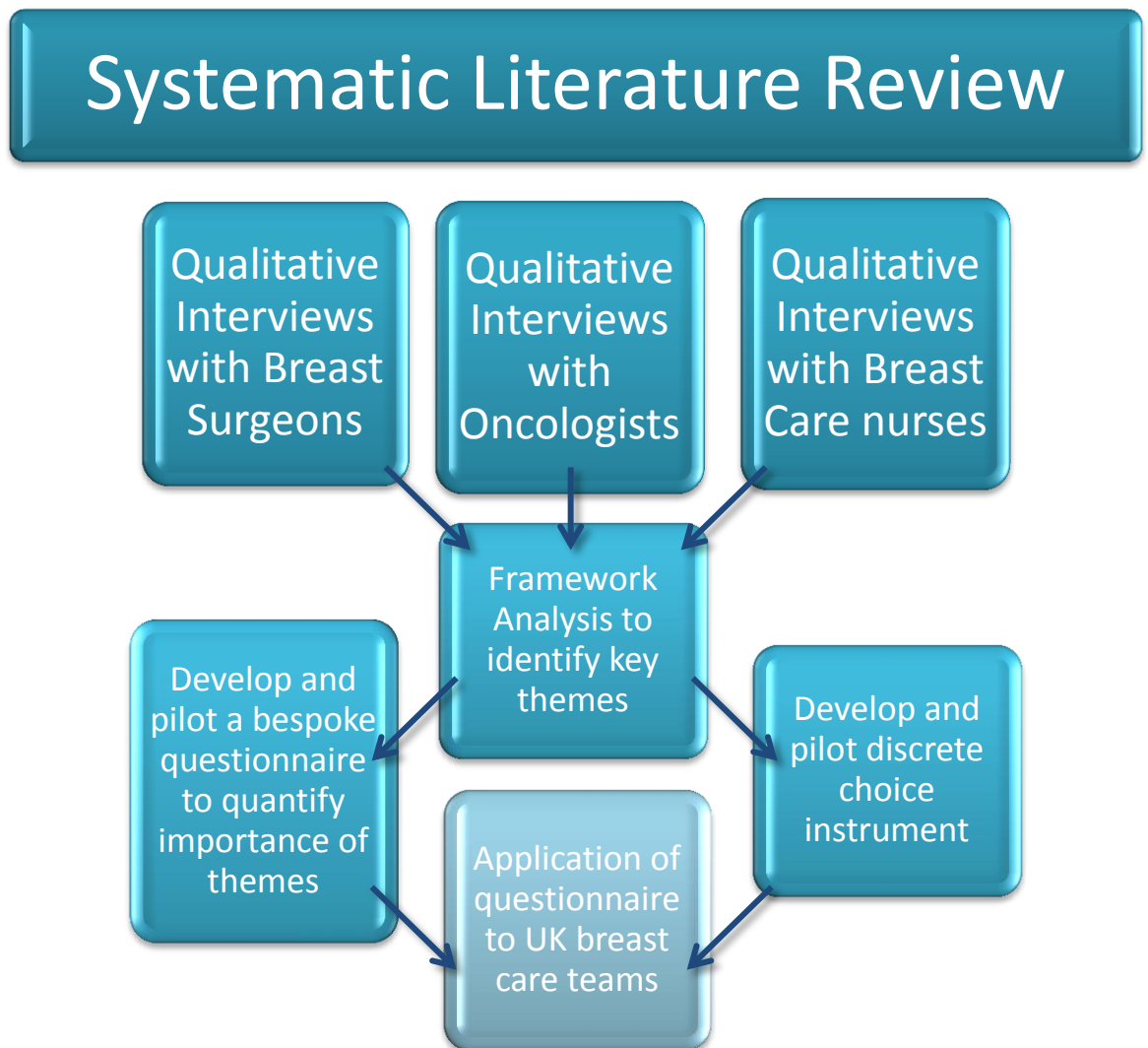
To determine the factors underlying treatment decision making in health care professionals relating to older women with breast cancer.

Secondary Outcome:

To determine the level of variance in decision making practice amongst health care professionals.

Research Methods.

Study Design:



Detailed Methodology.

Stage 1: Literature Review.

Search Strategy.

A systematic search of studies, both published and unpublished, focusing on the risks and benefits of PET versus surgery in older women (>70 years) with operable breast cancer will

be performed. Studies focusing on decision making and risk perception relating to health care professionals when treating older women, will also be reviewed. Additionally, cohort studies looking at the treatment of this group of patients will be sought to try and further clarify current practice.

The following electronic databases will be searched from as primary resources. The Cochrane Library, CRD databases (DARE, NEED, HTA), Medline, Embase, Psycinfo, CINAHL, Specialist databases (Cancer lit in PubMed, Oncolink and Scopus). Searching of key websites, for example The Royal College of Surgeons, will also be undertaken. Hand-searching of papers, grey literature (using the British Library's Integrated Catalogue), current research projects (NIHR Clinical Research Network Portfolio database, HTA database) and reference lists of relevant papers will also be reviewed.

Stage 2: Qualitative interviews with health care professionals

This study will establish the views and preferences of a range of health care professionals with expertise in breast care regarding the breast cancer treatment options; surgery (+ adjuvant endocrine therapy) and PET, and the factors influencing these. Data will be collected via semi-structured qualitative interviews. Maximal variation sampling will be used to include different types of HCP (surgeons, oncologists, and breast care nursing) and HCP from breast units with different rates of surgery or PET usage. Interview data analysis using the Framework Approach will occur alongside recruitment, and recruitment will cease on achievement of data saturation. From previous work in the field it is anticipated approximately 35 interviews will be required.

Regulatory Approvals.

Research and Development approval will be obtained for the project. All study researchers will have undergone full GCP training and hold valid NHS research passports.

Sites.

The study will recruit health care professionals from breast units across the UK. Units will be identified by examination of published rates of PET versus surgery for a particular region which is freely available via national cancer dataset such as the BCCOM audit [BCCOM Audit, 2007]. Within regions identified as having high, low or intermediate rates of PET, contact will be made with a local principle investigator who will be asked to identify surgeons, oncologists, and breast care nurses for contact. Data will be requested on rates of non-surgical treatment for each unit to validate registry and national audit data.

Units identified include:

PET rates	Units Identified	PI
High	Derby	KL Cheung
	Nottingham	Ms Ellie Gutteridge
	Newcastle	Mr Richard Bliss, Mr Andy Griffiths and Professor Tom Lennard
Intermediate	Sheffield	Lynda Wyld
	Leicester	Anne Stotter
	Cardiff	Professor Robert Mansel and Professor Helen Sweetland
Low	Oxford	Charlie Chan
	Whiston	Riccardo Audisio
	London, Guys	Michael Douek

Recruitment.

A local principle investigator (PI) will be identified at each site by direct contact from a member of the study team. The PI will be asked to provide a list of names of suitable health care professionals working within the unit who may be happy to be contacted by the study team. Individuals will then be sent a study pack by post which will contain the following: a letter of invitation, a participant information sheet (PIS), a study reply slip and a freepost envelope. A sample letter of invitation/PIS is contained in Appendix I. This will invite the HCP to complete a reply slip to agree to be contacted about taking part. A sample reply slip is in Appendix II. On receipt of a reply slip indicating agreement to participate, the research team will contact the interview candidate and arrange a time and place to meet. This will be agreed verbally and confirmed in writing before the scheduled date. A consent form will be signed before the interviews commence (Appendix III).

Conduct of the Interviews.

Participants will be contacted again the day before their interviews to ensure they still wish to proceed. They will be given an opportunity to decline if they so wish. All interviewees will be reassured that they may terminate or pause the interview at any point without stating a reason for doing so and that their participation is entirely voluntary. If wished, telephone interviews may be offered. All interviews will be digitally recorded and transcribed verbatim. All data collected will be pseudo-anonymous and databases password protected in accordance with the Data Protection Act. Feedback from the research will be offered to all study participants.

Interview Schedule and Content.

An interview schedule has been developed by the study team. This will enable the interviews to explore key issues but also give opportunity for free expression of views with

open questions. The areas for discussion are based on previous interviews with health care professionals [Hussain LS, 2007; Walters S, 2011] where similar issues were explored and which will serve as pilot projects for the present study.

The interviews will explore the following areas:

What treatment options would you normally consider for an older woman (over 70) with operable primary breast cancer?	
Prompts:	Would surgery form part of your potential management plan in all patients? Is PET an option for all patients in this group?
What do you feel are the risks and benefits of surgery and PET for this age group?	
Prompts:	Morbidity and mortality of surgery Local recurrence risks, local control Compliance
What factors influence your choice of management for a particular patient with primary operable breast cancer?	
Prompts:	Age of patient at diagnosis Frailty of patient Co-morbidities, including dementia Anaesthetic considerations Optimisation of other health issues Patient choice Carer preferences Guidelines Stage/operability of cancer Cancer biology (e.g. ER and HER2 status, mucinous subtype) Pre-operative assessment: anaesthetic assessment, formal geriatric assessment, "end of the bed" assessment
Are there any other factors that influence your overall practice in this patient group?	
Prompts:	Influence of cancer targets Influence of costs
If in such patients there is the potential for choice of either surgery or primary endocrine therapy, what level of involvement does the patient play in the management decision?	
What factors have influenced your personal strategy for dealing with these patients?	
Prompts:	Literature evidence Patient preference Experience of cases over the years Unit policy Training and mentoring Breast care nurse input
What affects the amount of information you relay to a patient following a diagnosis of breast cancer?	
Prompts:	Patient wishes Patient cognitive status Relative and carers information needs
What do you think elderly women feel about primary endocrine therapy?	

Prompts:	Easier than having surgery Safer than having surgery Less certainty of a cure Less hassle
What do you think elderly women feel about having surgery?	
Prompts:	Fear of death Disfigurement or loss of breast Fear of hospitalisation Burden on others Loss of independence Complications (e.g. arm swelling)
Any additional comments the participant would like to add	

Data Analysis.

Qualitative interview transcript analysis will follow the National Centre for Social Research Framework” approach, to identify recurrent themes [Richie J, 2003]. The Framework approach permits the systematic analysis of large volumes of textual data and permits within and across case and theme comparison. Analysis will be undertaken by Jenna Morgan with oversight/supervision from three experienced qualitative researchers (Dr Collins and Ms Wyld). A thematic index will be drawn up and applied to the data. Data will be distilled, summarised and entered into thematic charts to allow examination and interpretation of the data and to identify any relationships between themes.

Stage 3: Questionnaire Study.

In order to quantify the findings of earlier phases of the study and link them to participant and locality characteristics, a bespoke questionnaire will be developed based on the themes and findings of the qualitative interviews.

An initial pilot questionnaire will be developed and will be reviewed by means of several focus groups by health care professional members of the study team and the extended ‘bridging the Age Gap in breast cancer study team (LW, MWR, LC, RAA, AS, REC) and members of the surgical and breast care nursing team locally in Sheffield, to ensure it has content and face validity, is comprehensible and useable. The survey will be piloted to examine the length, acquiescent response set, flow, salience, ease of administration and response and acceptability to respondents [Boynton PM, 2004]. Respondents will also be asked to indicate how long it took them to complete the questionnaire and will be invited to comment on any questions which were difficult to interpret or to answer. Appropriate modifications will be made to the design and content of the questionnaire before it is sent out to the wider population of UK healthcare professionals.

The questionnaire will contain questions themed around risks, benefits and preferences for PET and surgery in older women with a variety of clinical characteristics and presentations. Age, sex, locality and professional status (trainee, consultant) and professional type (BCN, Surgeon, Oncologist) will provide baseline demographics. A preliminary version of the questionnaire to show the integral participant information sheet, format and probable content is attached to this document (Appendix IV) but will be modified by phases 1 and 2.

The questionnaires will be sent to relevant healthcare professionals via post and/or e-mail, along with a covering letter (Appendix VI) and individual participants will identify themselves to the research team by returning the completed questionnaire, thus ensuring participant confidentiality, and providing implied consent.

Recruitment.

The questionnaire will be sent to all members of the Association of Breast Surgeons, both surgeon and BCN members. It will also be sent to the Association of Cancer Physicians. Respondents will be asked to tick a box to state what UK health region they work in and whether their area is rural or urban, affluent, intermediate or deprived to allow estimation of whether they are in a high, low or intermediate PET rate region and will also be asked to estimate what percentage of their older breast cancer cases they treat with PET or surgery (tick box categories). Responses will thereby remain anonymous. The questionnaires will be prepared and made up into packs together with a prepaid envelope and sent to the association who will undertake the mailing to maintain confidentiality. Return of a completed questionnaire will be taken as indicative of consent.

A record of the number of packs sent out will be kept and correlated with the number returned to give the response rate. Based on our previous similar study we expect a response rate of 40%. No reminders will be sent.

Statistical Analysis Plan and Sample Size Calculation.

The first part of the questionnaire is essentially descriptive and will be analysed by calculation of median response and range to the Likert style questions. Correlation of response medians with HCP characteristics such as age subgroup and professional subtype will be performed using Chi squared test.

The discrete choice questionnaire wherein scenarios are described and treatment preferences for PET or surgery or undecided will be analysed. Discrete choice scenarios provide information on the relative weights individual professionals attach to the various dimensions (variables) involved in the decision making process and how willing they are to trade these off against each other in reaching a decision. Respondents will be provided with pair wise choices between hypothetical scenarios and asked to choose their preferred scenario from each pair. These choices can then be used to infer the trade-offs people are willing to make with respect to changes in the levels of the attributes.

This part of the survey will be developed in conjunction with Professor Stephen Walters. Scenarios will be evaluated by Professor Tom Robinson to determine whether all are realistic representations of real life older women and also to estimate whether individual scenarios would be associated with a predicted life expectation of less than 2 year, 2-5 years or greater than 5 years. These time periods have been selected as women with predicted life expectancies of less than 2 years will be likely to gain no benefit from surgery whereas those likely to survive for over 5 years are likely to develop disease progression without surgery, based on a median effect duration of PET from published literature of 24 months.

For pragmatic reasons (survey length and acceptability), a limited number of variables can be incorporated into the study design. The key variables included in this survey will be patient age, health status, cognitive function, functional status and breast cancer ER status. Scenario descriptions will then be generated by 'Orthoplan' software from SPSS, converting an orthogonal array of dimensions and their levels into an additive model, generating all possible combinations of levels of the key variables. The hypothetical combinations will be presented in the form of a survey, as scenarios composed of the different levels of the variables.

Respondents will be asked to make a choice between the different models proposed for each scenario. At this stage of the design it is not possible to specify the factors and levels to be included in the hypothetical scenarios for the discrete choice scenarios. However, previous work with health care professionals in the breast cancer area (Walters et al, 2010, Caldon et al 2007) has suggested that respondents can look at up to 25 scenarios with 5 factors (with up to five levels for some of the factors). For sample size purposes, with 100 responders to the DCE then for any hypothetical scenario, assuming say 50% of health care professionals would choose a woman with these characteristics to have PET, then we should be able to estimate this proportion within +/- 10% (i.e. 95% CI: 40 to 60%). With 60 responders to the DCE then for any hypothetical scenario, assuming say 50% of health care professionals would choose a women with these characteristics to have PET, then we should be able to estimate this proportion within +/- 12% (i.e. 95% CI: 38 to 62%).

Training of the Research Student in Qualitative Research Methods.

The student will be formally mentored by Ms Wyld and Dr Collins throughout her research attachment and will be entered into a qualitative research lecture module run by SCHARR at the University of Sheffield. She will also attend a 1 day training course on interviewing techniques run by Dr Michelle Winslow of the University of Sheffield (a specialist in oral history and qualitative interviewing techniques). The student will also be accompanied by Dr Collins or Ms Wyld during her first few interviews and quality control applied subsequently by means of review of audio recordings.

Project Gantt Chart and Time Lines.

Action (Months)	3	6	9	12	15	18	21	24
Literature Review								
Write-up literature review for publication								
Recruitment and interviewing								
Transcribe and analyse interviews								
Develop and send out questionnaire								
Data analysis								
Report, write up and publication								

Data Management.

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. A Site File of study documentation will be retained for a minimum of 15 years after study completion. All data collected will be pseudo-anonymised and databases will be password protected in accordance with the Data Protection Act. Data will be stored in a locked room at the Royal Hallamshire Hospital, Sheffield, for 15 years before being confidentially destroyed.

Ethics.

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the World Medical Association General Assembly, Seoul, Korea, October 2008. Informed written consent will be obtained from the older women and clinicians prior to entry into the study. The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. The study will be conducted in accordance with the

principles of GCP according to the EU Directive 2005/28/EC [Commission of the European Communities, 2005]. *The study does not require specific ethics approval as it is recruiting health care professionals rather than patients.*

Confidentiality.

The study will collect healthcare professional data that may include some participant identifiers. All data collected will be pseudo-anonymised and databases will be password protected in accordance with the Data Protection Act. A list of participant names will be stored separately from participant details. The study will comply with all aspects of the Data Protection Act 1998. Any information that would allow clinicians to be identified will not be released into the public domain. If a participant withdraws consent for their data to be used then it will be confidentially destroyed.

Archiving.

At the end of the study, data and the Study Site File will be securely archived for a minimum of 15 years. Following authorisation from the sponsors arrangements for confidential destruction will then be made. If a participant withdraws consent for their data to be used, it will be confidentially destroyed.

Indemnity.

This study will be sponsored by Sheffield Teaching Hospitals NHS Foundation Trust who therefore will be liable for negligent harm caused by the design of the study. There are no patients involved in this study and therefore the risks to patients associated with this study are minimal.

Study Sponsorship.

This study will be sponsored by Sheffield Teaching Hospitals NHS Foundation Trust.

Responsibilities and Operational Structure.

Ms Lynda Wyld (Senior Lecturer and Consultant Surgeon at STH) will be the research student's primary supervisor and project lead. Qualitative and mixed methodological expertise will be provided by Dr Karen Collins. Statistical advice will be provided for analysis of the questionnaire data by Professor Walters and Dr Shepherd.

Trial Management Group

The TMG will meet regularly to review progress. This will include the following team members:

Ms L Wyld, Dr K Collins, Prof MW Reed, Miss J Morgan, Dr N Shepherd.

Funding.

The day to day conduct of the study will be undertaken by the research fellow (during a 24 month research placement). Miss Morgan will be employed by Sheffield Teaching Hospitals NHS Trust for the duration of the project as a Clinical Research Fellow. Salary funding is provided by the STH Trust from the NIHR funded 'Bridging the Age Gap' programme grant. The necessary digital transcription machines are already available in the Department. Interview transcription will be provided by the Age Gap study administrative officer, Charlene Martin. Stationary, postage and printing costs for the study will be supported by the Age Gap study consumables budget.

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Appendix 7: University Ethics Approval Letter for Clinician Variation Study



The
Medical
School.

Miss Jenna Morgan
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Academic Unit of Surgical Oncology
University of Sheffield
Medical School
Sheffield, S10 2RX
23 November 2013
REF: SMBRER243
s.watkinson@sheffield.ac.uk

Medical School Office
Sara Watkinson
Research Ethics Administrator
University of Sheffield
Beech Hill Road
Sheffield S10 2RX
Telephone: +44 (0) 114 226 1458
Email:

Dear Jenna

Variation in Clinician Preference for Treatment of Older Women with Operable Breast Cancer

I am pleased to inform you that on 22nd November 2012 the School's Ethics Reviewers **approved** the above-named project on ethics grounds, on the basis that you will adhere to and use the following documents that you submitted for ethics review.

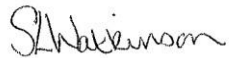
- i) Ethics form, version 1, 05/11/12 [approved – 22/11/12]
- ii) Variation in Clinician Preferences Protocol [approved – 22/11/12]

However, one small suggested amendment is that on page 17 it suggests analysis will be undertaken by Jenna Morgan and *three* experienced researchers, however, only two are listed. Is there to be two or three and if the latter please could you provide a name.

Please find attached the final versions of the documents you should use.

If during the course of the project you need to deviate from the above-approved documents, please inform me. The written approval of the School's Ethics Review Panel will be required for significant deviations from or significant changes to the above-approved documents. If you decide to terminate the project prematurely, please inform me.

Yours sincerely



Sara Watkinson

**School Research
Ethics Administrator**

Enc



Appendix 8: IRAS Application for Variation in Clinician Preference Study

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)

Variation in Treatment of Older Women with Operable Breast Cancer

1. Is your project research?

Yes No

2. Select one category from the list below:

Clinical trial of an investigational medicinal product

Clinical investigation or other study of a medical device

Combined trial of an investigational medicinal product and an investigational medical device

Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

Basic science study involving procedures with human participants

Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

Study involving qualitative methods only

Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

Study limited to working with data (specific project only) Research tissue bank

Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? No

b) Will you be taking new human tissue samples (or other human biological samples)? No

c) Will you be using existing human tissue samples (or other human biological samples)? No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

England Scotland Wales

Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

England

4. Which review bodies are you applying to?

NHS/HSC Research and Development offices

Social Care Research Ethics Committee

Research Ethics Committee

National Information Governance Board for Health and Social Care (NIGB)

Ministry of Justice (MoJ)

National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

It looks like your project is research requiring NHS R&D approval but does not require review by a REC within the UK Health Departments Research Ethics Service – is that right?

Yes No

4b. Please confirm the reason(s) why the project does not require review by a REC within the UK Health Departments Research Ethics Service:

Projects limited to the use of samples/data samples provided by a Research Tissue Bank (RTB) with generic ethical approval from a REC, in accordance with the conditions of approval.

Projects limited to the use of data provided by a Research Database with generic ethical approval from a REC, in accordance with the conditions of approval.

Research limited to use of previously collected, non-identifiable information

Research limited to use of previously collected, non-identifiable tissue samples within terms of donor consent

Research limited to use of acellular material

Research limited to use of the premises or facilities of care organisations (no involvement of patients/service users as participants)

Research limited to involvement of staff as participants (no involvement of patients/service users as participants)

5. Will any research sites in this study be NHS organisations?

Yes No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

Yes No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

Yes No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes No

9. Is the study or any part of it being undertaken as an educational project?

Yes No

Please describe briefly the involvement of the student(s):

The study will be part of an MD and the student is the Chief Investigator

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

Integrated Research Application System

Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study

NHS/HSC R&D Form (project information)

Please refer to the *Submission and Checklist* tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Variation in Treatment of Older Women with Operable Breast Cancer

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Variation in Clinician Preference for Treatment in Older Women with Operable Breast Cancer

A2-1. Educational projects

Name and contact details of student(s):

Title Forename/Initials Surname Miss Jenna Morgan

Address 3 Copperfield Close Sherburn-in-Elmet Leeds. LS25 6NP

E-mail jenna.morgan@doctors.org.uk

Telephone 07738257127

Give details of the educational course or degree for which this research is being undertaken: Name and level of course/ degree:

MD

Name of educational establishment: University of Sheffield

Name and contact details of academic supervisor(s):

Title Forename/Initials Surname Ms Lynda Wyld

Address EU36 Academic Unit of Surgical Oncology, University of Sheffield Medical School, Beech Hill Road, Sheffield, S10 2JF

E-mail l.wyld@sheffield.ac.uk **Telephone** 0114 2268640

Fax 01142713314

Title Forename/Initials Surname Dr Karen Collins

Address Reader in Health Services Research, Sheffield Hallam University, Sheffield, S10 2BP
E-mail k.collins@shu.ac.uk
Telephone 0114 2255732

Please state which academic supervisor(s) has responsibility for which student(s):

Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Miss Jenna Morgan	Ms Lynda Wyld. Dr Karen Collins

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

Student

Academic supervisor

Other

A3-1. Chief Investigator:

Title Forename/Initials Surname Miss Jenna Morgan

Post Clinical Research Fellow in Breast Surgery

Qualifications MB ChB, MRCS(Ed), PGDipMedEd

Employer Sheffield Teaching Hospitals NHS Trust

Work Address EU25 Academic Department of Clinical Oncology, University of Sheffield, Beech Hill Road, Sheffield, S10 2JF

Work E-mail j.morgan@sheffield.ac.uk

*** Personal E-mail** jenna.morgan@doctors.org.uk

*** Personal Telephone/Mobile** 07738257127

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

Title Forename/Initials Surname Ms Erica Wallis

Address Clinical Research Office, 11 Broomfield Road, Sheffield, S10 2SE

E-mail Erica.Wallis@sth.nhs.uk
Telephone 0114 2265931 **Fax** 01142265937

A5-1. Research reference numbers. Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available): STH 17054
Sponsor's/protocol number: 1.0
Protocol Version: 1.0
Protocol Date: 24/10/2012
Funder's reference number: RP-PG-1209-10071

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

A5-2. Is this application linked to a previous study or another current application?

Yes No

Please give brief details and reference numbers.

This study is part of the Bridging the Age Gap Study which is an NIHR funded programme of research looking at different aspects of how breast cancer is treated in older women. Various component projects are currently or recently undergoing review.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.

Breast cancer is common, with 48,000 cases diagnosed in the UK each year. A third of these occur in women over the age of 70 years (Breakthrough Breast Cancer, 2010). Recent reports demonstrate that patients aged over 70 years are the only group of cancer patients in the UK where the mortality from cancer is not falling and may even be rising. This is thought to be due, in part, to under-treatment.

Of particular concern is the widespread use of primary endocrine therapy (PET) where patients do not undergo surgery for their cancer and anti-oestrogen therapy is the only treatment. Whilst a valid treatment option in frailer older women, where operative intervention may be detrimental because of existing co-morbidities, frailty or patient preference, practice in the UK is highly varied. Additionally, with the aging population in the UK, life expectancy has risen, with many people still healthy and fully independent in their 70s and 80s. The resulting effect is that some older women may be under-treated, whilst others are over-treated.

We propose to elicit the views and preferences of specialist health care professionals regarding the benefits and risks of surgery and primary endocrine therapy through semi-structured, purposively selected interviews.

We will then use a bespoke questionnaire to quantify the strength of each theme identified in the interviews and will be supplemented by expert opinion of the research team. An initial pilot questionnaire will be developed and will be reviewed and piloted by a group of clinicians collaborating on the project. Amendments will then be made in response to feedback before it is sent out to all members of the Association of Breast Surgeons. This will permit the study team to determine levels of clinician practice variance.

A6-2. Summary of main issues. Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

This study raises no significant ethical issues. The study participants are clinicians and the study seeks their opinions about how to treat older women with cancer. There is no risk to participants who will either consent to be interviewed or to complete an anonymised questionnaire. The only inconvenience will be in the time these take (up to an hour for the interviews and 20 minutes for the questionnaire). Informed written consent will be obtained from clinicians prior to entry into the study for the interviews and presumed consent by their completion of the questionnaire. The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons.

The study does not require specific ethics approval as it is recruiting health care professionals rather than patients.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply:

Case series/ case note review

Case control

Cohort observation

Controlled trial without randomisation

Cross-sectional study

Database analysis

Epidemiology

Feasibility/ pilot study

Laboratory study

Metanalysis

Qualitative research

Questionnaire, interview or observation study

Randomised controlled trial

Other (please specify)

A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

To determine the factors underlying treatment decision making in health care professionals relating to older women with breast cancer.

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

To explore the views of specialist healthcare professionals towards to management of older women (>70yrs) with operable breast cancer, particularly in terms of PET versus surgery.

To determine whether there is a link between the maangement of older women with operable breast cancer and the local social and demographic factors.

A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.

In the UK there is wide variation in practice relating to the treatment of older women with breast cancer, with some areas demonstrating a 40% rate of PET, whilst in other areas the rate is only 10%.

The concern is that women in centres with low surgery rates will be inappropriately denied operative intervention, with the long-term consequences of local recurrence, necessitating a change in management. Conversely, in regions with high rates of surgery, women may be inappropriately subjected to the morbidity or even mortality of surgery with no benefit.

Regionally, variance may be explained, in part by deprivation levels as patient co-morbidities, frailty and preference are all potential causes. However, it is believed that clinician preference may also form a substantial cause of variance.

A13. Please summarise your design and methodology. It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

The study will recruit participants from breast units across the country. Using published national audit data we will identify sites with high, medium or low Primary Endocrine Therapy (PET) rates.

A local principle investigator (PI) will be identified at each site by direct contact from a member of the study team. The PI will be asked to provide a list of names of suitable health care professionals working within the unit who may be happy to be contacted by the study team. Individuals will then be sent a study pack by post which will contain the following: a letter of invitation, a participant information sheet (PIS), a study reply slip and a freepost envelope.

The study pack will invite the health care professional to complete a study reply slip to agree to be contacted about taking part. On receipt of a reply slip agreeing to participate, the research team will contact the interview candidate and arrange a time and place to meet. This will be agreed verbally and confirmed in writing before the scheduled date. A consent form will be signed before the interviews commence.

Participants will be contacted again the day before their interviews to ensure they still wish to proceed. They will be given an opportunity to decline if they so wish. All interviewees will be reassured that they may terminate or pause the interview at any point without stating a reason for doing so and that their participation is entirely voluntary. If wished, telephone interviews may be offered. All interviews will be digitally recorded and transcribed verbatim. All data collected will be pseudo-anonymous and databases password protected in accordance with the Data Protection Act.

The interviews will enable us to explore key issues but also give opportunity for free expression of views with open questions. The interviews will specifically explore the following areas:

Treatment options for older women with ER positive breast cancer

Methods for selection

Patient engagement in selection of treatment Role and importance of clinician preferences Role and importance of the BCN

Role and importance of the family and friends

Influence of co-morbidity Influence of frailty Influence of dementia

Influence of disease biology and stage/operability

Influence of HCP past experiences

Influence of costs

Influence of cancer targets

Interviews will continue until saturation of "themes" is reached - from previous research, we anticipate that we will require approximately 35 interviews to achieve this. Qualitative interview transcript analysis will follow the Framework' approach, to identify recurrent themes. Data will be entered into thematic charts and examined to allow interpretation of the data and to identify any relationships between themes.

In order to quantify the findings of earlier phases of the study and link them to patient characteristics, a bespoke questionnaire will be developed based on the themes and findings of the qualitative interviews. An initial pilot questionnaire will be developed and will be reviewed by means of several focus groups of health care professional members of the study team and the extended 'bridging the Age Gap in breast cancer study team (LW, MWR, LC, RAA, AS, REC, and members of the surgical and breast care nursing team locally in sheffield) to ensure it has content and face validity, is comprehensible and useable.

The questionnaire will be piloted to examine the length, acquiescent response set, flow, salience, ease of administration and response and acceptability to respondents (Boynton & Greenhalgh, 2004). Appropriate modifications will be made to the design and content of the questionnaire before it is sent out to the wider population of UK HCP.

The finalised questionnaire will then be sent out to members of the Association of Breast Surgeons (ABS) and the Association of Cancer Physicians. The questionnaires will be prepared and made up into packs together with a prepaid envelope and sent to the associations who will undertake the mailing to maintain confidentiality. Return of a completed questionnaire will be taken as indicative of consent.

From previous studies, we anticipate a response rate of approximately 40%. No reminders will be sent. There will be an initial section asking for respondent demographics and locality. Quantitative analysis of the questions will be undertaken and correlation between answers given to establish any relationships.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

Design of the research

Management of the research

Undertaking the research

Analysis of results

Dissemination of findings

✓None of the above

Give details of involvement, or if none please justify the absence of involvement.

We will not be involving patients, service users, and/or their carers, or members of the public as this study involves only NHS health care professionals. The wider age gap programme of research has extensive user involvement for all aspects related to patient contact but this is not relevant to this sub project of the larger programme of research.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- Blood
- Cancer
- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender: Male and female participants

Lower age limit: 18 Years

Upper age limit: No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

NHS Health Care Professionals working in breast cancer units in the UK.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

None

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Study Interview Information Pack	1	no	10minutes	Sent via post
Telephone contact with study team to arrange interview	1	no	10 minutes	Telephone, Chief
Investigator. Informed, written consent	1	no	5 minutes	In person, Chief
Investigator. Qualitative interview	1	no	30 minutes	In person, Chief
Investigator. Questionnaire	1	no	20 minutes	Sent via post

A21. How long do you expect each participant to be in the study in total?

We will not technically be "following-up" participants so their involvement in the study will be at discrete intervals. However, for those participants who take part in interviews and are members of the Association of Breast Surgeons (ABS) - there will be a period of approximately 12 months where they may be contacted about the study - i.e. that can expect to receive the questionnaire in the post.

For participants who are only sent the questionnaire this will be a one-off event and on receipt of their completed questionnaire they will not be contacted again.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

We have not identified any potential risks to participants however, it will be made clear that no one has to participate if they do not wish and they may withdraw at any time without providing a reason.

Participants may suffer some burden in respect to their time as the interviews will take approximately 30 minutes to contact and the questionnaire will also require time to complete, although we estimate this will be only approximately 15 minutes.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

Yes No

A24. What is the potential for benefit to research participants?

There will be no direct benefit to the research participants.

A26. What are the potential risks for the researchers themselves? (if any)

We have not identified any potential risks to the researchers.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

For the interviews, we will recruit participants from breast units across the country. Using published national audit data we will identify sites with high, medium or low Primary Endocrine Therapy (PET) rates. A local principle investigator (PI) will be identified at each site by direct contact from a member of the study team. The PI will be asked to provide a list of names of suitable health care professionals working within the unit who may be happy to be contacted by the study team. Individuals will then be contacted by post and invited to participate.

For the questionnaire, we will recruit participants through their membership to the Association of Breast Surgeons (ABS) and the Association of Cancer Physicians. This will be done via the association.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

Yes No

A29. How and by whom will potential participants first be approached?

With respect to the interviews, the potential principal investigators at different sites will be contacted directly by a member of the study team, usually by e-mail. Direct contact with the interview participants will initially be via the study pack which will be sent via post.

With respect to the questionnaires, the potential participants will simply be sent a postal questionnaire via the Association of Breast Surgeons or Association of Cancer Physicians.

A30-1. Will you obtain informed consent from or on behalf of research participants?

Yes No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

For the interviews, all participants will be sent a written information sheet with the invitation to participate. Full, written, informed consent will then be obtained from each participant in person, prior to the interview.

For the questionnaire, all participants will be sent a written information sheet with the questionnaire. Return of a completed questionnaire will be taken as consent to participate.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

✓ Yes No

A31. How long will you allow potential participants to decide whether or not to take part?

For both the interviews and the questionnaire studies, we will be sending the invitation to participate via post. Potential participants will not be contacted again as part of the questionnaire study and they will only be contacted again for the interviews if they return the study reply slip - there is no maximum time for them to do this, therefore allowing potential participants as long as they require to decide whether to participate. Clearly the study period will only be a finite amount of time and as such if potential participants haven't responded within six months it will be assumed that they do not wish to take part.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

None. By the nature of being health care professionals working within the NHS, there is an assumption that all potential participants will have the understanding, verbal and written English language skills in order to comprehend the information given. Should they require further information we have provided contact information on the participant information sheets.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

None. Again, by nature of being health care professionals working within the NHS, there is an assumption that Welsh participants will have adequate English language skills to understand and participate in the study.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

The participant would continue to be included in the study.

Not applicable – informed consent will not be sought from any participants in this research.

Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

As we are not recruiting patients and there is no follow-up period this is not applicable. Only participants able to provide informed consent at the time of their interview will be interviewed. Informed consent will not be taken for the questionnaire study as this will be implied by return of a completed questionnaire.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?(Tick as appropriate)

Access to medical records by those outside the direct healthcare team

Electronic transfer by magnetic or optical media, email or computer networks

Sharing of personal data with other organisations

Export of personal data outside the EEA

✓ Use of personal addresses, postcodes, faxes, emails or telephone numbers

✓ Publication of direct quotations from respondents

Publication of data that might allow identification of individuals

✓ Use of audio/visual recording devices

✓ Storage of personal data on any of the following:

✓ Manual files including X-rays

NHS computers

Home or other personal computers

✓ University computers

Private company computers

Laptop computers

Further details:

Participants may be contacted initially via e-mail/telephone/postal address. Interviews will be digitally recorded and transcribed verbatim.

Data will be stored in a pseudo-anonymised fashion on an electronic database on a university computer that is password protected and kept in a locked room in the Hallamshire Hospital Sheffield.

Consent forms and participant response forms will be kept in paper form in a locked drawer in a locked room in the hallamshire hospital, sheffield.

Publication of direct quotations from respondents may be used but these will be completely anonymous and no participant will be identified in any way.

A37. Please describe the physical security arrangements for storage of personal data during the study?

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. All data collected will be pseudo-anonymised and databases will be password protected in accordance with the Data Protection Act. Data will be stored in a locked room at the Royal Hallamshire Hospital, Sheffield, for 15 years before being confidentially destroyed.

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

All data collected will be pseudo-anonymised and databases will be password protected in accordance with the Data Protection Act 1998.

A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

The chief investigator and supervisors only.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Data generated by the study will be pseudo-anonymised by the Chief investigator. It will be analysed in combination with the supervisors and statisticians from the university of sheffield.

A42. Who will have control of and act as the custodian for the data generated by the study?

Title Forename/Initials Surname Ms Lynda Wyld

Post Lecturer in Clinical Oncology and Honorary Consultant Surgeon

Qualifications MB.ChB. B.Med.Sci. PhD. FRCS.

Work Address EU36 Academic Unit of Surgical Oncology University of Sheffield Medical School Beech Hill Road, Sheffield, S10 2JF

Work Email l.wyld@sheffield.ac.uk

Work Telephone 0114 2268640

A43. How long will personal data be stored or accessed after the study has ended?

Less than 3 months

3 – 6 months

6 – 12 months

12 months – 3 years

Over 3 years

If longer than 12 months, please justify:

Pseudo-anonymised data will be kept in a site file for 15 years before being confidentially destroyed.

A44. For how long will you store research data generated by the study?

Years: 15

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The data will be password protected and stored in a locked room in the Hallamshire Hospital, Sheffield, under the care of LW, all in accordance with the Data Protection Act 1998.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

Yes No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

Yes No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

Yes No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

Yes No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

Yes No

Please give details, or justify if not registering the research.

The project will be adopted into the NIHR portfolio and as such will be available on the NIHR website.

Registration of research studies is encouraged wherever possible.

You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

Peer reviewed scientific journals

Internal report

Conference presentation

Publication on website

Other publication

Submission to regulatory authorities

Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

No plans to report or disseminate the results

Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

We will not be using identifiable personal data in any published results.

A53. Will you inform participants of the results?

Yes No

Please give details of how you will inform participants or justify if not doing so.

Participants will be asked if they wish to receive details of the study results. Participant will be informed in writing of the results if they wish. Most participants, by nature of their healthcare professional status will have access to the published material.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

Independent external review

Review within a company

Review within a multi-centre research group

Review within the Chief Investigator's institution or host organisation

Review within the research team

Review by educational supervisor

Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The project has been extensively peer reviewed by the grant review board of the NIHR programme grant scheme. Extensive feedback and project modification was undertaken as a result.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

Review by independent statistician commissioned by funder or sponsor

Other review by independent statistician

Review by company statistician

Review by a statistician within the Chief Investigator's institution

Review by a statistician within the research team or multi-centre group

Review by educational supervisor

Other review by individual with relevant statistical expertise

No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title	Forename/Initials Surname	Professor Stephen Walters
Department	Clinical Trials Research Unit	
Institution	SchARR (School of Health and Related Research), University of Sheffield	
Work Address	Regent Court, 30 Regent Street, Sheffield, S1 4DA	
Telephone	0114 222 0730	
E-mail	S.J.Walters@sheffield.ac.uk	

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

To determine the factors underlying treatment decision making in health care professionals relating to older women with breast cancer.

A58. What are the secondary outcome measures? (if any)

To determine the level of variance in decision making practice amongst health care professionals.

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.

Total UK sample size: 150
Total international sample size (including UK): 150
Total in European Economic Area: 150

Further details:

As with all projects where qualitative interviews are undertaken, we will base our sample size on the attainment of saturation of themes. This is usually achieved after 20-25 interviews but as we intend to interview several different professional group (nurses, geriatricians, surgeons and oncologists) we may need to interview more. It is therefore not possible to put a precise limit on this at this stage.

For the questionnaire, our previous discrete choice experiment questionnaire required us to send out 250 questionnaires with a response rate of 40% to achieve the required sample size of 100 for meaningful analysis. We have based our present sample size on the same estimates, following statistical input from Professor Stephen Walters (professor of Medical statistics at SchARR). These calculations are outlined in the study protocol.

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

The interview sample size will be decided according to qualitative methods of "saturation of themes". Based on previous research undertaken by the study team, it is estimated that this may be achieved after 20-25 interviews but as we intend to interview several different professional group (nurses, geriatricians, surgeons and oncologists) we may need to interview more. It is therefore not possible to put a precise limit on this at this stage.

Again, for the questionnaire, the study size is based on previous work undertaken by the study group. A previous discrete choice experiment questionnaire required us to send out 250 questionnaires with a response rate of 40% to achieve the required numbers for meaningful analysis (approximately 100). We have based our present sample size on the same estimates, following statistical input from Professor Stephen Walters (professor of Medical statistics at SchARR). These calculations are outlined in the study protocol.

A61. Will participants be allocated to groups at random?

Yes No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

For the interview section:

Qualitative interview transcript analysis will follow the Framework approach, to identify recurrent themes. The Framework approach permits the systematic analysis of large volumes of textual data and permits within- and across- case and theme comparison. Analysis will be undertaken by the chief investigator with supervision from experienced qualitative researchers (KC and LW - student supervisors). A thematic index will be drawn up and applied to the data. Data will be distilled, summarised and entered into thematic charts before being examined to allow interpretation of the data and to identify any relationships between themes.

For the Questionnaire section:

The first part of the questionnaire will be descriptive and will be analysed by calculation of median response and range to Likert-style questions. Correlation of response medians with HCP characteristics such as age subgroup and professional subtype will be performed using Chi squared test.

The discrete choice questionnaire wherein scenarios are described and treatment preferences for PET or surgery or either will be developed in conjunction with Professor Stephen Walters. Discrete choice

scenarios provide information on the relative weights individual professionals attach to the various dimensions (variables) involved in the decision making process and how willing they are to trade these off against each other in reaching a decision. Respondents will be provided with pair wise choices between hypothetical scenarios and asked to choose their preferred scenario from each pair. These choices can then be used to infer the trade-offs people are willing to make with respect to changes in the levels of the attributes.

Scenarios will be evaluated by Professor Tom Robinson to determine whether all are realistic representations of real life older women and also to estimate whether individual scenarios would be associated with a predicted life expectation of less than 2 year, 2-5 years or greater than 5 years.

Correlations will be assessed between clinician choices and region/age/sex/healthcare role to see if there are any associations.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

Title Forename/Initials Surname Professor Thomson Robinson
Post Professor in Ageing and Stroke Medicine / Honorary Consultant Physician
Qualifications B.Med.Sci, BM.BS, MRCP, MD, FRCP Employer University of Leicester
Work Address Department of Cardiovascular Services, University of Leicester, Level 5 (room 539), Leicester Royal Infirmary, Infirmary Square, Leicester, LE1 5WW
Telephone 01162523183 **Work Email** tgr2@le.ac.uk

Title Forename/Initials Surname Mr Neil Shephard
Post Medical Statistician
Employer Clinical Trials Research Unit, SCHARR
Work Address Regent Court, 30 Regent Street, Sheffield, S1 4DA
Telephone 0114 222 5203 **Work Email** n.shephard@sheffield.ac.uk

Title Forename/Initials Surname Dr Erica Wallis
Post Senior Research Coordinator **Qualifications** MBChB
Employer Sheffield Teaching Hospitals NHS Foundation Trust
Work Address Clinical Research Office, 11 Broomfield Road, Sheffield, S10 2SE
Telephone 0114 2265931 **Fax** 01142265937
Work Email Erica.Wallis@sth.nhs.uk

Title Forename/Initials Surname Professor Malcolm Reed
Post Professor of surgical oncology, consultant breast surgeon
Qualifications MB.ChB, B.Med.Sci, MD, FRCS
Employer Sheffield University

Work Address FU20 Academic Unit of Surgical Oncology University of Sheffield Medical School Beech Hill Road, Sheffield S10 2JF

Telephone 0114 2713326 **Work Email** m.w.reed@sheffield.ac.uk

Title **Forename/Initials Surname** Professor Stephen Walters

Post Professor of Statistics

Qualifications BSc, PCGE, MSc, PhD, CStat

Employer ScHARR (School of Health and Related Research), University of Sheffield

Work Address Regent Court, 30 Regent Street, Sheffield, S1 4DA

Telephone 0114 222 0730 **Work Email** S.J.Walters@sheffield.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status: NHS or HSC care organisation

Commercial status: Non-Academic Commercial

Pharmaceutical industry Medical device industry Local Authority

Other social care provider (including voluntary sector or private organisation)

Other

If Other, please specify:

Contact person

Name of organisation Sheffield Teaching Hospitals NHS Foundation Trust

Given name Simon

Family name Heller

Address Clinical Research Office , 11 Broomfield Road, S10 2SE

Country UNITED KINGDOM

Telephone 0114 2265938 **Fax** 01142265937

E-mail s.heller@sheffield.ac.uk

Is the sponsor based outside the UK?

Yes No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

Funding secured from one or more funders

External funding application to one or more funders in progress

No application for external funding will be made

What type of research project is this?

Standalone project

Project that is part of a programme grant

Project that is part of a Centre grant

Project that is part of a fellowship/ personal award/ research training award

Other

Other – please state:

Please give details of funding applications.

Organisation National Institute of Health Research

Address Room 132, Richmond House, 79 Whitehall, London

Post Code SW1A 2NS **Telephone** 02033286700

Fax 02076265128

Email enquiries@nhr.ac.uk

Funding Application Status: Secured In progress

Amount: £1.7M

Duration

Years: 5

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

NIHR Programme Grants for Applied Research

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? Please give details of subcontractors if applicable.

Yes No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname Dr Erica Wallis

Organisation Sheffield Teaching Hospitals NHS Foundation Trust

Address Clinical Research Office, 11 Broomfield Road, Sheffield, S10 2SE

Work Email Erica.Wallis@sth.nhs.uk

Telephone 0114 2265931 **Fax** 01142265937

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A69-1. How long do you expect the study to last in the UK?

Planned start date: 03/12/2012

Planned end date: 03/10/2014

Total duration:

Years: 1 Months: 10 Days: 0

A71-1. Is this study?

Single centre

Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

England Scotland Wales Northern Ireland

Other countries in European Economic Area

Total UK sites in study 20

Does this trial involve countries outside the EU?

Yes No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

NHS organisations in England 19

NHS organisations in Wales 1

NHS organisations in Scotland

HSC organisations in Northern Ireland

GP practices in England GP practices in Wales GP practices in Scotland

GP practices in Northern Ireland

Social care organisations

Phase 1 trial units

Prison establishments

Probation areas

Independent hospitals

Educational establishments Independent research units Other (give details)

Total UK sites in study: 20

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

Yes No

A73-2. If yes, will any of these organisations be NHS organisations?

Yes No

If yes, details should be given in Part C.

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The study is a low risk study involving health care professionals giving interviews and completing questionnaires. As such there is no requirement for safety monitoring. Study progress will be monitored by a trial management group which will meet once every 6 months to discuss progress and milestones.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

NHS indemnity scheme will apply (NHS sponsors only)

Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

NHS indemnity scheme will apply (protocol authors with NHS contracts only)

Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

Yes No Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

IN1

NHS site Non-NHS site
Forename Lynda Family name Wyld
Country: England Email l.wyld@sheffield.ac.uk
Qualification MB.ChB. B.Med.Sci. PhD. FRCS
Country UNITED KINGDOM
Organisation name SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Address NORTHERN GENERAL HOSPITAL, HERRIES ROAD SHEFFIELD SOUTH YORKSHIRE, S5 7AU

IN2

NHS site Non-NHS site
Forename Kwok Leung Family name Cheung
Country: England Email Kwok_Leung.Cheung@nottingham.ac.uk
Qualification (MD...) MBBS, DM, FRCS, FACS
Organisation DERBY HOSPITALS NHS FOUNDATION TRUST UNITED KINGDOM
Address DERBY CITY GENERAL HOSPITAL UTTOXETER ROAD DERBY DERBYSHIRE DE22 3NE

IN3

NHS site Non-NHS site
Forename Eleanor Family name Gutteridge
Country: England
Organisation name NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST
Email Eleanor.Gutteridge@nuh.nhs.uk Qualification (MD...) FRCS
Address TRUST HEADQUARTERS QMC CAMPUS, DERBY ROAD NOTTINGHAM NG7 2UH

IN4
✓ NHS site Non-NHS site
Country: England
Forename Andrew Family name Griffiths
Email andrew.griffiths@ncl.ac.uk Qualification (MD...) FRCS
Organisation name THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON, NEWCASTLE-UPON-TYNE, NE7 7DN

IN5
✓ NHS site Non-NHS site
Country: England
Organisation name UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST
Forename Anne Family name Stotter
Email anne.stotter@uhl-tr.nhs.uk Qualification (MD...) MA, MBBS, PhD, FRCS
Country UNITED KINGDOM
Address GWENDOLEN HOUSE GWENDOLEN ROAD LEICESTER LEICESTERSHIRE LE5 4QF

IN6
✓ NHS site Non-NHS site
Country: England
Organisation name UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST
Forename Zenon Family name Rayter
Email Zenon.Rayter@UHBristol.nhs.uk Qualification (MD...) MBBS, MS, FRCS
Country UNITED KINGDOM
Address MARLBOROUGH STREET BRISTOL AVON BS1 3NU

IN7
✓ NHS site Non-NHS site
Country: England
Organisation name ST HELENS AND KNOWSLEY HOSPITALS NHS TRUST
Forename Riccardo Family name Audisio
Email raudisio@doctors.org.uk Qualification (MD...) FRCS
Country UNITED KINGDOM
Address WHISTON HOSPITAL WARRINGTON ROAD PRESCOT MERSEYSIDE L35 5DR

IN8
✓ NHS site Non-NHS site
Country: England
Organisation name: GUY'S AND ST THOMAS' NHS FOUNDATION TRUST
Forename Michael Family name Douek
Email michael.douek@kcl.ac.uk Qualification (MD...) MD, FRCS
Country UNITED KINGDOM
Address TRUST OFFICES GUY'S HOSPITAL GREAT MAZE POND LONDON GREATER LONDON SE1 9RT

IN9
✓ NHS site Non-NHS site
Country: England
Organisation name: DARTFORD AND GRAVESHAM NHS TRUST
Forename Seema Family name Seetharam
Email seemaseetharam@nhs.net Qualification (MD...) FRCS
Country UNITED KINGDOM
Address DARENT VALLEY HOSPITAL DARENTH WOOD ROAD DARTFORD KENT DA2 8DA

IN10
✓ NHS site Non-NHS site
Country: England
Organisation name: ROYAL BERKSHIRE NHS FOUNDATION TRUST
Forename Stephen Family name Courtney
Email stephen.courtney@royalberkshire.nhs.uk Qualification (MD...) MCh. FRCS
Country UNITED KINGDOM
Address ROYAL BERKSHIRE HOSPITAL LONDON ROAD READING BERKSHIRE RG1 5AN

IN11
✓ NHS site Non-NHS site
Country: Wales
Institution name UNIVERSITY HOSPITAL OF WALES

Forename Helen Family name Sweetland
Email Sweetland@cardiff.ac.uk Qualification (MD...) MB.ChB. MD. FRCS
Country UNITED KINGDOM
Street address HEATH PARK Town/city CARDIFF Post Code CF14 4XW

IN12

✓NHS site Non-NHS site
Forename Martin Family name Lee
Country: England
Organisation name UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST
Email martin.lee@uhcw.nhs.uk Qualification (MD...) MB.ChB, MA, MSc.
FRCS
Country UNITED KINGDOM
Address WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY WEST MIDLANDS CV2 2DX

IN14

✓NHS site Non-NHS site
Country: England
Organisation name: PLYMOUTH HOSPITALS NHS TRUST
Forename Roger Family name Watkins
Email roger.watkins@phnt.swest.nhs.uk Qualification (MD...) MB BChir,
FRCS
Country UNITED KINGDOM
Address DERRIFORD HOSPITAL DERRIFORD ROAD PLYMOUTH DEVON PL6 8DH

IN15

✓NHS site Non-NHS site
Country: England
Organisation name: DONCASTER AND BASSETLAW HOSPITALS NHS FOUNDATION TRUST
Forename Clare Family name Rogers
Email clare.rogers@dbh.nhs.uk Qualification (MD...) MBChB MD FRCSEd
(Gen.Surg.)
Country UNITED KINGDOM
Address DONCASTER ROYAL INFIRMARY ARMTHORPE ROAD DONCASTER SOUTH YORKSHIRE DN2 5LT

IN16

✓NHS site Non-NHS site
Country: England
Organisation name: CHESTERFIELD ROYAL HOSPITAL NHS FOUNDATION TRUST
Forename Steve Family name Holt
Email Steve.Holt@chesterfieldroyal.nhs.uk Qualification (MD...) MB.ChB, FRCS
Country UNITED KINGDOM
Address CALOW CHESTERFIELD DERBYSHIRE S44 5BL

IN17

✓NHS site Non-NHS site
Country: England
Organisation name: YORK TEACHING HOSPITAL NHS FOUNDATION TRUST
Forename Rana Family name Nasr
Email rana.nasr@york.nhs.uk Qualification (MD...) FRCS
Country UNITED KINGDOM
Address YORK HOSPITAL WIGGINTON ROAD YORK NORTH YORKSHIRE YO31 8HE

IN18

✓NHS site Non-NHS site
Country: England
Organisation name: THE ROTHERHAM NHS FOUNDATION TRUST
Forename Inder Family name Kumar
Email Inder.Kumar@rothgen.nhs.uk Qualification (MD...) FRCS,
General Surgery
Country UNITED KINGDOM
Address MOORGATE ROAD ROTHERHAM SOUTH YORKSHIRE S60 2UD

IN19

✓NHS site Non-NHS site
Country: England
Organisation name: BARNSELY HOSPITAL NHS FOUNDATION TRUST

Forename Julia Family name Dicks
Email jdicks@nhs.net Qualification (MD...) MBChB, FRCS Gen, MRCS
Country UNITED KINGDOM
Address GAWBER ROAD BARNSELY SOUTH YORKSHIRE S75 2EP

IN20

NHS site Non-NHS site

Country: England

Organisation name: NORTHERN LINCOLNSHIRE AND GOOLE HOSPITALS NHS FOUNDATION TRUST

Forename Rajesh Family name Vijh

Email rvijh@nhs.net Qualification (MD...) MS, FRCS(ed)

Country UNITED KINGDOM

Address DIANA PRINCESS OF WALES HOSPITAL SCARTH ROAD GRIMSBY NORTH EAST LINCOLNSHIRE DN33 2BA

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

I Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.

I May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.

I May be seen by auditors appointed to undertake accreditation of RECs (where applicable).

I Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication(Not applicable for R&D Forms)

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

Chief Investigator

Sponsor

Study co-ordinator

Student

Other – please give details

None

Access to application for training purposes (Not applicable for R&D Forms) Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Miss Jenna Morgan on 16/11/2012 12:52.

Job Title/Post: Clinical Research Fellow

Organisation: University of Sheffield

Email: jenna.morgan@doctors.org.uk

Signature: Print Name: Jenna Morgan

Date: 13/11/2012 (dd/mm/yyyy)

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Dr Dipak Patel on 16/11/2012 12:39.

Job Title/Post: Research Manager
 Organisation: Sheffield Teaching Hospitals NHS Foundation Trust
 Email: dipak.patel@sth.nhs.uk

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.
2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.
3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.
4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by lynda wyld on 19/11/2012 14:31.

Job Title/Post: consultant Organisation: University of sheffield Email: l.wyld@sheffield.ac.uk

Academic supervisor 2

This section was signed electronically by Dr Karen Collins on 16/11/2012 16:15.

Job Title/Post: Reader in Health Care Research Organisation: Sheffield Hallam University
 Email: k.collins@shu.ac.uk

Appendix 9: NHS R&D approvals

Sheffield Teaching Hospitals

NHS Foundation Trust

17 Jan 2013

Ms Lynda Wyld
University of Sheffield
Surgical Oncology
Academic Unit Surgical Oncology
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Ms Wyld

Project Authorisation NHS Permission for Research to commence

STH ref: STH17054
NIHR CSP ref: 117503

REC ref: SMBRER243
MHRA ref: CTA no.: N/A **EudraCT no.:** N/A

Study title: Variation in Clinician Preferences for Surgery in Older Women with Operable Breast Cancer

Chief Investigator: Ms Jenna Morgan, Clinical Research Fellow, Sheffield NHS Teaching Hospitals Foundation Trust
Principal Investigator: Ms Lynda Wyld, University of Sheffield

Sponsor: Sheffield NHS Teaching Hospitals Foundation Trust
Funder: NIHR Programme Grants
URMS ref: 127870

The Research Department has received the required documentation as listed below:

- | | |
|--|-------------------------------------|
| 1. Sponsorship Agreement | N/A |
| Clinical Trial Agreement | N/A |
| Material Transfer Agreement | N/A |
| Funding Award Letter | NIHR Programme Grant
05 Mar 12 |
| 2. Monitoring Arrangements | N/A |
| 3. STH registration document | R & D Form
J Morgan, 16 Nov 2012 |
| 4. Evidence of favourable scientific review | N/A |
| 5. Protocol – final version | V1.0, 24 Oct 12 |
| 6. Participant Information sheet | V1.0, 24 Oct 12 |
| 7. Consent form | V1.0, 24 Oct 12 |
| 8. Letter of indemnity arrangements
Insurance Certificate | N/A |



Chairman: David Stone OBE • Chief Executive: Andrew Cash OBE

Ref: STH17054/EWS

smoke-free
Hospitals

- | | |
|---|---|
| 9. ARSAC certificate / IRMER assessment | N/A |
| 10. Ethical review- Letter of approval from NHS REC/ UREC | University of Sheffield
SMBRER243
23 Nov 12 |
| 11. Site Specific Assessment | SSI Form
L Wyld, 07 Jan 2013 |
| 12. Clinical Trial Authorisation from MHRA | N/A |
| 13. Evidence of hosting approvals | STH Finance Form |
| - STH Principal Investigator | L Wyld, 13 Jan 13 |
| - Clinical Director | P Skinner, 16 Jan 13 |
| - Research Finance | E Fraser, 17 Jan 13 |
| - Data Protection Officer | N/A |
| - CRF | N/A |
| - Pharmacy | N/A |
| - MIMP/Academic Radiology/WPH DXA/BRU DXA | N/A |
| - Laboratory Medicine | N/A |
| - Diagnostic Cardiology | N/A |
| - Respiratory Function Unit | N/A |
| 14. Honorary Contract/Letter of Access | N/A |
| 15. | |
| • Health Care Professional Cover Letter | V1.0, 24 Oct 12 |
| • Clinician Preference Study HCP Prompt Sheet | V1.0, 24 Oct 12 |
| • Clinician Preferences Study Reply Form | V1.0, 24 Oct 12 |
| • Clinician Preferences Questionnaire | V1.0, 24 Oct 12 |

This project has been reviewed by the Research Department. NHS permission for the above research to commence has been granted on the basis described in the application form, protocol and supporting documentation, on the understanding that the study is conducted in accordance with the Research Governance Framework, GCP and Sheffield Teaching Hospitals policies and procedures (see attached appendix).

Yours sincerely



ff Professor S Heller
 Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
 Telephone +44 (0) 114 2265934
 Fax +44 (0) 114 2265937

cc. - J Morgan

Ref: STH17054/EW/SB

St Helens and Knowsley Teaching Hospitals

NHS Trust
Whiston Hospital
Birch House
Warrington Road
Prescot
L35 5DR
Website: www.sthk.nhs.uk

Jenna Morgan
Academic Surgical Oncology Unit
The University of Sheffield
K Floor
Royal Hallamshire Hospital
Sheffield
S10 2JF

15th January 2013

Dear Jenna

Letter of access for research

This letter confirms your right of access to conduct research through **St Helens and Knowsley Teaching Hospitals NHS Trust** for the purpose and on the terms and conditions set out below. This right of access commences on **15th January 2013** and ends on **15th January 2014** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **St Helens and Knowsley Teaching Hospitals NHS Trust** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **St Helens and Knowsley Teaching Hospitals NHS Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **St Helens and Knowsley Teaching Hospitals NHS Trust**, you will remain accountable to your employer **Academic Surgical Oncology Unit** but you are required to follow the reasonable instructions of the manager in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

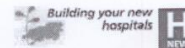
Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **St Helens and Knowsley Teaching Hospitals NHS Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **St Helens and Knowsley Teaching Hospitals NHS Trust** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **St Helens and Knowsley Teaching Hospitals NHS Trust** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.



University Clinical Education Centre



St Helens and Knowsley Teaching Hospitals

NHS Trust
Whiston Hospital
Birch House
Warrington Road
Prescot
L35 5DR
Website: www.sthk.nhs.uk

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

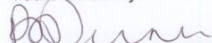
You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

St Helens and Knowsley Teaching Hospitals NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely



**Paula Dunn, Acting Employment Service Co-ordinator, on behalf of
Anne-Marie Stretch, Director of Human Resources, St Helens and Knowsley Teaching
Hospitals NHS Trust**

cc: R&D office at St Helens and Knowsley Teaching Hospitals NHS Trust
HR department of Department of Primary Care & Public Health

Dear Miss Morgan,

RJ113/n041

Variation in Clinician
preference for treatment in
older women with operable
breast cancer no ethics required

Thank you for submitting your research project to the R&D Department. The project has now been approved by the Trust and has been allocated the Trust R&D registration number RJ113/N041. The project has been registered on the Trust's research database.

Please quote the R&D registration number in any communications with the R&D Department regarding your project.

Conditions of Approval:

- The principal investigator must notify R&D of the actual end date of the project.
- The Principal Investigator is responsible for ensuring that Data Protection procedures are observed throughout the course of the project.
- The agreed protocol must be followed. R&D must be notified of any changes to the protocol prior to implementation.

In line with the Research Governance Framework, your project may be randomly selected for monitoring for compliance against the standards set out in the Framework. For information, the Trust's process for the monitoring of projects and the associated guidance is available from the Trust's intranet or on request from the R&D Department. You will be notified by the R&D Department if and when your project has been selected as part of the monitoring process. No action is needed until that time.

Please ensure the recruitment figures for GSTFT sites are uploaded to the UKCRN monthly. GSTFT will need to inform the lead site as the lead site will need to upload the figures to the UKCRN.

Many thanks for registering your research project

With best wishes

Elizabeth
Elizabeth Bruna
Research & Development Governance Specialist
NIHR GSTFT/KCL Biomedical Research Centre
T: +44 (0)20 7188 7188 Ext: 51682 | F: 0207 188 8330 |
T: elizabeth.bruna@gstt.nhs.uk | W: www.guysandstthomas.nhs.uk/

Research and Development Directorate

email: barnsley.research@nhs.net

Research Governance Office
Barnsley Hospital NHS Foundation Trust
Tel: 01226 730000
Extension: 2348
Fax: 01226 208159

Gawber Road
Barnsley
S75 2EP

26 February 2013

Tel: 01226 730000
Fax: 01226 202859
Minicom: 01226 321014

CONFIDENTIAL

Ms Julia Dicks
Consultant Breast and Oncoplastic Surgeon
Barnsley Hospital NHS Foundation Trust
Gawber Road
Barnsley
South Yorkshire
S75 2EP

Dear Ms Dicks

Study Title: Variation in Clinical Preferences for Surgery in Older Women with operable Breast Cancer
Chief Investigator: Ms Jenna Morgan
Sponsor: Sheffield Teaching Hospitals
Barnsley Reference: BHNFT539
REC Reference: n/a
EudrACT number: n/a
CSP ID: 117503

Thank you for submitting the above project. The project was considered by the Research Governance Committee of Barnsley Health and Social Care Research and Development Alliance at a meeting and I am pleased to confirm that the committee agreed to approve the project.

Reviewed study documentation:

- Protocol (V1.0 24 October 2012)
- Participant Information Sheet (V1.0 24 October 2012)
- Consent letter (V1.0 24 October 2012)
- Cover letter (V1.0 24 October 2012)
- Interview prompt sheet (V1.0 24 October 2012)
- Study reply form (V1.0 24 October 2012)
- Questionnaire (V1.0 24 October 2012)

In acting as Principal Investigator for Barnsley on this project, you must make yourself familiar with, observe and comply with:

- The informed consent and procedures approved by the Ethics Committee.
- The Department of Health Research Governance Framework and conduct your research in accordance with its principles.
- The Trust's Health and Safety policy.
- The Trust's procedure for the recording and reporting of adverse incident. In the event of an adverse incident the Ethics Committee and Research Governance Office must also be notified.
- The Trust's Equal Opportunities policy.
- The Trust's Information Security and Confidentiality policy.
- The Trust's Financial Regulations and procedures, if applicable.

You must also:

- Immediately notify the Ethics Committee and the Research Governance Office of any changes in protocol or new information that would raise questions about the continued conduct of the research.
- Ensure that all data and documentation is available for auditing purposes.

Chairman: Stephen Wragg
Chief Executive: Paul O'Connor

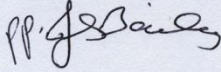
ASSOCIATE TEACHING HOSPITAL



Basic information on the project will be entered into the Trust's research database and may be submitted to the Department of Health. The research office may seek further information from time to time in order to fulfil the information requirements of the Trust or NHS Executive.

I should be grateful if you could provide a brief annual report on the progress of the research to the Research Office, including reference to any publications that have arisen from the research. This report should be submitted during March each year, so that pertinent information can be included in the Trust's Annual Research Report.

Yours sincerely



Professor S G Parker

Director of Research & Development

cc Jenna Morgan – jenna.morgan@doctors.org.uk

Research & Development Department
 Head of R&D: Ceri Jones - Tel: 024 7696 6196
 R&D Divisional Finance Manager: Chris Moore - Tel: 024 7696 6198
 Deputy R&D Divisional Finance Manager: Reena Savani - Tel: 024 7696 6199
 Research & Development Business Manager: Natasha Wileman - Tel: 024 7696 6197
 Research Associate: Isabella Petrie - Tel: 024 7696 6202
 Research Associate: Claire Bacon - Tel: 024 7696 4995
 Administration Specialist: Joanna Geraghty – Tel 024 7696 4995
 Research Portfolio Development Manager: Deborah Griggs - Tel: 024 7696 6195

04 February 2013

Mr H Khan
 Breast Care Consultant
 University Hospitals Coventry & Warwickshire NHS Trust
 University Hospital
 Clifford Bridge Road
 Coventry
 CV2 2DX

Dear Dr Khan

Study Title: Variation in Treatment of Older Women with Operable Breast Cancer
Project Code: 117503/HK114212

Thank you for submitting the above study for consideration by the Research & Development Office. I am pleased to inform you that your study has been approved.

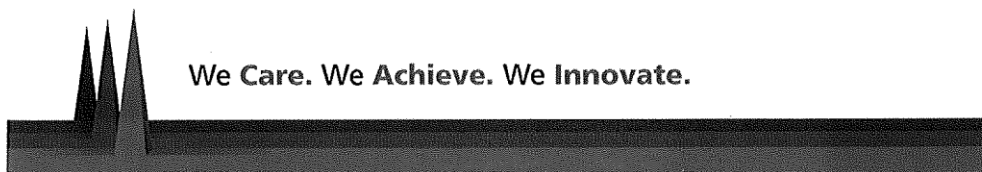
Approved documents

The documents approved for use in this study are:

Document	Version	Date
Clinician preferences study HCP Consent	V1.0	24.10.12
Clinician preferences study prompt sheet	v1.0	24.10.12
Clinician preferences study reply sheet	v1.0	24.10.12
Clinician preferences study questionnaire	v1.0	24.10.12
Professional cover letter	v1.0	24.10.12
Patient Information Sheet	V1.0	24.10.12

Conditions of Approval

- Should you wish to make any changes to the documents listed above, you must obtain R&D approval prior to use.
- A Development Safety Update Report (DSUR) should be submitted to R&D. The first report is due on 04.02.2014. The DSUR replaced the Annual Safety Report (ASR) on 01 September 2011. Guidance on the DSUR can be found in SOP 5 'Regulatory Approvals and



Communication' on the Trust R&D Intranet.

- Notification of any serious breaches of GCP or the trial protocol must be reported to the R&D Department and a DATIX Clinical Adverse Event form completed within 24 hours of any suspected breach being identified and confirmed.

Sponsorship & Indemnity

Your research is covered by NHS indemnity as set out in HSG(96)48.

Your project may be subject to ad hoc audit by our department to ensure these standards are being met.

May I take this opportunity to remind you that, as a researcher, you must ensure that your research is conducted in a way that protects the dignity, rights, safety and well-being of participants. Trust R&D Approval assumes that you have read and understand the Research Governance Framework and accept that your responsibilities as a researcher are to comply with it, the Data Protection and Health & Safety Acts.

The Trust wishes you every success with your project.

Yours sincerely



Natasha Wileman
R, D&I Business Manager

Cc:
Ceri Jones Head of Research, Development & Innovation
Jenna Morgan, CI
Ms Erica Wallis, Sponsor

R&D Reference: HK114212

Version 3, 1st December 2011

Page 2 of 2



Calow
Chesterfield
S44 5BL

Tel: 01246 277271
Minicom: 01246 512611
www.chesterfieldroyal.nhs.uk

Research Department
Clinical Standards and Governance

Tel: 01246 513632
e-mail: sue.glenn@chesterfieldroyal.nhs.uk

13 February 2013

2013/01 (CSP – 117503)

Mr S Holt
Consultant Breast Surgeon
CRH

Dear Mr Holt

Re: Variation in treatment of older women with operable breast cancer

I write to confirm that NHS permission for the above research study has been granted on the basis described in the application form, protocol and supporting documentation. Documents approved are as follows:

- Protocol v.1.0 (dated 24 October 2012)

Approval is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, ICH GCP and NHS Trust policies and procedures (if applicable). This approval is only for the activities for which a favourable opinion has been given by the Research Ethics Committee (and where relevant which have been authorised by the MHRA).

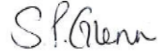
You must comply with the following requirements:

- Ensure that a site file is prepared and kept up to date.
- Produce and disseminate a summary of results in accordance with the study protocol and original IRAS application.
- NHS indemnity or other insurance / indemnity arrangements will apply as identified in the IRAS application.
- In accordance with Trust policy, report all adverse events/serious unexpected adverse events to the R&D office, Ethics Committee, Study Sponsor and Patient Safety Team, if appropriate.
- Manage all data in accordance with the Data Protection Act.
- Report any Health and Safety issues involving patients, staff or visitors, arising out of research activities to the R&D Department, Patient Safety Team or the Environmental Risk Team as appropriate.
- Comply with local guidance on compliance with the Human Tissue Act regarding the use of human tissue in research.
- Alert the trust to any concerns regarding suspected misconduct or fraud resulting from a research project.

Please confirm your agreement by signing and returning one copy of this letter.

If you require further advice on any of these issues, do not hesitate to contact me. I hope your study progresses successfully.

Yours sincerely



Sue Glenn
Matron for Clinical Research

Copy to:
Lauren Osborne, RM&G Facilitator, CRH
nuhnt.trenclrn@nhs.net
l.wyld@sheffield.ac.uk

For information:
Julie Toms, Research Nurse, CRH
richard.shanahan@nhs.net

I agree to comply with the above condition and return one copy duly signed.

Name: Signed: Date:

Research & Development
Northern Lincolnshire & Goole
Hospitals NHS Foundation Trust
Tel: 01724 – 290410

19th March 2012

Miss Jenna Morgan
Clinical Research Fellow in Breast Surgery
Sheffield Teaching Hospitals NHS Trust
EU25 Academic Department of Clinical Oncology
University of Sheffield
Beech Hill Road
Sheffield
S10 2JF

Dear Miss Jenna

STUDY TITLE: Variation in Clinician Preference for treatment in Older Women with Operable Breast Cancer

The above research study was reviewed and processed by the Northern Lincolnshire & Goole Hospitals NHS Foundation Trust Research & Development Department and is compliant with the requirements of Research Governance.

In addition to the University School Research Ethics approval, of which the Trust has been informed, I am pleased to confirm that NHS permission for the above research at **NORTHERN LINCOLNSHIRE & GOOLE HOSPITALS NHS FOUNDATION TRUST**, has been granted on the basis described in the application form, protocol and supporting documents. A 'Letter of Access' has been sent to you.

THE FINAL LIST OF DOCUMENTS APPROVED BY THE TRUST ARE AS FOLLOWS:

DOCUMENT	VERSION	DATE
Ethics Form	1	05/11/2012
Variation in Clinician Preferences Protocol	1.0	24/10/2012
Consent	1.0	24/10/2012
Interview Prompt Sheet	1.0	24/10/2012
Interview Study Reply Form	1.0	24/10/2012
Letter to HCP re Questionnaire	1.0	24/10/2012

Permission is only granted for the activities for which a favourable opinion has been given by the REC and you are required to inform the Trust Research & Development Department of any significant proposed changes to the original protocol, adverse events or issues of safety. Your

project will be subject to monitoring in line with the requirements for Research Governance. In addition the Trust Research & Development Department will require an end of study notification.

Should you require any further assistance regarding this study, please do not hesitate to contact me.

Wishing you every success.

Kind regards

D Bates

Debrah Bates
Head of Research & Professional Development
Northern Lincolnshire & Goole Hospitals NHS Foundation Trust

Darent Valley Hospital
Darent Wood Road
Dartford
Kent
DA2 8DA
Tel: 01322 428393

Ms Seema Seetharam
Consultant Breast and Oncoplastic Surgeon
Darent Valley Hospital

Wednesday, 15th May 2013

PROJECT TITLE: Variation in Clinician Preference for Treatment in Older Women with Operable Breast Cancer
REC Reference: -
CSP Reference: 117503
R&D Reference: DVH190
Protocol version #: 1.0
Protocol date: 24th October 2012

Dear Ms Seetharam,

Thank you for submitting the above study to the Research and Development committee for consideration. The information submitted consisted of the following documents:

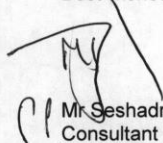
Document	Version	Date
Protocol	1.0	24 th October 2012

Having reviewed all documentation I am pleased to say that the project was approved with this Trust acting as a PIC Site.

Please note under the terms of the research governance framework the study will be subject to monitoring and audit and you will be contacted later in the year regarding this.

Thank you for submitting this study to the committee and it only remains for me to wish you good luck with the project.

Best wishes



Mr Seshadri Sriprasad
Consultant Urologist,
Chair of R&D committee

CC **Miss Jenna Morgan**, Chief Investigator, Sheffield Teaching Hospitals NHS Trust, EU25 Academic Department of Clinical Oncology, University of Sheffield, Beech Hill Road, Sheffield S10 2JF
Ms Erica Wallis, Clinical Research Office, 11 Broomfield Road, Sheffield S10 2SE
Rachel Ryan, Research office, Darent Valley Hospital

Doncaster and Bassetlaw Hospitals

NHS Foundation Trust

Doncaster Clinical Research

Joint Research Office with NHS Doncaster and
Rotherham, Doncaster and South Humber NHS Foundation Trust
Tel: 01302 366666 Ext: 4708
Email: doncasterclinicalresearch@dbh.nhs.uk

Doncaster Royal Infirmary
Armthorpe Road, Doncaster,
South Yorkshire DN2 5LT

03 June 2013

CONFIDENTIAL

Miss Jenna Morgan
Clinical Research Fellow in Breast Surgery
Sheffield Teaching Hospitals NHS Foundation Trust
EU25 Academic Department of Clinical Oncology
University of Sheffield
Beech Hill Road
Sheffield
S10 2JF

Tel: 01302 366666
Fax: 01302 320098

www.dbh.nhs.uk

Dear Miss Morgan,

Study Title: Variation in Clinician Preference for Treatment in Older Women with Operable Breast Cancer
Chief Investigator: Miss Jenna Morgan
Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust
DBHft Reference: 0514/2012/NCT
CSP ID: 117503

I am pleased to inform you that the above project has now been given authorisation to commence within Doncaster & Bassetlaw Hospitals NHS Foundation Trust. For your information, the project reference is **0514/2012/NCT**. I would be grateful if you could quote this number in any further correspondence with this department.

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework ICH GCP (where applicable) and NHS Trust Policies and Procedures.

Documentation

Your authorisation has been granted based on submission of the following documentation:

- Study Protocol (Version 1.0, 24 October 2012)
- IRAS R&D Form (Submission code: 117503/385807/14/702 signed by Miss Jenna Morgan on 16 November 2012)
- IRAS SSI Form (Submission code: 117503/448805/6/191/182193/271678 signed by Miss Clare Rogers on 09 May 2013)
- CV of Miss Jenna Morgan (signed and dated 31 May 2013)
- CV of Miss Clare Rogers (dated 13 May 2013)
- Health Care Professional Cover Letter (Version 1.0, 24 October 2012)
- Health Care Professional Information Sheet (Interview) (Version 1.0, 24 October 2012)
- Health Care Professional Study Reply Form (Interview) (Version 1.0, 24 October 2012)
- Health Care Professional Consent Form (Interview) (Version 1.0, 24 October 2012)
- Health Care Professional Questionnaire (Version 1.0, 24 October 2012)
- Health Care Professional Interview Prompt Sheet (Version 1.0, 24 October 2012)

Under the harmonised edition of the Department of Health publication 'Governance arrangements for research ethics committees: a harmonised edition' published 01 September 2011, there is no requirement for this research to obtain a favourable Research Ethics Committee opinion.

Become a Trust member and make a difference to the care our hospitals provide. Call (01302) 381355 or visit www.dbh.nhs.uk

Associate teaching hospital of the University of Sheffield Associate college of Sheffield Hallam University

1
WPR11993
Nov 2010

Please note that approval is limited to the dates stated on the research application form and that you are obliged to notify the Research Governance Department of any adverse events that arise during the course of the project. You are also obliged to inform us if your project deviates in any way from the original proposal / documentation you have submitted. This may result in the suspension of your project until changes have been agreed with the Trust.

The Research Sponsor, or the Chief Investigator, or the local Principal Investigator, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The Research Governance office must be notified that such measures have been taken. The notification must include the reasons why the measures were taken and the plan for further action. The Research Governance office must be notified in the same timeframe as notifying the Research Ethics Committee and any other regulatory bodies, where applicable.

Amendments

This approval covers the document versions stated above; any revised documents must be submitted for approval by the Research Ethics Committee and other regulatory bodies, where applicable, in accordance with guidance in the Integrated Research Application System (IRAS). If the study has been adopted onto the NIHR Portfolio, any amendments to the study must be reported to the Lead CLRN. In addition, all amendments must receive separate approval from Doncaster & Bassetlaw Hospitals NHS Foundation Trust.

Permissions

This letter authorises you in principle to undertake research within the Trust. However, it is your responsibility to ensure that individuals appropriate to your work have no objections to your studies. This department accepts no liability for non co-operation of staff or patients.

Contracts

It is your responsibility to ensure you have sufficient indemnity to undertake this project. In addition, it is also your responsibility to ensure that letters of access / honorary contracts are in place where necessary.

Good Clinical Practice training

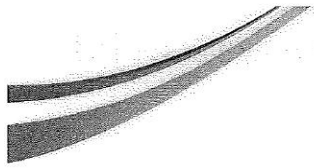
In accordance with ICH GCP guidelines and the UK Statutory Instruments, all key personnel involved in a Clinical Trial as part of the research team, must have completed GCP training within the last three years. It is your responsibility to ensure the research team have received this training. For information regarding upcoming GCP training courses, please contact the Research Governance team.

Auditing

I would strongly urge you to maintain an accurate and up to date site file for your documentation, as the Trust randomly audits projects to assess compliance with the relevant legal frameworks and legislation. If your study is selected, you will be notified in writing not less than two weeks prior to the required submission date of documentation. In addition, where monitoring and auditing procedures are carried out by the Sponsor, you will be required to cooperate, where appropriate.

Monitoring

In order to ensure adequate monitoring of ongoing studies, the Research Governance department will send through periodic monitoring forms which require completion by the Principal Investigator or delegated individual. These will be in two formats. The first is a monthly letter requesting recruitment information. The second form is an annual study progress report. These forms need to be completed and sent through to the Research Governance department as a condition of the approval of this study.



Nottingham University Hospitals **NHS**
NHS Trust

Research & Innovation
Nottingham Integrated Clinical Research
Centre

C Floor, South Block
Queen's Medical Centre Campus
Derby Road, Nottingham NG7 2UH

Tel: 0115 9249924 ext 70659
www.nuhrise.org

Dr Eleanor Gutteridge
Nottingham Breast Institute
Nottingham University Hospitals NHS Trust
Hucknall Road
Nottingham

08 AUG 2013

NG5 1PB

Dear **Dr Eleanor Gutteridge**

Re: 12BS002

CSP 117503

REC

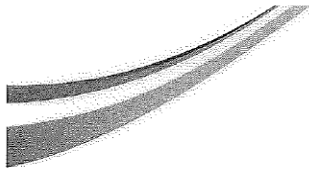
Variation in Treatment of Older Women with Operable Breast Cancer

The R&I Department have reviewed the following documents and NHS permission for the above research has been granted on the basis described in the application form, protocol, and supporting documentation. The documents reviewed were:

University Ethics Approval dated 23/11/2012
Protocol, v1.0, 24/10/2012
Health Care Professional Cover Letter, v1.0, 24/10/2012
Reply Form, v1.0, 24/10/2012
Consent form, v1.0, 24/10/2012
Health Care Professional Information Sheet (Interview), v1.0, 24/10/2012
HCP Prompt Sheet, v1.0, 24/10/2012



We are here for you



Health Care Professional Questionnaire, v1.0, 24/10/2012

Your study now has NHS permission, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

The Principal Investigator is responsible for

1. Compliance with all relevant laws, regulations and codes of practice applicable to the trial including but not limited to, the UK Clinical Trials Regulations, Medicines for Human Use (Clinical Trial) Regulations 2004, principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version), the Human Rights Act 1998, the Data Protection Act 1998 the Medicines Act 1968, the NHS Research Governance Framework for Health and Social Care (version 2 April 2005). Should any of these be revised and reissued this will apply. Copies of the up-to-date regulations are available from the R&I Office or via the R&I website <http://nuhrise.org>
2. Submission of study amendments to the Ethics committee and MHRA in accordance with the IRAS guidelines. Amendments and information with regards to changes in study status must be sent to R&I, (this includes changes to the local study team). Within 35 days from the receipt of a valid amendment submission, NUH will inform you if may not locally implement the amendment. If no objections are raised NHS permission is valid and the amendment may be implemented.

When submitting documents for studies adopted into the NIHR portfolio please send the information to NUHNT.TRENTCLRN@nhs.net

When submitting documents for all other studies please use the email address rdamend@nuh.nhs.uk

3. Ensuring all study personnel, not employed by the Nottingham University Hospitals NHS Trust hold either honorary contracts/letters of access with this Trust, before they have access to any patients or staff, their data, tissue or organs or any NUH facilities.
4. In accordance with the Department of Health's Plan for Growth, for initialising and delivering research within the NHS the 'first patient, first visit should occur 70 days from receipt of a valid submission in R&I. Therefore for all research where:
 - The sponsor is a commercial partner
 - NUH holds a funding contract with the National Institute for Health Research (NIHR)
 - The research is classed as a "clinical trial" on the IRAS filter page.

The research team is expected to collaborate with the department of R&I in reporting recruitment data to



We are here for you

HH/JF/DF/10512

Ms Pankaj Roy
Consultant Oncoplastic Breast Surgeon
Oxford University Hospital NHS Trust
John Radcliffe Hospital
Oxford. OX3 9DU

From the R & D Lead
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865) (5)72240
Fax: (01865) (5)72242
Debbie.Franklin@ouh.nhs.uk

1st October 2013

Dear Ms Roy

Re: Variation in Clinician Preference for Treatment in Older Women with Operable Breast Cancer

NIHR CSP Reference: 117503
Research and Development Reference: 10512
Research Ethics Committee Reference: SMBRER243

Confirmation of Trust Management Approval

On behalf of the Oxford University Hospitals NHS Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval

Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Recruitment

The agreed total recruitment target for your study at the OUH site is 3 participants by 31.12.2013 as specified in the SSI form.

To support requirements of the OUH Trust and national recruitment targets, we will be monitoring and publishing outcomes of recruitment for your study. This will include reporting performance against the 70 calendar day period from the time of receipt of a valid research application in R&D to the time of recruitment of the first participant to your study.

Your first participant recruitment target date is 26.11.2013

In the meantime, if you recruit your first participant into the study then please send the date to researchrecruitment@nhs.net

The R&D office will contact you in due course by email to ask about the recruitment progress against this target.

Ethics Correspondence

In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Research Sponsorship

It is noted that National Institute for Health Research has agreed to Sponsor this trial.

Site Specific Assessment

This Trust Management Approval letter also incorporates site specific assessment for the Oxford University Hospitals NHS Trust site.

Approved Documents

Document Type	Version	Date
Protocol	1	24.10.2012
University REC Approval(Sheffield)		23.11.2012
HCP Cover Letter	1	24.10.2013
Participant Information Sheet	1	24.10.2012
Consent Form	1	24.10.2012
HCP Questionnaire	1	20.10.2012
HCP Interview Prompt Sheet	1	24.10.2012
Investigator's CV	Pankaj Roy	
	Jenna Morgan	
NHS R&D Form		
NHS SSI Form	OUH NHS Trust	

I wish you every success with the study.

Yours sincerely,



Ms Heather House
Research and Development Lead

Title: Variation in Treatment of Older Women with Operable Breast Cancer
CI: Jenna Morgan
IRAS number: 117503
REC number: N/A
R&D Reference: 3042

I am pleased to confirm North Bristol NHS Trust (NBT) NHS permission for the above study.

FULL R&D APPROVAL

You have permission to begin recruitment

Please forward a copy of the updated R&D form – listing NBT as a research site by 01 July 2013.

I understand that Sheffield Teaching Hospitals NHS Foundation Trust will act as sponsor for this study.

We acknowledge that this project does not require ethical review by a NHS Research Ethics Committee under the UK Health Departments' Governance Arrangements for Research Ethics Committees (GAfREC), however it may be necessary to contact the University Research Ethics Committee (UREC).

If your study is an interventional clinical trial, there is a new target to enter your first patient into the study within 70 days of submitting a full & valid R&I application. Please notify us of the date of the first patient first visit. If you experience any problems recruiting, please contact the R&I office for advice and support.

We wish you every success with your study. We are keen to support good research at North Bristol NHS Trust and are pleased that you have decided to conduct your project here.

The lead Research Governance Officer for this study is Stephanie Macpherson, who will remain your ongoing main point of contact. They can be reached at the following email address: research@nbt.nhs.uk.

Approval is given on the understanding that this project be carried out according to Good Clinical Practice and UK Statutory Instrument, and within the guidelines of the NHS Research Governance Framework for Health and Social Care, and NHS Trust policies, procedures, and SOPs which are available online at <http://www.nbt.nhs.uk/research>.

In particular you have responsibility for:

- Ensuring that, all participants sign informed consent (whenever applicable).
- Adhering to the protocol and ensuring your co-workers do the same.

- Ensuring all recruitment figures are uploaded to the Edge database on a weekly basis.
- Providing us with information about any amendments to the protocol, changes in funding, personnel or end date.
- Informing us of any research-related adverse events.
- Ensuring that any staff working on this study at this site have been issued with a contract with NBT (honorary, substantive or bank) or a letter of access before they commence work on the study at this site.
- Maintenance of an Investigator Site File and/or Trial Master Files.

Researchers who hold substantive or honorary contracts with North Bristol NHS Trust (NBT) will be covered against claims of negligence by patients of NBT under the Clinical Negligence Scheme for Trusts (CNST). This scheme does not cover ‘no fault’ compensation and the Trust is precluded from taking out separate insurance to cover this. Any patient or volunteer taking part in the study is entitled to know that if they suffered injury as a result of participating in the study they would first have to prove negligence in a court of law before they could gain compensation. If the study involves patients of any other Trust or healthcare organisation, you will need to confirm the indemnity arrangements with that organisation.

In addition, other information may be requested from time to time and lay summary of the results will be requested from you at the end of the study.

This full R&D approval document will need to be filed in your Investigator Site File and/or Trial Master Files.

In accordance with the NBT Research Monitoring and Audit policy, this study is subject to audit by the R&I Office. We will contact the Principal Investigator to make appropriate arrangements for this.

Many thanks

Nicola Williams
Deputy Director
Research & Innovation
North Bristol NHS Trust

Tel: 0117 323 6468

Fax: 0117 323 6192

<http://www.nbt.nhs.uk/research>

Research and Development Office

DHFT Research &
Development Dept.
Issue' 10 APR 2013

TRUST APPROVAL LETTER

Tel: 01332 340131
Minicom: 01332 254944
www.derbyhospitals.nhs.uk

Mr Kwok Leung Cheung
Clinical Associate Professor & Honorary Consultant Breast Surgeon
University of Nottingham
School of Graduate Entry Medicine & Health
Royal Derby Hospital
Derby
DE22 3DT

Dear Mr Cheung, 

Re: "Variation in Treatment of Older Women with Operable Breast Cancer" Study

R&D Ref: DHRD/2013/029

CSP Ref: 117503

Further to the Research Ethics Committee approval for the above study, I am pleased to confirm Trust management approval for you to proceed in accordance with the agreed protocol, the Trust's financial procedures for research and development and the Research Governance Framework (which includes the Data Protection Act 1998 and the Health & Safety at Work Act 1974).

Please supply the following to Dr Teresa Grieve, Assistant Director of R&D:

- the actual start and end dates of this study (**before the study commences**).
- details of any publications arising from this research project.
- a final report and a report every six months if the study duration is greater than six months.
- notification of any SUSARS, amendments, urgent safety measures or if the trial is abandoned.

Please note that approval for this study is dependent on full compliance with all of the above conditions.

I would like to take this opportunity to wish you every success with this study.

Yours sincerely,



Prof. Richard Donnelly MD, PhD, FRCP, FRACP
Director of Research & Development



Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 254944
www.derbyhospitals.nhs.uk

Short Study Title: **Variation in Treatment of Older Women
with Operable Breast Cancer**
R & D reference: **DHRD/2013/029**
CSP ID #: **117503**

In accordance with your application and subsequent R & D approval dated 10/04/2013, the following documentation was reviewed and may therefore be used on the above study with Trust approval.

List of reviewed documents:

The University of Sheffield School Research Ethics approval letter dated 22nd November
Variation in Clinician Preferences Protocol



DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: Professor D Rowbotham

Assistant Director: Dr David Hetmanski

R&D Manager: Carolyn Maloney

Direct Dial: (0116) 258 8351

Fax No: (0116) 258 4226

08-04-2013

Miss Anne Stotter Consultant Breast Surgeon
University Hospitals of Leicester Glenfield Hospital
Groby Road Leicester LE5 4PW

Dear Miss Anne Stotter

Research & Development Office Leicester General Hospital
Gwendolen Road
Leicester LE5 4PW

Ref: UHL CSP: 117503

Title: Variation in Clinician Preference for Treatment in
Older Women with Operable Breast Cancer

Project

Status: Approved End Date: 03/10/2014

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed with the Sponsor. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&D Office.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first patient will be recruited within 30 days of the date of this letter. If there is likely to be a problem achieving this target, please contact the office as soon as possible. You will be asked to provide the date of the first patient recruited in due course. In addition, the Title, REC Reference number, local target recruitment and actual recruitment for this study will be published on a quarterly basis on the UHL Trust external website.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Title	Version	Date	REC
Protocol	1	24-10-2012	N/A
Clinical Preference Questionnaire	1.0	24-10-2012	N/A
Health care Professional Information Sheet (Interview)	1.0	24-10-2012	N/A
Clinician Preferences Study HCP	1.0	24-10-2012	N/A
Clinician Preferences Study Reply	1.0	24-10-2012	N/A

Health Care Professional Cover Letter	1.0	24-10-2012	N/A
Clinician Preference Study HCP Prompt Sheet	1.0	24-10-2012	N/A

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&D pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting www.leicestershospitals.nhs.uk/aboutus/education-and-research

The R&D Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office. Our contact details are provided on the attached sheet.

This study has been reviewed and processed by the Leicestershire, Northamptonshire & Rutland Comprehensive Local Research Network (LNR CLRN) using the Coordinated System for gaining Trust Permission (CSP). If you require any further information on the approval of this study please contact the LNR CLRN office on 0116 258 6185 making reference to the CSP number which is located at the top of this letter.

We wish you every success with your research.

Yours sincerely



Carolyn Maloney

R&D Manager

Encs: .R&D Office Contact Information

Appendix 10: Interview Consent Form

Variation in Clinician Preference for Treatment of Older Women with Operable Breast Cancer.

Health Care Professional Consent Form (Interview)

Please initial each statement in the boxes provided and sign at the bottom of the page.

I confirm that I have read and understood the information leaflet dated 24th October 2012 (version 1.0) for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I give permission for the interview to be audio recorded.

I understand that quotes from my interview may be used within written reports or publications and that any quotes would be completely anonymous and could not be linked to me in any way.

I understand that relevant interview data collected during the study may be looked at by individuals from the Sheffield Teaching Hospitals NHS Foundation Trust or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to these records'.

I agree to take part in the above study

I give permission to be contacted in the future about participating in a follow-up interview.

Name of Participant

Date

Signature

Name of Person taking consent

Date

Signature

When completed, 1 for participant, 1 for researcher site file

Appendix 11: List of principal investigators at each site for interview component

Trust	Local PI	Local R&D number (if applicable)	Date of R&D approval
Sheffield Teaching Hospitals NHS Foundation Trust	Miss L Wyld	STH17054	17/01/2013
St Helen's & Knowsley Teaching Hospitals NHS Trust	Mr R Audisio	RBN 836	31/01/2013
Guys & St Thomas Foundation Trust	Mr M Douek	RJ113/n041	15/02/2013
Barnsley Hospital NHS Foundation Trust	Miss J Dicks	BHNFT539	26/02/2013
University Hospitals Coventry and Warwickshire NHS Trust	Mr H Khan	HK114212	04/02/2013
Chesterfield Royal Hospital NHS Foundation Trust	Mr S Holt	CSP: 117503	13/02/2013
Northern Lincolnshire & Goole Hospitals NHS Foundation Trust	Mr R Vijh	CSP: 117503	19/03/2013
Derby Hospitals NHS Foundation Trust	Mr KL Cheung	DHRD/2013/029	10/04/2013
University Hospitals of Leicester NHS Trust	Miss A Stotter	UHL CSP: 117503	08/04/2013
Dartford & Gravesham NHS Trust	Ms S Seetharam	DVH190	15/05/2013
Doncaster & Bassetlaw Hospitals NHS Foundation Trust	Miss C Rogers	0514/2012/NCT	03/06/2013
North Bristol NHS Trust	Mr M Shere	3042	18/06/2013
Nottingham University Hospitals NHS Trust	Miss E Gutteridge	12BS002	08/08/2013
Oxford University Hospital NHS Trust	Miss PG Roy	10512	01/10/2013

Appendix 12: Participant information sheet (PIS) for interviews



The
University
Of
Sheffield.



Sheffield
Hallam University

SHARPENS YOUR THINKING

Variation in Clinician Preferences for Treatment in Older Women with Operable Breast Cancer.

Health Care Professional Information Sheet (Interview)

Invitation to participate in the study

We would like to invite you to take part in a research study being organised by the University of Sheffield and Sheffield Hallam University. Please take time to read the following information carefully and feel free to contact us for further information.

What is the purpose of the study?

In the UK there is wide variation in practice relating to the treatment of older women with breast cancer, particularly with reference to rates of Primary Endocrine Therapy (PET). Whilst some of this variance may be explained by variance in patient characteristics such as health and fitness, education, deprivation and disease stage, clinician preference may also play a part. We would like to interview a number of specialist health care professionals who are involved in either the management of breast cancer or care of the elderly about their views regarding the management of older women with operable breast cancer to give us a better understanding of why this variance exists.

Do you have to take part?

Your taking part in this study is entirely voluntary. If you do not want to take part, you do not have to give a reason and you will not be contacted again about this study. If you decide to take part but later change your mind, you can withdraw from the study at any time and do not have to give a reason.

What will happen if you take part?

If you wish to take part in the study, follow the instructions below and a member of the study team will then contact you to arrange an interview at a time and place most convenient to you. Interviews will take between 20-30 minutes to conduct. The interview will be recorded with your consent. Recordings will be stored electronically and anonymously, and will only be available to the study team.

Contact for further information

If you would like any further information, or have any questions concerning this study, please contact Miss Lynda Wyld (Senior Lecturer and Consultant Surgeon), EU36, University of Sheffield Medical School, Beech Hill Road, Sheffield, Royal Hallamshire Hospital, Sheffield. Telephone: 0114 2268640.

What do I need to do now?

Whether you decide to take part in this study or not, we would be grateful if you would complete the Study Reply Form accompanying this information leaflet and return it to us in the FREEPOST envelope provided. You do not need a stamp.

If you decide not to take part, please tick the box beside 'No, I do not wish to take part in this study' and return the form to us. You do not need to fill in any other details on the form.

If you wish to take part in the study, please tick 'Yes, I would like to take part in this study', fill in the contact details section on the Study Reply Form and the consent form provided and return them.

Please keep this information leaflet for future reference.

Thank you for reading this information sheet and for taking an interest in the research study.

Appendix 13: Outline of interview topics for participants

At start:

Issues that may be raised during interview:

What treatment options would you normally consider for an older woman (over 70) with operable primary breast cancer?

Prompts: Would surgery form part of your potential management plan in all patients?
 Is PET an option for all patients in this group?

What do you feel are the risks and benefits of surgery and PET for this age group?

Prompts: Morbidity and mortality of surgery
 Local recurrence risks, local control
 Compliance

What factors influence your choice of management for a particular patient with primary operable breast cancer?

Prompts: Age of patient at diagnosis
 Frailty of patient
 Co-morbidities, including dementia
 Anaesthetic considerations
 Optimisation of other health issues
 Patient choice
 Carer preferences
 Guidelines
 Stage/operability of cancer
 Cancer biology (e.g. ER and HER2 status, mucinous subtype)
 Pre-operative assessment: anaesthetic assessment, formal geriatric assessment, "end of the bed" assessment

Are there any other factors that influence your overall practice in this patient group?

Prompts: Influence of cancer targets
 Influence of costs

If in such patients there is the potential for choice of either surgery or primary endocrine therapy, what level of involvement does the patient play in the management decision?

What factors have influenced your personal strategy for dealing with these patients?

Prompts: Literature evidence
 Patient preference
 Experience of cases over the years
 Unit policy
 Training and mentoring
 Breast care nurse input

What affects the amount of information you relay to a patient following a diagnosis of

breast cancer?

Prompts: Patient wishes
Patient cognitive status
Relative and carers information needs

What do you think elderly women feel about primary endocrine therapy?

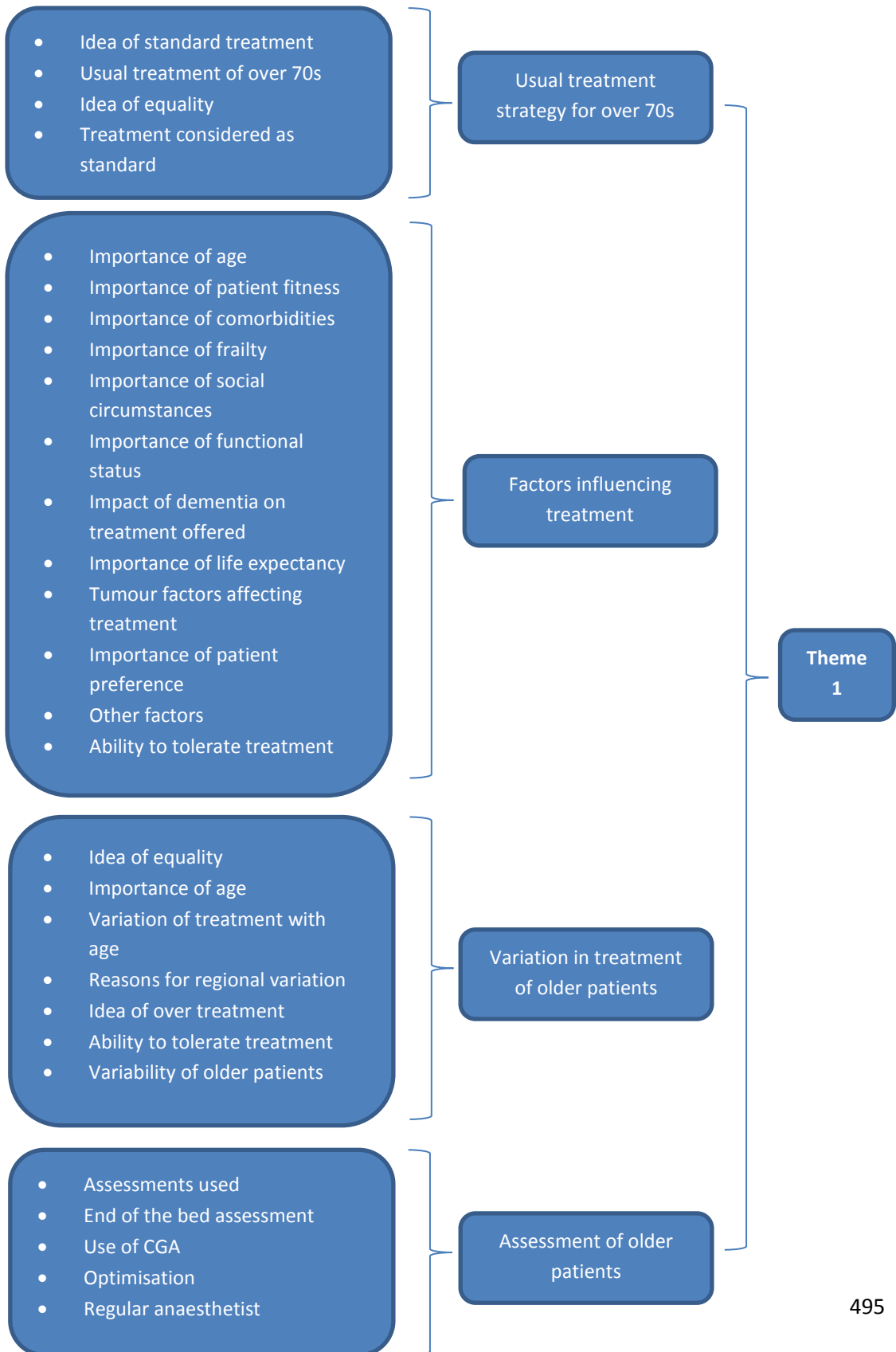
Prompts: Easier than having surgery
Safer than having surgery
Less certainty of a cure
Less hassle

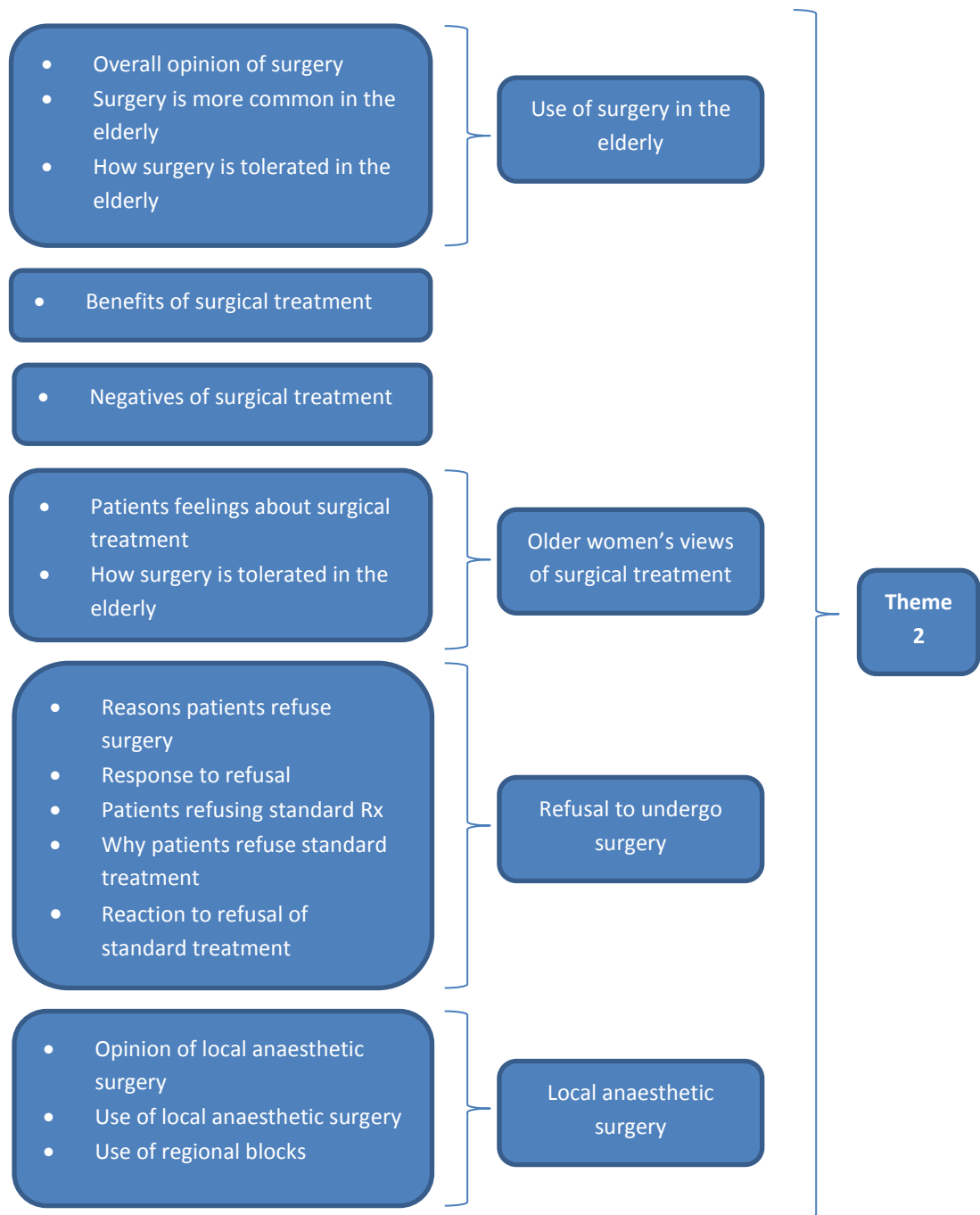
What do you think elderly women feel about having surgery?

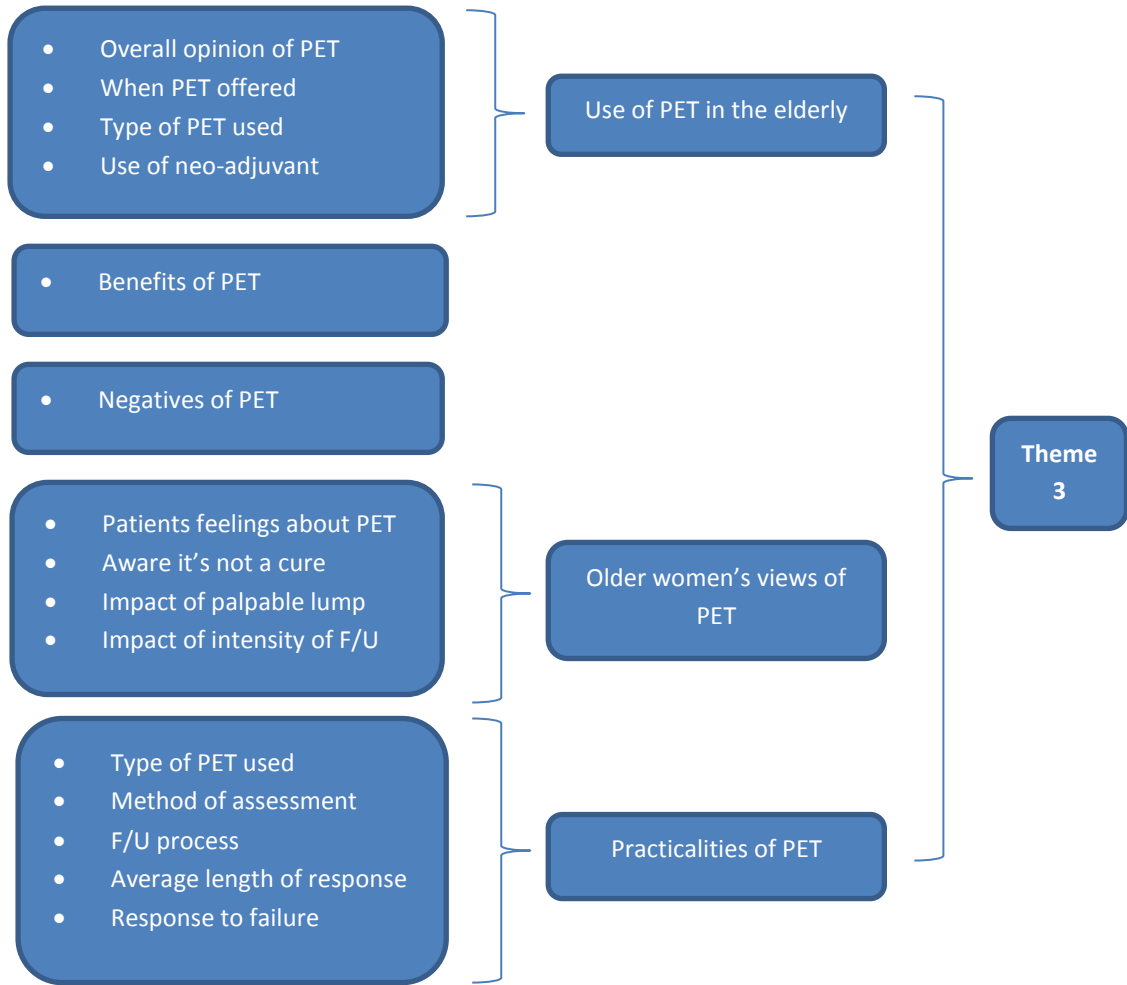
Prompts: Fear of death
Disfigurement or loss of breast
Fear of hospitalisation
Burden on others
Loss of independence
Complications (e.g. arm swelling)

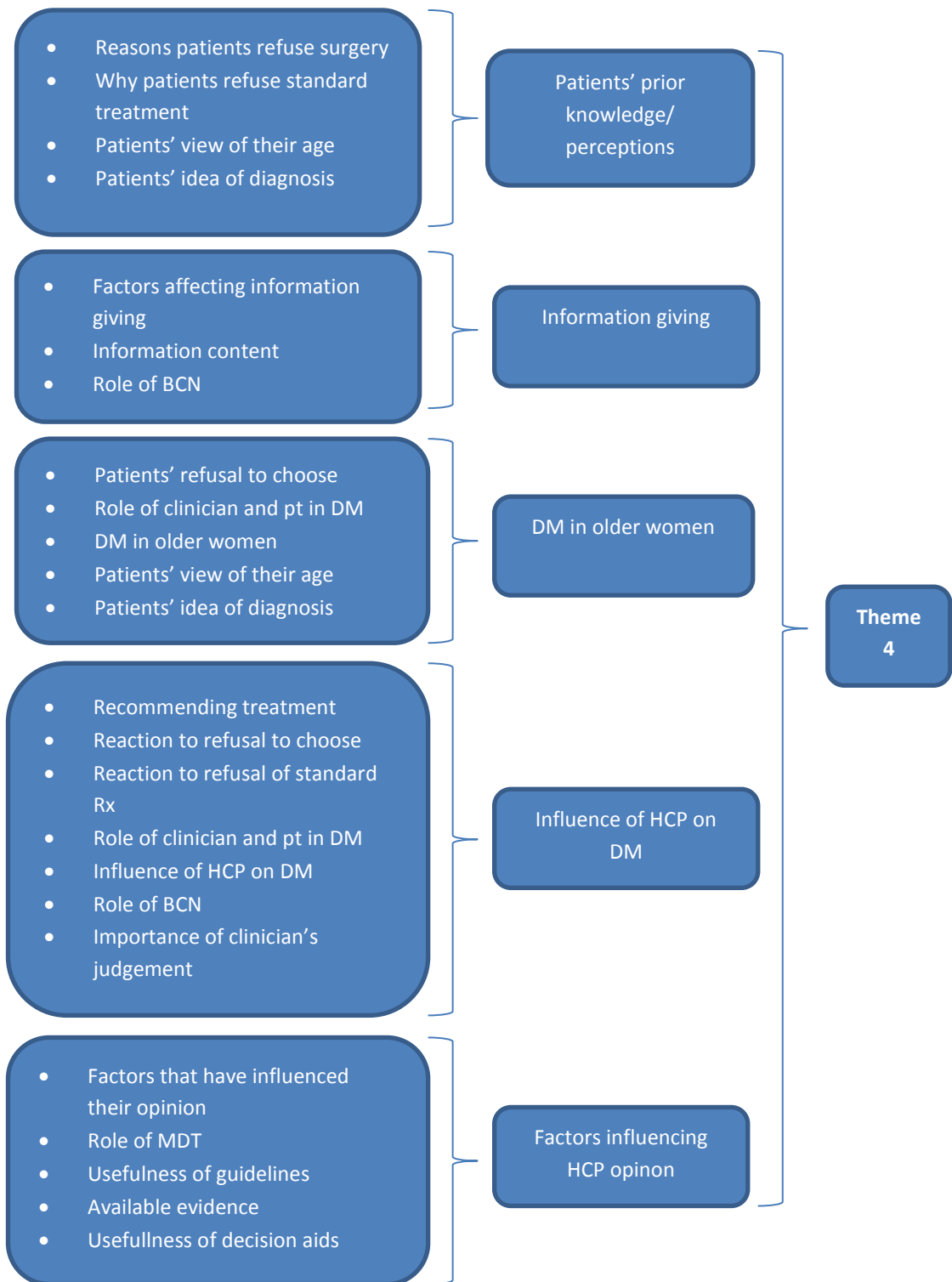
Any additional comments the participant would like to add

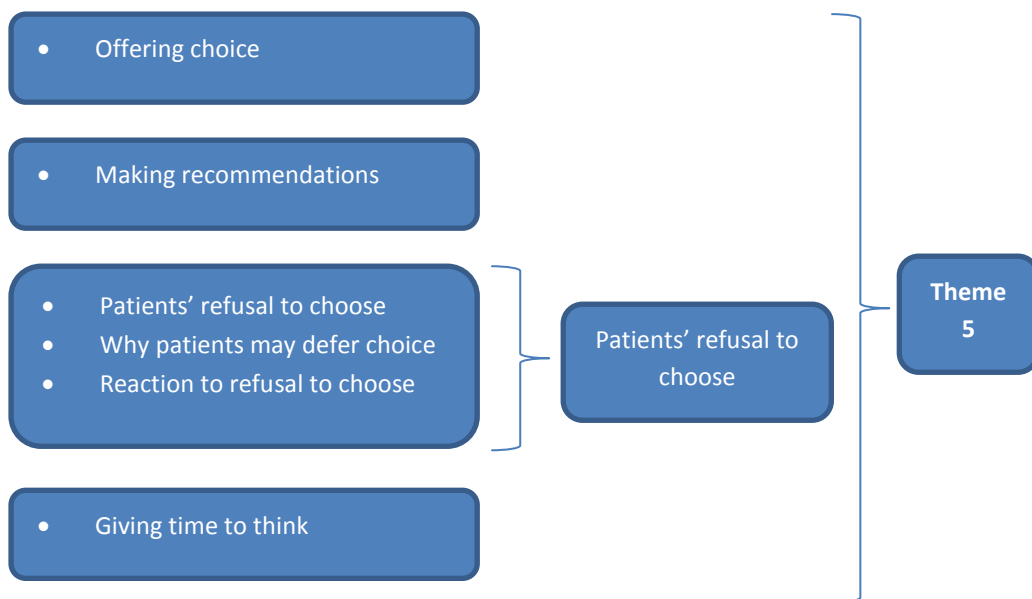
Appendix 14: Relationship between interview codes and themes











Appendix 15: Interview Framework Matrix

Theme 1: Attitudes towards treating older women with breast cancer

	1.1 Impact of age on treatment of breast cancer	1.2 Factors influencing treatment	1.3 Assessment of older patients	1.4 Variation in the treatment of older women
S01 Female High PET	<p>As you would treat a woman of any age. Normal Rx as per the protocol for a woman of any age. Mentions Mx, ANC, chemo. Ideally like to treat... in the most aggressive way that you possibly can. Someone who is clearly fit... should offer them an operation. I do consider it (PET) for women in this age group. Treats pts as individuals, tailors accordingly, consider her ability to tolerate the Rx.</p>	<p>Take into account fitness. Not fit for a haircut = PET. Should be based on biological fitness. Not doing her any favours by treating her with that degree of aggression if has life-limiting co-morbidities. Mentions: lung cancer, COPD, cardiac problems, AF. Very frail lady... probably better off with tablets. Slightly demented... better off with tablets...may have a preference... have to respect that. ER & HER2 status. Take into account her preferences. Pt views obviously have the primacy. Views of relatives. Ability to tolerate the Rx.</p>	<p>Anaesthetic assessment useful in "borderline" group. No geriatricians involved. Might want... anaesthetic assessment... let's put the actual risk of an anaesthetic into the mix. End of bed assess leads to full anaesthetic assessment. Everything's based on the... opinion of the surgeon as to their fitness... everyone's got different thresholds... means that people haven't got a clue what they're doing. Doesn't use CGA. Comorb... Refer them... optimisation. Different anaesthetists have different thresholds for who's fit for a GA. Team effort. Anaesthetist calculates risk.</p>	<p>Used to an over 70s policy- one of my colleagues used to put everyone on PET if they were over 70. When I was a newly qualified doctor, there was generally the view that anyone over 70 was too old to have anything. Definition of old is changing... "70 is old" is now become "80 is old". Nowadays 70 is not regarded as old. At the moment everything's based on the preference or the opinion of the surgeon...there's no guidance and everyone's got different thresholds. May be more Rx than she actually needs. You're not doing her any favours by treating her with that degree of aggression. Consider her ability to tolerate the treatment. It's a very heterogeneous population.</p>

<p>S02 Male High PET</p>	<p>Considers surgery for every pt. Uses PET probably in three situations. I would want to comply with standard guidelines... unless there's a reason not to. If it's easy to treat (breast cancer in the elderly) then why wouldn't you?</p>	<p>Regardless of age. Contradicts: Everyone does take age into account... you can't help it. biological age. ability to withstand certain Rx's. Pivot age... into the 80s... more likely to die of something else than BC. If F&W recommend op. Rare that someone is so unwell that they couldn't have an op. Tries not to let dementia or being in a wheelchair influence. IADL important in Rx DM. Life expectancy important in Rx DM: predicted survival of <2-3 yr there's no... benefit from surgery... > 5 yr... definite role for surgery... between... 2-5 yr... choice to be made. Other than strongly (ER) positive... would be recommending surgery. Try not to go on 1st impressions.</p>	<p>Anaesthetic opinion to make a more rational judgement. No formal Charlson/questionnaires. It's largely having a background knowledge of the important factors but not accurately and confidently measuring them. Don't do a CGA at the moment and don't have access to that. Thinks CGA should be done if the pt has any degree of frailty.</p>	<p>I would want to comply with standard guidelines... unless there's a reason not to. Everyone does take age into account, and you can't help it. "pivot age"... somewhere into the 80s, where you're more likely to die of something else than BC. The thing that's resilient is that around 40% of older people are not getting operations. I would like to see... a narrowing in the variation in Rx. Thinks the fact that older women get all info from HCP is perpetuating the variation in Rx. It's about narrowing the variation in practice which is due to the HCP preference. Lack of benefit: surgery is not going to be of significant benefit. Predicted survival of <2-3 yr there's no additional benefit from surgery. If you're 90 and it's only 20-25% of people die of BC, it's still a significant cause of death. Thinks size or Rx effect was misrepresented, resulting in a collective under-Rx.</p>
<p>S03 Male Low PET</p>	<p>Consider... surgical option... or I would consider a non-surgical option if the lesion is ER+. I've not ever made up my mind <i>a priori</i> - I want to offer the best Rx to every single individual pt.</p>	<p>Crucially important is pt's fitness. Frailty is the only parameter. Considers lack of mobility because of risk of VTE with Tam. These pts (dementia) need double consenting and surgery. Cope better with half an hour surgical procedure rather than with a full life of PET. Two Rxs are not entirely superimposable, unless she is going to die before the cancer comes back. ER positivity. Pt's preference... crucially important. Several older pts cannot comply with Rx (PET).</p>	<p>Uses "Timed Up and Go," "Groningen Frailty Index" and "VES13" to assess fitness. Mandatory to have frailty assessments otherwise you are biased in an ageist decision which is not evidence-based. Routinely performs frailty assessments on all patients 70 and above. Talk to the geriatrician... cardiological assessment when they've got swollen legs. Not even a CGA is entirely 100% reliable.</p>	<p>I want to offer the best Rx to every single individual pt. Thinks reason for variation in Rx is because of the Dundee report in the 80s that presented... PET as the panacea, that surgery was not needed and lazy surgeons buy this without any critical mass. The question is, is this beneficial for the pt? Is the pt going to take advantage of the surgery or is she going to die before?</p>

<p>S04 Male Low PET</p>	<p>Offer the same options as... a lady who's under 70 yr old. Standard Rx is surgery. It's difficult to avoid offering surgery to pts... of any age. Offers both BCS and Mx if appropriate.</p>	<p>Age doesn't impact on Rx offered. Difficult to avoid offering surgery to pts... of any age. If they're fit for an op then I would operate on them. Significant co-morbidity such as significant other cancer might make a pt not suitable for surgery Contradiction: offer the same surgical options even with significant co-morbidities. Frailty doesn't impact Rx. Significant dementia may not be suitable for surgery. ER positivity. Pt who declines surgery.</p>	<p>Routine anaesthetic assessment, doesn't influence decision: happens after I've made a decision to operate. Decision re: fitness for operation made by the clinician/nurse who sees the pt. Don't have a regular anaesthetist - we're lucky if we see the same person every week.</p>	<p>I would offer the same options as I would offer to a lady who's under 70 years old. I try to avoid falling into the trap of let's give them a more radical operation with more risk of lymphoedema just because we don't want to operate again. I don't like, or I don't agree with the notion that because they are old you've got to offer them Mx and ANC to avoid the second anaesthetic. That doesn't make sense to me. Benefit of surgery is small, particularly in older, frailer women.</p>
<p>S05 Male Low PET</p>	<p>All the options that I would a fit 30 y.o, as I would a fit 70 y.o. In terms of... quality... or the nature of surgery it wouldn't change. Cautious with chemo. Rx needs to be individualised, it needs to be tailored, it's bespoke Rx. Rx that the cancer deserves and not an age deserves. Never differentiate on age because I wouldn't want that to be done to me. Done a reconstruction on an 85 y.o. Pt's best interest.</p>	<p>Don't differentiate... on age. 70+... same Rx as would anyone else. Rx that the cancer deserves and not an age deserves. Fitness influences. Severe co-morbidity you're not going to take her breast off. Wouldn't normally operate on a very frail old lady. Considers dementia but would always aim to get optimal Rx. ER status. Pt choice biggest factor but if you tell them what's best for them they would eventually come around to your POV. Pt-driven decision, rather than a surgeon-driven. Important can withstand surgery. Loss of independence post-op so may benefit from masterly inactivity & PET.</p>	<p>Full assessments performed by elderly care team - they would tell us "Yes, there's no reason why this pt can't have a GA". Decides in clinic whether a pt needs further assessments and refers her to elderly care team. Use PET whilst optimising them and leave on PET if can't optimise.</p>	<p>Give all the options that I would a fit 30 year old, as I would a fit 70 year old. So a 70-year old, or 70+, would get the same treatment, as would anyone else in our unit. I don't think anyone should treat anyone purely because she's 70. I would never differentiate on age because i wouldn't want that to be done to me and so why would I do it to someone else? Done a reconstruction on an 85 yo. You give the pt Rx that the cancer deserves and not an age deserves. Clinicians bias, particularly of the older generation of surgeons. Surgeon-driven decisions - dysfunctional MDT means surgeons dictate what is happening. Spare her the mastectomy, when we know that her COPD may kill her before her breast cancer does. The co-morbidities will kill them before their cancer. We can't just generalise and say I'm going to do this for everyone over the age of 70. You would individualise the treatment.</p>

<p>N06 Female Low PET</p>	<p>Don't think they're limited. Offered all ranges that are appropriate to the pt. Look at the pt as an individual. Example of offering a 72 y.o. chemo.</p>	<p>Age is a number, doesn't determine Rx. Not physically fit may only be offered PET. Only if the anaesthetist says "this lady cannot go under anaesthetic" - is it the anaesthetists that ultimately decide Rx then? Chronic morbidities, e.g. heart disease, may prevent pts being fit. Depends how frail they are. NH + dementia: there's no way we would be able to do surgery on her. Dementia may prevent pts being fit for surgery.</p>	<p>Assessed by specialist older person's team and anaesthetic opinion - even if they look like they're unfit: we would always send someone...for an assessment... even if they look like they're not physically fit, we would always get that second recommendation and only if the anaesthetist says "this lady cannot go under an anaesthetic".</p>	<p>Example of offering a 72 y.o. chemotherapy - I think they're offered all ranges that are appropriate to the patient. I think we look at the patient as an individual. Age is a number - it doesn't determine a treatment. Less variation between surgeons now in terms of treatment options - thinks because of strict MDM recommendations. Although occasionally surgeons deviate from the recommendation - which has been known to happen, surgeons just say "well actually, I think this way". Becoming more aggressive with all Rx now compared to previously. You can have a very fit 80 y.o. Inherent bias, stresses "even" with older ladies - even at that age. Body image is so varied, even with older ladies.</p>
<p>S07 Female High PET</p>	<p>Treat any pt surgically first. Most women at 70 are perfectly fit for an anaesthetic. Standard Rx unless a reason not to. I'm sure there are those who come, looking frail, with carers and they're 86 and we just go have this nice tablet.</p>	<p>With 70 y.o's, I wouldn't be having this conversation (about PET)... it's mostly over 80s. More about co-morbs than age. Biological age. If somebody's fit for surgery. Multiple meds, MIs, CVAs, diabetes... may not benefit from op. I'm sure there are those who come, looking frail... and we just go have this nice tablet. Daily activities influence. Dementia: discuss PET, depends how they'd cope with hospitalisation. If... going live >5 yrs... probably going to come to the end their E... T. ER positivity. Would offer a choice of PET if they look appalled at the thought of an op. Anaesthetist opinion important.</p>	<p>Anaesthetic assessment. Hard to put a finger on exactly what point do you look at somebody and think we'll talk about ET. Doesn't use CGA. Regular anaesthetist, so my pts would be discussed with her. Helps to have someone you work with regularly: she knows what the op involves... potential morbidity.</p>	<p>Some clinician bias - I'm sure there are those who come, looking frail, with carers and they're 86 and we just go have this nice table. I wouldn't generally with 70 year olds, I wouldn't be having this conversation... it's mostly over 80s. Most women at 70 are perfectly fit for an anaesthetic but there are some who aren't. Older pts vary - describes a very unfit 86 y.o. who wanted an operation vs 84 y.o. who's fit as a fiddle and PET not really working but won't entertain an operation.</p>

<p>S08 Male High PET</p>	<p>Between 70-80... we'd really want them to be having surgery. 80+ would be happy to discuss PET but if fit will still be pushing surgery. Once they get to 85 and above, then I would be certainly talking to patients about PET in equal terms as surgery.</p>	<p>From 70 to 80... I would certainly not consider PET in that group. 80+ PET a concept that I would be happy to discuss. 85+ certainly talking to pts about PET in equal terms as surgery. If not fit very happy to consider PET. Serious co-morbs would prevent surgery. Would be pushing the primary surgery if I feel that they have very few morbidities. Rx decision influenced by: co-morbs, multiple meds, immobility, recent cardiac/resp probs. Frailty not best marker unless so frail they can't survive surgery. Doesn't look at NH status. Immobility influences Rx decision. 1st impressions: if she comes storming in. Dementia doesn't influence Rx decision. Rx must be geared towards the pt lifespan. Locally advanced should get surgery. Really want them to be having surgery unless they absolutely say... they don't want it. Whether they can withstand surgery important deciding factor.</p>	<p>If there are any queries then I would refer on to the anaesthetist, for an anaesthetic opinion. Told by the anaesthetist that she would probably be unlikely to survive surgery. If you or they are not sure then a referral to anaesthetic department for a much more intensive review. Uses anaesthetic r/v to back up decision not to operate. It is purely bedside history-taking and a frank discussion with the pt. Doesn't use CGA. Regular anaesthetists in some lists but not others.</p>	<p>70 to 80 I don't consider elderly. Age dictates Rx options offered. Talks about no survival advantage for either Rx after 85 yo. When you're 80-82 y.o. & you've got BC, whether you do a lumpectomy or you do PET, I don't think they're going to live any longer and I don't think the local control is that much of an issue that we ought to take everyone down for surgery. So why do surgery & RTx & everything when these pts- they're not going to live any longer than their natural lifespan. There is a significant group that will not tolerate surgery & therefore it's worth...give them tablets, see how it does. Although there are some patients who are in their mid-70s who are clearly not for surgery.</p>
<p>N09 Female High PET</p>	<p>If fit & healthy - surgery. I think I'm of the opinion that surgery is the gold standard.</p>	<p>Would like to think age doesn't play a factor in Rx decision. Thinks Rx decision is based on fitness. PMH discussed at MDT and helps form provision Rx plan. Medical conditions that might impact on their anaesthetic risk - e.g. very high BP, chest problems, repeated MIs, cardiac problems, wheelchair-bound, arthritic, very disable - those kind of things might come into all of the equations about making decisions. Dementia comes into DM - discuss with family what they feel would be beneficial for their loved one - doesn't mean to say we don't do surgery on patients with dementia, but we don't want to put patients under unnecessary distress. Mentions issue of compliance with PET.</p>	<p>Anaesthetic assessment to assess surgical risk. May be fit on paper but then clinician sees them and feels they're not then there may be a change in Rx plan.</p>	<p>Would like to think age doesn't play a factor in Rx decision. 70 is not old these days, so you're looking at you're 80s and 90s now. Rx varies between clinicians - some will offer a choice of either option and others won't - some surgeons will do that, others don't, so it's very clinician dependent. Talks about some pts being very worried about surgery, others just want to get on with things.</p>

<p>S10 Male High PET</p>	<p>We usually do sentinel node for them, so we tried to avoid axillary clearance to stop them from having lymphedema. We don't discriminate pts on age, so whether she's young or 70 or even 80, if the cancer is operable, I would offer them surgery. Either WLE +SNB or Mx + SNB.</p>	<p>Don't discriminate on age. Majority pts 85+ would be for PET: at that age, they are not very keen to go for surgery, or the family... are not very keen, especially if they are very frail. 70-85 if they are fit we usually offer them surgery. If fit, go ahead with surgery. If high risk will operate if the anaesthetist is happy/pt accepts risk. Mentions DM, asthma, stroke, angina, heavy smoker. Severity important: not every co-morb means I should... go for HT. You don't like to lose your pt, if she has got a lot of comorbidities, to put her under anaesthesia, especially if you have an alternative... it's better to be safe. If they are very frail... & the relatives are happy to go with HT, we try...not to enforce the Rx on them. Mobility not a contraindication. Dementia: go for surgery if the pt/relatives happy. ERPR status. Cancer type doesn't matter. If pt is happy. Targets/cost don't influence.</p>	<p>Seems to leave decision to anaesthetist - will operate unless the anaesthetist says they are not happy. Anaesthetic pre-assessment clinic - they will tell us fit or not fit for surgery. Doesn't use CGA. Usually write to physician about comorbidities in terms of severity and fitness for surgery or optimisation. Has a regularly anaesthetist but his pts may not be seen by his anaesthetist.</p>	<p>We don't discriminate patients on age. Majority of pts 85+ would be for PET. Reason for 85 as cut off: at that age, they are not very keen to go for surgery, or the family, the relatives, they are not very keen, especially if they are very frail.</p>
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<p>N11 Female Low PET</p>	<p>Surgery would be the main Rx that would be discussed in the first instance. People shouldn't be prejudiced against because of an age. We've operated on a lot of older pts, 80+, 90. It would be unfair not to offer it (surgery).</p>	<p>Age seems more important to pts than HCP: age is an important factor because when people say "am I too old"... people shouldn't be prejudiced against because of an age. Take fitness into account. If unfit for surgery would discuss that surgery not the best option. Co-morbs influencing fitness for surgery include heart problems, warfarin, lots of medication - these would make somebody think "is this (surgery) the best thing?" Take frailty into account. Physical frailty more important than mental health. Size of tumour may affect Rx - e.g. neo-adjuvant to downsize. Most important for deciding Rx is the pts opinion - they come thinking... "I won't be able to do this" but they leave thinking "I'm quite happy to go for this" - is this really pt preference or is it reassuring and persuading them that surgery is the best?</p>	<p>Use PACE questionnaire to assess how fit someone is. Get anaesthetic assessment of fitness before discussing surgery not being the best option. Anaesthetic opinion as second opinion. Pre-op assessment reassures pts. Take into account anaesthetic r/v. Uses other assessments combined with a few simple questions to decide whether a pt is able to have surgery. Questionnaire used in clinic, looks at the whole person - mental capacity, depression, family support, ADLs, eyesight, hearing, mobility - holistic look at the person. Also timed stand-up and go. Combine this with the anaesthetic review to decide if the pt is able to have surgery.</p>	<p>People shouldn't be prejudiced against because of an age. Age seems more important to pts than HCP in DM. 70 is young. Take into account a person and the word "old" can't be used about a lot of people.</p>
<p>N12 Female High PET</p>	<p>Let's assess her... and take the surgical option forward.</p>	<p>Consider PET if ladies can't withstand a GA. If a lady has a lot of co-morbidities... it would be more focussed towards PE(T). PET a good option for pts who are not mobile, come into clinic in a wheelchair. PET would be an option for pt with complete senile dementia with poor QoL. Importance of quality of life - I think you have got to address certain QoL issues.</p>	<p>Pre-op assessment - allows us to reassure pts that surgery is safe. Always have general pre-op, incl: ECG, PFT, CXR, bloods + anaesthetic assessment to ensure not going to do more harm than good. Get anaesthetic assessment to check ok to offer surgery. Getting more thorough about assessing pts for surgical options.</p>	<p>I always try to give the same information out, whether a patient's in their 20s or their 90s. Surgery for elderly more common in recent years than it used to be - you don't sort of see primary endocrine as the only choice now for the elderly lady. I think doctors generally are getting better at steering patients towards the surgical options more so than perhaps 8 years ago.</p>

<p>N13 Female High PET</p>	<p>Primarily surgery + then the add-on Rx as per surgery results. I think if you asked sort of almost all of us that worked in the unit "what would you offer someone as a first line treatment" it would always be surgery if they were fit for it. Choice of WLE/Mx. Usually axillary surgery - but some pts where we're willing to compromise - does this suggest less aggressive with extremes of age?? Offer chemo if fit and would benefit. Offered immediate recon to a 76 y.o. - there was no reason not to.</p>	<p>Used to be about age but not anymore. We're so not ageist now. Irrespective of age, don't really offer PET to fit pts. You're trying to work out are they fit enough: Nothing we won't do if someone's fit. Look at all co-morbs when deciding suitability for surgery. Usually health issues that steers Rx decision. Dementia doesn't exempt them from surgery but Usually family that sways us into PET - last thing they want is to put their - parents usually - through surgery. Talks about life-expectancy may be shortened by something else but will still operate: if we can then let's get rid of it. Hormone sensitivity. Very much personal choice. About what they want... it's about not judging that and just doing what they want you to do. Look at whether could withstand GA. Look very carefully at can we afford to give them an anaesthetic or would PE(T) be far safer for them.</p>	<p>If sceptical about how well they'd tolerate a GA would get an anaesthetic consultant to assess them for level of risk. Anaesthetic assessment is a risk stratification. Do a basic performance status and co-morbidity score - helps determine fitness level, what they could withstand and what could we recommend for them. Occasionally anaesthetist will refuse to put a pt to sleep - they'll say someone's risky for an anaesthetic, it's not often they'll say you know "we really can't do this". Generally work with a similar anaesthetist. We've got one who's extremely cautious.</p>	<p>It used to be about age but not anymore. You assume that in an older lady they've used their breasts for what they work for and they don't actually have a use... so I think we assume that they're not going to be bothered (about disfigurement). I think we're so not ageist now compared to how we used to be. More often than not we're wanting to Rx something that probably won't actually end their life. Talks about decision re: Rx impacted by what Rx would benefit the pt - therefore Rx may not be of benefit. You learn what's acceptable for some is not acceptable for everybody else. More open-minded now. I've seen us operate on people... in more recent times that in the olden times... we'd have thought "do you know what? That's too risky!" I think we're so not ageist now compared to how we used to be.</p>
<p>S14 Male High PET</p>	<p>Primarily surgery, BCS if possible, & Mx with whatever axillary assessment is required. Also are given the option of PET.</p>	<p>PET mainly used for pts 77-90, there are very few 70-77 who are treated with PET. Wherever they are fit for anaesthesia they would go for surgery. Co-morbs determine suitability for surgery - pts with severe COPD, CCF or CVAs would be more unsuitable for surgery as they're high risk for GA - would still be offered LA surgery. Frailty contributes to life-expectancy. If in NH need info from carers on things like compliance. Dementia... they would probably be recommended PET. Compliance can be an issue for dementia pts which would influence decision - surgery an option if won't take tablets. Pt choice an influence. Not targets or costs.</p>	<p>Anaesthetic assessment for high risk pts to quantify surgical risks before we decide on surgical Rx. I occasionally get them to see a geriatrician for their life-expectancy. If in my view they are high risk then I would send them to the anaesthetist for their assessment. No regular anaesthetist - used to at last hospital.</p>	<p>Mainly used for pts 77-90, there are very few 70-77 who are treated with PET.</p>

<p>S15 Female High PET</p>	<p>Boils down to...is this woman fit for standard Rx? Choice of Mx and WLE, SNB if no evidence of axillary disease, ANC if they have, adjuvant ET if ER+, RTx with same indications as for younger women. Acceptance of chemo for women >70 has been quite slow.</p>	<p>Boils down to is this woman fit for standard Rx. Certain co-morbs have a significant chance of death if you operate on them. Recent serious illness (MI, PE, acute pancreatitis) - we use ET until they're well and then operate. Very frail elderly pts generally don't want an operation and lose their natural defence against cancer. Severe dementia is associated with short life-expectancy so Rx with PET if ER+ vs. Poor mental function not associated with short life-expectancy (e.g. brain damage) we need to get them through surgery. Rx decision mostly about life expectancy: A woman who is likely to live >2 yr, & certainly anyone who is likely to live >5 yr, will be talking about the limited efficacy of ET if it's used on its own. Life expectancy is key. ER status.</p>	<p>Assessment of pt's BC, PMH, mental & physical function, fitness for GA (ASA). Anaesthetic and geriatric assessments. 3 assessments key to assessing life-expectancy: MMSE, Bartel, ASA: anyone who scores poorly on 1+ = short life expectancy, 3 = very likely to die. Referred to specialist clinic based on an eyeball. Not very accurate -a lot of the pts when they've come through the assessment, are actually fit. Have a geriatrician in specialist elderly clinic and assess multiple factors. Geriatrician's opinion of life-expectancy important. "you wouldn't hesitate to refer someone to an oncologist... if they've got cancer ... so why don't you involve a geriatrician in management?". Not always the same anaesthetist but generally have a regular one - I will talk to him about particularly difficult cases ahead of time. Regular anaesthetist hugely helpful.</p>	<p>We're all biased and we're not supposed to be biased but we all are... older people are unattractive - tries to visualise them as they used to be, ask about thier job/past. How can it be uniform when there's no evidence base to base it on? Now we can't do that anymore (make it up as we go along) because we now have some evidence which we've been presenting but mostly nobody knows about it, it's quite difficult to get the whole surgical community aware of stuff. Talks about working out whether someone has a good chance of surviving long enough to benefit - i.e. some will not benefit from surgery as will die before. People say that you can get any pt through BC surgery, though why would you want to if she's not likely to benefit. Far, far more variable than younger people.</p>
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<p>G16 Male High PET</p>	<p>Mentions some pts who surgeons felt uncomfortable offering standard Rx to.</p>	<p>Co-morbs limiting life-expectancy impact on Rx decision. Co-morbs are not just present or absent, there are stages of severity. Most important factor is functional assessment - gives an idea about what limitations their co-morbs have on their ability to live. Important to assessment cognition because impairment more common when formally assessed, need to know capacity before deciding, & severe impairment results in significant reduction in life-expectancy. Impaired cognition is a very important predictor of not just total life expectancy but disability-free life expectancy. Life-expectancy impacts on Rx decision. Past experience - If your last 80 y.o. died, then actually you're going to remember "I knew it was wrong, I knew I was right not to have operated on somebody who was 80, because all 80 y.o.'s do badly".</p>	<p>Questionnaires: Personal Activities of Daily Living, Domestic Activities of Daily Living, Cognitive Impairment, co-morb assessment (amalgam of Satariano, Charlson and MRC C-FAS. Also Geriatric Depression Score: screening tool and doesn't really influence DM. Use assessments when there's uncertainty about best Rx to get more info. Clinic uses CGA applied by a non-geriatrician as well as resident geriatrician in the clinic. Use it as a decision-informing tool. You often find that people are not best Rx'd, when they see somebody who knows what they are doing, then actually you can make Rx changes that actually improve their underlying comorbidity. Few pts you diagnose something new, a few with established co-morbs who have worsened or not on current best Rx, a few need preventative Rx - in total maybe 15% need optimisation. Ability to optimise or not does help with making a final decision in about half.</p>	<p>I think it became clear that in most centres, certainly in the UK, there seemed to be a very different % of pts having surgery and % of pts having PET once they got to a certain age... Rx appeared to be being influenced by the fact of their age rather than how they were. You've got that teaching... over years where there's a certain age where you're always taught people get complications. Previously decisions were based on age, now based on whether pt is F&W (in Leicester due to clinic). Mentions that for someone with lots of other medical problems the BC's actually not the major problem. Important issues vary from person to person as we're all individuals. I think people have seen that, I think the amount of surgery in the over 70s has increased and there is less reliance on PET.</p>
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<p>N17 Female High PET</p>	<p>Older pts, are treated equitably. You've got to be able to say that "we will consider that we are going to treat this 80 y.o. lady the same as we would a 50 y.o. lady". Discuss all Rx available - including surgery, RTx, chemo, ET.</p>	<p>Don't preclude by age now. "it's not about your chronological age, it's about your biological age". I think they (surgeons) can be... looking at somebody and saying "they're too old". 10-12 years ago Rx used to be based on age. If not at all fit to have surgery... you go down the route of talking about ET. Obviously look at any comorbs. People look at some pts and think "she looks too frail, we shouldn't be thinking about Rx'ing her". Look at what they do on a day-to-day basis, where they live. Severe dementia impacts on life expectancy so perhaps should think about PET but if fit and family agrees then surgery. This lady is going to be around for another 10 yr or more, so we should be Rx'ing the cancer thoroughly, and that would include surgery vs. This lady is probably only going to survive another couple of yr then we should be thinking about not operating and perhaps giving ET. Take into account cultural issues.</p>	<p>Full assessment allows pts to make an informed decision. Full assessment gives the pts confidence about surgery. After assessments may be apparent that they're not at all fit to have surgery. Pts referred to specialist clinic all have staging - bloods, CXR, ECG +/- CT. Functional assessments limited - for instance, 'can you walk upstairs?', and they say "no, I live in a bungalow"... you can very easily take their independence away from them.</p>	<p>Older pts, are treated equitably. You've got to be able to say that "we are going to Rx this 80 y.o. lady the same as we would a 50 y.o. lady". We don't preclude by age now - even offer chemo. They (some surgeons) can be... looking at somebody and saying "they're too old". 10-12 years ago Rx used to be based on age. Somebody that's 80 can be biologically 60. And then you get somebody that's 60 that can be, they've got the body of an 80 year old. Age changes its meaning as well as you get older. 20yrs ago would have been guilty of saying she's too frail for surgery but now realises that Rx should be equal despite age. 10-12 years ago there were more pts on PET because people said they were "too old" for surgery.</p>
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<p>S18 Female High PET</p>	<p>May just offer them surgery. May discuss PET. May discuss neo-adjuvant PET + WLE under LA +/- RTx. May not stage axilla if USS negative. Treating them exactly the same as we would with any normal patient - "normal" pt - are the >70s not normal?</p>	<p>If a pt is completely fit... I might only offer surgical Rx. In pts who are very fit, I do feel uneasy about using PET. Some pts where it's clear there's no way they'll be fit so puts on PET. Rx options depend on PMH & medication. Even pts with quite significant PMH do often live a substantial amount of time. Rx options depend on how the pt looks and behaves. I might ask them how far they can walk, whether they can do stairs, how many pillows they sleep on, that sort of thing. I always take into account how they arrive as well, if they've walked in. Pts with dementia assess how they would cope with admission. Pt's life expectancy is quite important though... pts often do better than their life expectancy because medical Rx is getting better. Discuss PET if ER+. Rx options depend on pt's wishes & desires. If pt enquires about PET would discuss it.</p>	<p>Anaesthetic assessment - her opinion of pts fitness determines whether they are referred for formal anaesthetic assessment. Some pts it's clear (end of bed) they're not fit and getting an anaesthetic assessment would be wasting everybody's time so advises PET. Asks PMH, med list, how they get to clinic, to build up a picture of their health. The majority of pts now I've got a feel, just because I've been a consultant for long enough, where an anaesthetic might be an issue. Has a regular anaesthetist which makes a big difference.</p>	<p>Treating them exactly the same as we would with any normal patient - "normal" pt. I have no idea why there is regional variation. Thinks she did much of her training in a region that was keen on PET. Talks about a surgeon in their trust who has a very high surgical rate ~95% including elderly pts and then talks about another surgeon who was quite keen on PET - so surgeon as a cause? Surgeons not doing their own F/U don't see the consequences of Rx - if you only see the failures of PET that would give you a negative view. I sometimes talk about... cancers that pts might die from and cancers that pts would die with. We increased our surgery rate - in response to data released showing that older women had poorer survival due to inadequate Rx.</p>
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<p>N19 Female Low PET</p>	<p>Options usually would be a wide excision or Mx... limited use of recon...and sometimes, even if it's deemed to be operable, HT would be considered as an option instead of surgery.</p>	<p>Age cut-offs for things like recon - being over 70, she was well out of the league then (for recon). But I guess for some people in their 70s, that should still be an option. Existing health problems impact on Rx options. You think "she looks quite frail; is she going to be strong enough to withstand hospitalisation, anaesthetic, the going home, the recovery. Social circumstances, health of family members influence Rx DM from pt's perspective. Pt who's a carer tendency to think would recover quicker from Mx cos no RTx. Can be influenced by the circumstances. Mobility/activity impacts on suitability for surgery. Rx depends on degree of dementia. Severe dementia greatly influences DM, would Rx with PET. ER status. Pt choice: if it becomes evident that surgery is not... what she wants then it would be narrowed down to one of the other options like HT.</p>	<p>No comments.</p>	<p>Thinks there are age cut-offs for things like reconstruction - being over 70, she was well out of the league then (for recon). But I guess for some people in their 70s, that should still be an option. Thinks age cut-offs are changing because of increasing the screening age. Thinks variation in Rx it could be to do with the health variation of different populations. Variability of pts - some people in their 70s who have only recently finished work, are still very active & independent, travel, do all their own housework, cooking, cleaning, whereas some people in their 50s are already immobile, see themselves as disabled, don't see themselves as independent. Variability in outlook too - somebody is very +ve they will have a more swift recovery as opposed to somebody that's very -ve in their life.</p>
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<p>S20 Male High PET</p>	<p>Normal Rx would be surgery. 3 groups: 1) definitely surgery (70s, minimal co-morbs); 2) definitely PET (significant co-morbs, would kill her by doing surgery); 3) choice of both (oldish, some co-morbs, life expectancy >2-3yr, ER rich tumour). If we're not careful, it'll be lopsided in the sense we'll just Rx them like younger people. If we don't Rx them like younger people, we'll be accused of being ageist, which in my view is wrong, because as I told you, they have the geriatric needs and their tumours are different biologically, therefore it would be a dis-service to them.</p>	<p>Age important due to life exp. Don't assess them based on their chronological age, but biological age... but you have to admit that as the age increases they have more problems. Considers fitness for surgery: whether a pt can actually withstand an op. Uncommon that someone is unfit. Pts with co-morbs may be fit enough for surgery but life expectancy may be shorter. Cardio- & cerebro-vascular disease more relevant as competing causes of death than chronic conditions. Mentions frailty. Degree of dementia: dementia itself should not be just a label that they should be having PET. Compliance issues. Life-exp: PET doesn't give enough duration of benefit for someone to survive another 10, 20 yrs. Biology of tumour. Considers pt choice: I don't see any reason why she can't have that choice if she understands the consequences.</p>	<p>Anaesthetic assessments vary between anaesthetists: have one anaesthetist who, I won't say he's courageous, but he's someone who would be quite prepared to take on difficult cases. For some, which we feel that routine anaesthetic assessment may not be sufficient, we send them to him and he's very prepared to see them. Thinks we should be assessing tumour biology & geriatric elements more thoroughly. Most people eye-ball the pt. Formal assessments make it more objective but whether that's better than eye-balling or not we don't know. If we think the pt would benefit from anaesthetic assessment we arrange that accordingly. Don't use CGA or tools to assess co-morbs or fitness. Sends some pts to a geriatrician for their input.</p>	<p>There's a bit of ageism... which I'm quite against. It's been highlighted that we need to pay attention to their care but if we're not careful, it'll be lopsided in the sense we'll just Rx them like younger people. If we don't Rx them like younger people, we'll be accused of being ageist. Rx of older women seems to be changing. Some variation in Rx due to ageism of HCPs incl BCNs, generalist vs specialists. There is the attitude that older pts don't view survival as important. You have a surgeon who always operates... and you have someone who would always... puts them on medication - I've got a feeling that we should blame the HCPs more rather than pts. ">70" means a wide range, it could be >90 or >100. Tend to push a bit more for surgery now... people tend to think surgery is the best otherwise you're ageist.</p>
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<p>S21 Female High PET</p>	<p>Much the same irrespective of age.</p>	<p>I think age does not matter, it's the fitness of the pt to cope with an anaesthetic. If they are fit, anaesthetically fit to have surgery, they will be offered the option of having surgery. Even if pt not fit for GA would do it under LA if pt wanted surgery. Comorbs would prompt anaesthetist assessment - only put them on PET if they write back and say "the risk is very high". With pts who lack capacity will discuss with carers the best management plan and come to a decision as a group, not my decision... I'm not there, I don't know. You would probably think "do no harm" don't operate on them... having said that we've had ER negative pts and you have to operate on them. If they feel that they do not want to have the operation then I will accept their decision and put them on hormone therapy. Women who want surgery I will make every effort - I never say no - seems to place greatest importance on this.</p>	<p>Anaesthetic assessment. Only if they say the risk is very high does it influence her. If anaesthetist says not fit for GA there are other ways of doing surgery. If I feel that the pt has a number of comorbidities I will not list the pt for surgery, but instead I would refer her to my anaesthetic colleague for a full medical assessment.</p>	<p>I think age does not matter. Personal choice of the clinician. I think that a lot of clinicians have their own personal views - compares hospital she trained in with one now, says [Place] they were seen in a different clinic and didn't get any imaging and were only seen by certain people if they were Rx'ed with PET, here they get exactly the same as if they were 35. Pts aren't being offered choice - they don't even know... "I wasn't given a choice, I was just told this is the operation I was going to have". Most... adults having a GA will take at least a fortnight to just recover from that trauma of surgery. The elderly will take a little longer.</p>
<p>N22 Female High PET</p>	<p>They're given the same options as any pt that comes through the door really. Ideally we'd like to start with surgery. There are other potential Rxs if surgery is deemed inappropriate.</p>	<p>We don't look at DOB really. You can have fit 80/90 y.o., 100 y.o. pts and an unfit 40 y.o. Surgery is the preferred choice if they're fit for an anaesthetic and the procedure. Based on co-morbs: A few aren't offered a choice of Rxs because of their comorbs. ER status. Very much guided by the pt's feelings towards Rx. Some of them look really quite keen when you talk about surgery, some will say "is there another way?"</p>	<p>If any concerns about a pts fitness will do an anaesthetic assessment to assess suitability for surgery. All pts attend pre-op assessment so things are picked up and addressed, e.g. murmurs HTN. We don't rule them out... we let somebody who is the right person decide if they're fit for an anaesthetic or not. Can assess as they're coming through the door really, so they turn up out of breath before they've even sat down to start the process, you can glean a lot from that. So really it's inspection, so you look at the pt, you get a sense whether they're going to be ideal candidates straight off. If they turn up looking cyanosed, breathless, you know potentially that they're not going to be fit.</p>	<p>They're given the same options as any pt that comes through the door really. You can have fit 80/90 y.o., 100 y.o. pts and an unfit 40 y.o. We know a lot of it is clinician-led. We know the units with high mastectomy rates were given choices, we know the ones with the low they weren't even- had a hint of mastectomy. So I think a lot of it is clinician-led because they're not given true choices. In my opinion. If they're given a choice, I think they'd be higher surgery rates. When I first started... you saw a date of birth and though "oh well she'll be tablets" but very much you don't go on that at all now... I think that has changed. Think pts know more about Rx options. We're not scared to talk about cancer anymore.</p>

<p>N23 Female Low PET</p>	<p>The same as anybody else of any other age. If they're fit when they walk through the door we're thinking about surgery first. Contradicts herself: Says: They all get offered recon; everybody that has a Mx gets offered recon - Then says: because of your heart disease I'm afraid we won't be able to offer you that" or "well we could do an implant, as a quick operation"... if they're well into their 80s and frail we don't mention it. Oldest lady that's had recon after Mx is 75. Talks about one 70 y.o. who's having chemo.</p>	<p>Age isn't really a factor. Not about their age, it's about what they are like with their age.70... would really be trying to move that person away from thinking about ET. Well into their 80s doesn't mention recon. Rx DM based on general health. If they're fit when they walk through the door we're thinking about surgery first. Lots of co-morbs then Rx becomes a conversation. Fitness for surgery was in doubt would offer them PET. Mentions breathlessness, heart disease. Start mentioning PET if somebody was really generally crumbly. Would give them (very frail pts) the offer of surgery as well as (P)ET. Dementia: mentions PET. Cancer biology. Talk to them about... surgery first... if they seem... not that keen, we would say "there is this alternative". Deprivation affects pt expectations: people from deprived areas... they're not treated quite the same in life... so... sometimes it's like "well why is he giving me a choice?"</p>	<p>Have an anaesthetic assessment. We do a social needs assessment as they're coming in, so we identify if they're going to need any help - in the 6yrs been doing it less than a handful have required social services input. Majority have an anaesthetic opinion because a day case would just get the nurse doing it. Might refer back to specialist if known to them for an opinion, e.g. cardiology. Not often that anaesthetist says can't have on operation because most have been screened out for LA or PET. We're going for the op unless the anaesthetist tells us otherwise". Decide re: fitness for surgery based on GP referral letter, PMH, first impressions - it's a judgement I think when then walk in. Don't go for a geriatric opinion. Have a regular anaesthetist.</p>	<p>A 70 y.o. is not old...80 if you've not got medical conditions and 90 is neither. Also not having cut-off points of ages, it's not an ageism. Age has shifted - 70 no longer "old" - thinks should be mid-80s. I think attitudes towards the elderly have changed. The elderly have changed as well. Thinks there could be a north/south divide - people up north are a bit more stioc. A lot more people are going for surgery nowadays. I'm 100% confident that far more people go for surgery nowadays... whereas that was in the minority 10 years ago. I think attitudes towards the elderly have changed.</p>
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<p>S24 Male Low PET</p>	<p>Up until 3 yrs ago, all of my pts over the age of 70 as soon as I got to [Place], we offered them hormone treatment or an operation. Now we still offer them a drug option, although we say to them the best Rx is surgery. The majority of my elderly pts will have their WLE under local.</p>	<p>70's not really my cut off now, it's more like 80. Either they're fit or they're not fit for a GA... that's the... game-changer. Rx & life expectancy depends on comorbidities. Pts that I'm thinking are fit for an op... have probably only got 1 comorb. Mentions COPD, cardiac failure, cardiac disease limiting function & LTOT. In a wheelchair... pretty much a no-goer... frailty is a very clear decision that they're not fit. Associates wheelchair-bound with frailty? Then: Some people are in a wheelchair for other reasons. NH residence doesn't impact Rx. Comorbs limiting function (can't climb stairs) makes them unfit. Try really hard to not operate on people who are demented. Dementia is the one indication for PET in my book. Life expectancy of >15 yr = surgery. ER status. Tumour size: likely to recommend surgery if WLE but may not give RTx. Pt choice most important, it's the pt's decision: I wouldn't turn anyone down.</p>	<p>Everyone goes through pre-assessment and those that are at high risk will see an anaesthetist. The pre-assessment filters those out. Probably some pts who don't go for pre-assessment because they're obviously not fit - But they will have expressed an interest in not having an operation probably. Well I think that's a very important end-of-the-bed assessment, frailty. No CGA. Used to have a regular anaesthetist but not now.</p>	<p>I would say 70's not really my cut off now, it's more like 80. This kind of drive to do more surgery for elderly patients has actually raised the definition of 'elderly' from 70 to 80. I think we're now dealing with the same questions but with a population of 10 years older. Practice changed from offering everyone 70+ straight choice because evidence came out that we have worst survival for older pts.</p>
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<p>S25 Female Low PET</p>	<p>If they are F&W, we offer them surgery. I'm quite aggressive with managing these pts with surgery. Thinks elderly pts are better with Mx than WLE- one definitive operation, one recovery, no RTx, F/U is easier, saving the breast is less important. Does a lot of LA surgery but doesn't stage the axilla. In these pts again, you don't really set out to do a totally curative operation. Talks about a 70 y.o. who demanded recon and did it cos looked 50. I offer them surgery, that's what I would do with my younger pts. I wouldn't tell my 40 year old patients "I'll put you on tablets".</p>	<p>Immaterial of the age... dependent on their general health. Not their chronological age, it's their physiological age. More likely to do Mx in older pts. If... F&W and can withstand anaesthetic and an op we offer them surgery. Apart from the very severe comorb... we do offer surgery to all our pts. Talk pts out of surgery if significant co-morbs e.g. MI/CVA: risks of surgery are far too high to justify it. If no co-morbs would operate even if in 90s as life-expectancy is 5-10yrs. Wheelchair bound pts tend to have comorbs. Severely demented, putting them through a major op... very difficult to justify... when... PET may work equally well. Pt choice... some... older women... choose not to have an op. Suitability for surgery about ability to recover. Independence... very important... If... you leave them with a very poor QoL... older pts... would rather die... than lose that independence and end up in a home: if likely will choose PET.</p>	<p>If lots of co-morb and concern re: fitness for GA get an anaesthetic assessment pre-op by cons anaesthetist to see if they're suitable we leave it to the anaesthetists to decide. Still operates on high-risk pts if pt willing to accept the risk. Pick out the ones who are high risk and get an anaesthetic assessment. BCNs do social history and assessment. No CGA - because most of our pts are generally off the couch the next morning. Regular anaesthetist most of the time.</p>	<p>Live in a world where most of our pts are older and older so using a particular cut-off doesn't seem to work anymore. Having more elderly pts come through. Lean towards Mx in older pts, saving the breast less important to older pts & risks go up. Socioeconomic status... level of education amongst pts... stage at which they are presenting to you... so surgeon preference is probably one of many factors. Surgeons have attitudes and preferences but I doubt very much if that is the single most important factor. Risks of... op far outweighs any benefit. Rarely die from these cancers, something else gets them. They will die of something else much before the BC kills them. They would rather die of the cancer than lose that independence and end up in a home. Rx tailored to that pt - one size does not fit all. Pts are living longer and getting older... a lot of them self-refer to screening even beyond the screening age.</p>
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<p>S26 Male Low PET</p>	<p>My primary choice would be to do surgical intervention. I do WLE... & SNB on them... sometime if you have to re-do the margins, sometimes they're close, they still have the second operation to have the margin sufficient rather than jumping in to have full Mx & if RTx is indicated they go for RTx. So age is not a cut-off.</p>	<p>Age is not a big thing for me. Primary aim is to see whether the pt is fit enough to surgery. Look at the ASA status. If they are fit at that time then I am going to offer surgery. Severe cardiac comorbidity or severe respiratory problems such that can't do GA would go for PET. Prev DVT, PV bleed: bit jittery to start on certain things. Talks about using PET - these are clearly the ones who are wheelchair bound. By and large in those type of pts who can't even stand up... we tend to do PET. Demented pt in a NH - clear cut not fit for anaesthetic. I mean it's very rare we end up doing surgery... I can't think of where I've subjected somebody who's totally demented, signed a form 4 and took them to surgery, no. The other argument is whether pts will succumb to something else in the interim period. ER status. Skin tethering/puckering/ involvement would talk to them about ?neoadj PET. Pt choice. Provided pt is happy to undergo surgery.</p>	<p>If the anaesthetists are happy. We do get the anaesthetic opinion sometimes. All three, we all have a regular anaesthetist.</p>	<p>There is no big consensus, if you read the literature there is no didactic thing to say. That's why different people have different... people varied in their opinions. The other argument is whether pts will succumb to something else in the interim period. I've seen change in the management of these patients of a period of years- used to do more ANC, now SNLB/OSNA - used to do more Mx, now more WLE. Seeing more pts in 6th/7th/8th rounds of screening.</p>
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<p>N27 Female Low PET</p>	<p>If fit, surgery - including WLE if suitable and SNLB/OSNA. I would say we don't treat them any different to a woman in her 40s, 50s or 60s. WLE + SNLB/OSNA + ET + RTx.</p>	<p>We don't tend to be ageist. Look at their level of fitness to see whether they were fit for anaesthetic. If they were fit you would probably discuss surgery. Depending on their comorbidities would look at ET. CVAs, heart problems, DM, COPD, asthma - might stop them offering surgery. If had CVA Tam might not be suitable. Arthritis means Arimidex not used. It very much depends on their mobility. We would never not treat them because they've got dementia. If we feel that that was in their best interest... we'd want to offer them optimum treatment the same as anybody else. Some people don't want to have surgery. Ultimately, it's patient choice. It's all down to patient choice and information. Talks about ER/PR status.</p>	<p>They would potentially then have an anaesthetic assessment with all that encompasses, looking at ECG, heart. They would have a holistic assessment as well to see who was at home and things as well to get a comprehensive idea of what sort of support would need to be put in. It's down to the anaesthetist to see whether they would consider or think it's viable to put them under anaesthetic - if so we would offer them surgery.</p>	<p>I would say we don't treat them any different to a woman in her 40s, 50s or 60s. We don't tend to be ageist.</p>
<p>S28 Female Low PET</p>	<p>We tend to offer them surgery. We have lower thresholds... we are relaxed enough to offer them (P)ET. I don't follow a dogmatic scheme. We don't talk about any fancy breast surgery, it's always straight-forward and simple unless somebody's very fit, 70-looking-50 then it's different and I've done reconstruction on 70+ but very few pts who are incredible fit.</p>	<p>Not the chronological age it's the fitness age... which is important. 80 above... lower threshold to offer them ET, between 70 and 80 most people go through the knife. First focus is surgery. Unit's policy: if fit for GA = surgery. Co-morbs prompting full assessment: Heart, lungs, vascularpath with MI/CVAs, breathless when walk. Impacts choice of surgery: bad lungs + left BC = rather do Mx than WLE to avoid RTx. More often pt physiology. Pts from NH: tend to stick them on ET. Can go up a flight of steps they can walk from the entrance to your clinic, you know they'll be ok for a GA. Somebody who's stopped 3 times walking 200m you know they're not the best candidates. Memory loss, dementia, tends not to offer surgery. Do I see this pt still independent in 5 yrs. Nodal disease: less comfortable about leaving about them on ET. If they refuse surgery... relaxed enough to offer them ET. Pt preference. Targets are never an issue.</p>	<p>If the fitness is an issue... subject them to the full testing rather than giving them high risk GA. Get the assessments because what you don't want them to do is to render them dependent because of the problems of recovering. Anaesthetist/physician decide whether pt is fit for GA. Pre-assessed by regular anaesthetist. She organises tests before referring to physicians for optimisation to speed up the process. I don't follow a dogmatic scheme, I think it's a bit of eye-balling the pt in the clinic. There's a lot of pts you can eyeball, if they can go up a flight of steps they can walk from the entrance to your clinic, you know they'll be ok for a GA. Eye-balls them to guesstimate their life-expectancy > or < than 5 years. Don't use CGA. These pts (elderly) are put on a list where there's a regular anaesthetist, although that's often easier said than done.</p>	<p>80 above is where we have a lower threshold to offer them endocrine therapy, between 70 and 80 most people go through the knife. Pts of this age group, particularly if they have significant comorbidities... the low grade cancer... is unlikely to kill them and they are more likely to succumb to the other comorbidities. Investigating pt more aggressively now and therefore we know the extent of the disease and know what the pt needs.</p>

<p>S29 Female Low PET</p>	<p>If she had operable breast cancer and she was fit enough for surgery then that would be my first recommendation to her. I think the guidelines that every pt having a Mx should be offered breast recon is nonsense and I really feel quite strongly about that, I think it's reasonable to discuss what a Mx will look like, but to actually start offering 89 year olds a TRAM flap or a breast implant when one breast is down here and an implant would be up here, I think it is guidelines gone mad.</p>	<p>More likely to stage elderly pts. Depend on her general fitness. Illness which are going to compromise their life-expectancy (recent MI, other cancers)... make a difference to what I recommend. Lt BC with active cardiac disease might recommend Mx to avoid RTx. Frailty... difficult thing to quantify... gut feeling... if you blow on them they would fall over. Wizened... not got much strength... they are a difficult group to know how they are going to respond to anaesthesia. Dementia: Cannot understand what you're planning... have to have a very strong indication to operate (e.g. ulceration, bleeding). Important... you're not swayed unduly...by their carers or the family. Limited life-expectancy... will make a difference to what I recommend. ER status. Many pts... prefer not to go down that route (surgery).Unusual... not to survive anaesthetics... might not necessarily mean that it has no impact on... their QoL.</p>	<p>Normally get a pre-operative assessment and see whether the anaesthetist felt she was suitable for surgery. There are obviously some pts who, even to surgeons, it's obvious they're not going to be suitable for anaesthesia. It's really cardiac function, respiratory function that I'd be thinking about, when I was trying to assess end-of-the-bed-wise they were fit enough for surgery. Doesn't use CGA but thinks they are in the pipeline - I suspect there is a role for that. I work with a, my anaesthetist happens to also be an intensivist and it's actually really unusual that he will say someone is really not fit for surgery.</p>	<p>70s, I don't really regard as old. It's often put down to... pt choice, I suspect that it's part of the issue and I suspect the way it's put to pts is probably bigger part of differences. There's a misconception that BC in the elderly is a relatively benign disease. Relatively unusual for a pt actually not to survive anaesthetics these days - not necessarily mean that it has no impact on their next few months and their QoL. Difficult to predict which pts an operation will affect their QoL. Much fewer now (pts Rx'd with PET) than I would have done perhaps 5 yr ago. Some yrs ago you'd just say "oh, this 84 yr old with, I'll just pop her on Tam"... (now) you're more likely to be challenged and therefore have to justify your decision. I would hope that that change in practice, has not only been peer-pressure, but it's been evidence-based as well.</p>
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<p>N30 Female Low PET</p>	<p>Generally they are offered surgical options. But they can also be offered PET.</p>	<p>If... fit enough... they are always offered surgery. Important to be mindful of comorbs: whether they would be safer on HT. Also be offered PET if... pt feels that home circumstances are such that they can't cope with surgery. NH isn't really a barrier to having surgery... if it's a RH... they're probably even more suitable... because you know when they're discharged they've got somebody looking after them & supporting them. If their dementia is such that it's going to upset them... generally people with dementia can cope just as well with surgery... depends on their family. ER status. Tumour size: might try neo-adjuvant to downsize. Some pts have an initial preference that they say 'actually, I'd prefer not to have surgery if I didn't need to' and so I think that's something that has to be taken into consideration. Some people have very strong views on what's right for them.</p>	<p>One would hope that in the thorough, robust assessment process, you would ensure that risk is not inordinate but as low as you can and you'd optimise the pt as much as possible.</p>	<p>No comments.</p>
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<p>N31 Female High PET</p>	<p>Exactly the same, apart from- I'd say if you were 90... couldn't have recon of course because of all the complications that come with that. But we have had a lady had- was she 78, or 76?- she went for a DIEP reconstruction that she wanted. So the choices are the same unless we feel it is unsafe or the length of the anaesthetic would be a problem. Mentions chemotherapy for women in their 70s.</p>	<p>Age is irrelevant really... it's the individual person themselves. PET would start to be offered as a choice in 86 plus. Would always want to do surgery if it was fit. Anything that would affect a GA - mentions obesity, heavy smokers, alcoholics, breathlessness - at the end of the day is it going to be unsafe to do that procedure on the lady. We don't want to do more harm. She was so frail. You'd have to look at that definitely. If someone was in a NH with dementia, we'd include the family... we'd still look at that (surgery). A lot of ladies are living to their late 90s and if they're 80 that's a long time isn't it so it's more likely or possibly that they're going to be offered surgery. ER status: as long as they're ER positive of course. But also it's choice: some women would rather take the risk of PET. One of only reasons not to operate is if lady absolutely doesn't want a GA.</p>	<p>We would look at the medical history, if they had a lot of problems, if they were on a lot of medication that would affect the anaesthetic... we'd send them for anaesthetic assessment. Only reason we won't operate is if the consultant anaesthetist says we can't do a GA. Try not to go on first impressions: We'd ask first, we wouldn't just judge. We'd look at her notes and ask her medical history.</p>	<p>Exactly the same. Ladies in their 70s are like my ladies that were yrs ago in their 50s or 60s... I would class now 70 is young, is like the 60 y.o.s from years ago. Age is irrelevant really isn't it, it should be. And you can have a fit 84 year old who's fitter than someone who's 54. Would start to be offered as a choice in 86 plus. So I think although it looks on paper that people are treating older women differently, sometimes it's a lot of pt choice. I mean we do treat differently throughout the UK don't we because it's people's opinions as well.</p>
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<p>S32 Female High PET</p>	<p>My preferred option, if at all possible, would be surgery.</p>	<p>Biological age rather than chronological age. Pts who are considered high-risk for surgery... pt suitability for GA. Mainly co-morbs: recent MI, CVA, anti-coagulant. If they (radiologist) feel... the pt is very frail they... feed them into that non-surgical... clinic. If they're very frail... obviously PET would be more ideal. Looking at the new referral proforma... and it says 83, NH resident, wheelchair bound... you're already thinking "I wonder if she's ER+?" If lack capacity: can only impose surgery upon them if you feel that it is in their best interests... you've got to be in a situation where there isn't an alternative. How can you be sure that the pt's taking the PET. Weigh that up against what their life expectancy would be from other things. More likely to die of the consequences of her underlying disorder than she is of this tiny incidental cancer that's been found. ER status. Pt preference... a pt who genuinely doesn't want to have surgery.</p>	<p>Anaesthetic assessment - The consultant anaesthetist will then feed back to us whether they feel that they're a high risk for a GA or not. We see and assess the pts, if we have any concerns about their fitness for GA then they go for a formal anaesthetic assessment. They're first of all assessed by us, any problems flagged up. Don't have access to a geriatrician routinely, but (recently)... everybody over 70 had to have a frailty score done and so the frailty score was an eye-ball by the clinician that saw the pt and then the pt's own assessment of their own ability to do the activities of daily living, etc. We have a list... where the high-risk pts tend to go because we have a critical care anaesthetist that is the consultant on that particular list. So if we have very high risk ladies, that tends to be where they're best managed, he does lots of paravertebral blocks and bits and pieces.</p>	<p>It's going to be pt factors, it's going to be clinician factors isn't it... I suppose you would infer... that it was socio-economic, class & education of pts... perhaps a more well-educated pt is more able to weigh up the choices and make an informed decision... there's no denying that it's clinician preference as well and sometimes it is driven by things like research projects... I think that it would be very difficult to try to produce a standardised way of managing these pts. Important to have a unified approach within a unit otherwise like throwing pts into a lottery. You've got your tennis playing 75, 78, 80 year olds and you've got your decrepit 71 year olds. We've got a big history of PET in this unit and with the academic department moving away to Derby there's been a sea-change more towards surgery. Definitely we operate on more than we used to here.</p>
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S33 Female High PET	Predominately surgery, and a choice between wide local and Mx, and sometimes more complex surgery, breast reductions and reconstruction if they're very fit. My focus was always to offer surgery first.	Age impacts decision: life expectancy is obviously different. Not their calendar age, but their physiological function. Discuss more complex surgery if they're very fit. If not fit for GA and need an axillary procedure we'd discuss the endocrine option. Pts with complex comorbidities it (surgery) would not be my preferred choice. Cardiac or respiratory problems... make me think we should be discussing endocrine as an option here. Frailty important in DM - because I think it's really important not to affect their long-term QoL. We still operate on ladies from NHs but it is more complex to organise. Wouldn't operate if can't consent to surgery. I think they do get comparable outcomes if their life expectancy's probably less than 10 years. ER status. Some pts say "I definitely don't want a GA" - that's easy. Previous exposure to endocrine agents. QoL after Rx is underestimated... or... not really considered.	If we think they're fit they just get routine pre-op assessment, if think unfit then we'd request a specific anaesthetic assessment with a consultant anaesthetist and we have got access to one of the geriatricians is running a rapid access system as well for us. Some ladies where they come back and say after we've arranged some investigations and we wouldn't consider them suitable for a GA, in which case, obviously we'd discuss LA options and endocrine. There are some ladies where they say "umm, they're risky but we feel you could safely get them through an anaesthetic..." in which case we'd talk to the ladies. Sometimes after that complex discussion they no longer want the risks of an anaesthetic. All have regular anaesthetists.	If you're 80...or if you're 95 and F&W your long-term life expectancy is obviously different. I think there's several reasons, I think locally here in Nottingham there was a big interest in PET as a research and any unit that's doing research into anything will generally use more of that Rx as an option. And then I think that once ladies in the community know that their friends have been on tablets for five years they'll sometimes say "actually well, my friend's had tablets, can't I just do that?". Most of the cancers are not going to be what would kill them if it went untreated, let alone with ET. The general approach in the west midlands was for surgery first and I think that's generally being promoted a lot more at all meetings in the last few years for surgery whenever possible.
N34 Female High PET	I think any lady who's fit for surgery is initially offered surgery. They can be offered a variety but generally if they're fit for surgery, that's what they're offered. We even have 70 year olds who have reconstruction believe it or not- subconscious bias .	We look at age more medically than actually years. If they're fit for surgery, that's what they're offered. If they're not well enough, you're going to kill them on the table, then there's no benefit giving them surgery. Talks about a pt with dementia that couldn't get to clinic so just recommended the GP start on Letrozole. Gives an example of a pt with mild memory impairment who wanted surgery so had it. If they really, really don't want it and they're saying "I really don't want this surgery" there's another option.	Anaesthetic assessment.	Ultimately I would say it comes down to choice... perhaps ladies are not given the choice I would have to argue. Or it's not given in a way, in a non-biased way possibly. It depends how many of those ladies are coming for screening... and if your uptake for screening at that age is not as good... perhaps the bigger lumps are not so operable.

Theme 2: Experience of surgical treatment in older women with breast cancer

	2.1 Opinions on surgery	2.2 Pros and cons of surgical treatment	2.3 Older women's views of surgery	2.4 Refusal to undergo surgery	2.5 Local anaesthetic surgery
S01 Female High PET	Should offer surgery if fit. It's the best thing for them and you shouldn't really be messing around with anything less than that.	Pros: Better way of getting symptomatic control. what the surgery gives you is enhanced local control. Metastatic control the same. Enhanced local control. Well tolerated. Cons: Complications and the risks of surgery may be higher. Risks include: not surviving the anaesthetic, pain, discomfort, hospitalisation, loss of function, confusion, disfigurement, lymphoedema, mutilation, haematoma, bleeding.	Most of them are pleasantly surprised by breast surgery... it's better than they thought it was going to be. Few who have significant SEs... "well if I'd known this was going to happen I wouldn't have let you do the operation". Pt's have a good opinion where it goes well.	You might get someone... who says "oh, I don't want an op"... you can't ignore those views even if you think that that's perhaps not the right thing for them.	You should offer an op and that doesn't necessarily just mean... under GA. Depends on whether WLE or Mx - trying to do a Mx under local... is not a nice thing to do. Epidurals... intra-pleural blocks... those kind of regional techniques... permit you to do full surgery in an awake patient. Varies according to anaesthetist.
S02 Male High PET	Definite role for surgery if predicted survival >5yrs. Having an op has no impact on 1 yr survival at all.	Pros: Under 80, surgery probably does have a (survival) benefit as long as you haven't got severe co-morbs. Cons: May be no additional benefit from surgery. Surgery probably doesn't have much, if any impact on survival in people over 90.	Everyone worries about surgery.	No Comments.	No comments.

S07 Female High PET	Surgery is the standard Rx: the first option I would discuss. If somebody's fit... I would tend to favour surgery. Most women at 70 are perfectly fit for an anaesthetic. Had a 90 y.o. recently have a Mx and she did very well.	Pros: Minimise future morbidity. Surgery is getting rid of it... then it's gone. Had a 90 y.o. recently have a Mx and she did very well. Cons: Coming into hospital is a risk for losing their independence. Implies about recurrence.	Some of them worry about losing any independence.	Less fit women perhaps don't want an op. I don't want any more messing, just leave me alone. Certainly a number of pts who refuse. Personal experiences. Bizarre reasons: donating body to university. Present pros and cons. Have the right to make their own decisions. Respect their reasons even if thinks strange: wasn't the most logical reason but it was her reason. Put on PET but keep saying to her "this isn't working very well - it's going to end up growing".	You can do a WL(E) under LA... it doesn't seem to be something we do. Can't do axilla under LA. Sometimes use LA, not often. Women either... happy with a short anaesthetic... or they... don't want an operation... so it's (LA) not an option that seems readily taken up.
S08 Male High PET	Better for pts with fungating tumours. Important to offer surgery in younger pts with life expectancies of 5+ yrs. Offers less aggressive surgical options in the elderly, quicker, only one operation. Surgery is the best Rx.	Pros: Better for local recurrence. Better local control. WLE - quick, less morbidity and easier recovery. You're not truly worried about the cosmesis in elderly: bias/stereotype? Cons: Whether they can withstand surgery.	The group that chooses surgery feels that it will get rid of the cancer. The ones that choose to have surgery are delighted by surgery and they don't seem to regret that at all.	We'd really want them to be having surgery unless they absolutely say to me that they don't want it. The pt didn't want surgery so we put her on tablets. If the pt is adamant... then I wouldn't, that's illegal to do so.	If they're not fit for GA, we really do question your rationale for why you're doing them (under LA). I do about one or two a year. So if not fit for GA get PET rather than LA surgery.
S10 Male High PET	Surgery is the best option.	Pros: Get ET afterwards anyway to reduce risk of recurrence. Low morbidity. Example of a high-risk pt doing well: I did it and she is OK. Cons: Mentions surgical and anaesthetic risk - including death. Specifically mentions lymphoedema, infection.	I think 85... at that age, they are not very keen to go for surgery.	At that age, they are not very keen to go for surgery.	Can't ensure a clear margin under local. Likes LA. Use if doesn't respond on PET. Used to use LA a lot but less now as AIs are effective so try to push them to PET, also heavier case load - we don't have enough time to do this under local.
S14 Male High PET	Primarily the Rx that is mostly advised is surgery. Surgery is the first line. Things are safe now, anaesthesia's better.	Pros: It's more curative. Surgery allows you to get hold of the disease much earlier. Generally doesn't restrict their independence after surgery.	About 70% are happy to go ahead with surgery.	Usually I find that they just don't want to have surgery - that is the main driving force behind their decision. I certainly tell them which is the preferable option.	Just take out the primary tumour under LA, that would be offered to them. Offer LA for high risk pts who still want surgery. Used to regularly give thoracic epidurals to pts and here we don't have anybody who's giving thoracic epidurals.

S15 Female High PET	Surgery is best Rx: pt says "I want the best Rx" then it would be incongruous to be talking about... (P)ET. About 2/3 pts have surgery.	<p>Pros: Get rid of the lump. Like not to have to come and see us.</p> <p>Cons: A few pts...if you operated on them there was a significant chance that they would die. Mentions risk of stroke... bleed... chest infection... heart attack. Loss of independence, end up in residential care. Some surgical pts don't F/U anymore. Seromas after Mx.</p>	Example of a depressed pt who wanted surgery as she thought it would kill her. They know if you come into hospital, something bad could happen. Not worried about dying, they're concerned about loss of independence. An urban myth that... surgery cures you... still a lot of people who think that. They think it's going to hurt more than it does. Pts who have Mx don't like getting seromas. Mostly not afraid of anaesthetics.	Picking up on uncertainty is really an important component of why older women say no. They'd rather die than lose their independence... their priorities are very different... It's not about survival.	Not geared up for LA surgery in UK - if you say to somebody "we could do your operation under LA", they are potentially more distressed by that than they would be by having a GA. Have to decide, is it going to be safer to have them asleep and pain free... or anxiety, what's more likely to put the blood pressure up, down, whatever. If she's not fit for a GA, she can have a LA. Doesn't often operate under LA.
S18 Female High PET	Surgery under GA is the gold standard. We increased our surgery rate in response to data released showing that older women had poorer survival due to inadequate Rx.	<p>Pros: Better chance of doing well.</p> <p>Cons: SEs from... surgery & RTx. Mentions short-term limitation in movement, pain and swelling, travelling for RTx.</p>	Some women want to avoid surgery, despite poorer survival. Most of them hate the idea of having to come into hospital.	Historical ideas. Many pts are quite clear they don't want complications, would rather just take a tablet. Maintenance of independence. Previous experience of surgery. Don't like being in hospital. Educate them. They want to prioritise QoL over quantity of life.	Uses LA about once a month (~1/10 pts) - by offering it as a third option Been able to persuade a few pts who were quite resistant to the idea of surgery to having surgery. Good option for pts with dementia because it avoids admission. Will put anybody under LA... I would literally operate on anybody. Anaesthetist does intercostal blocks... may open up the possibility of Mx under LA if needed for disease control.
S20 Male High PET	Surgeons take a dichotomous approach: fit = surgery; not fit = ET. Pts in their 70s, minimal co-morbs should definitely have surgery as PET cannot beat surgery. Overall... we tend to recommend surgery. Tend to push a bit more for surgery now than before... people tend to think surgery is the best otherwise you're ageist.	<p>Pros: Better... local control. Doubt is to whether surgery offers a survival benefit. If someone cannot live with having a tumour there then surgery is better. Surgery is very safe. Depending on their circumstances, surgery can make them worry less.</p> <p>Cons: Losing a breast. Surgery can make them worry more. Also SEs of ET - it's not either or.</p>	They're worried about caring for their spouse, or being on their own. Could bring their worries worse or could be less depending on their individual circumstances.	Survival may not be the most important thing to older pts. I don't see any reason why she can't have that choice if she understands the consequences. I would not make a derogatory comment on PET if she asks the question. "oh I don't want to go through this".	I know some people have done Mx & things under paravertebral block, local - I have not personally done that but I think it's possible.

<p>S21 Female High PET</p>	<p>Considers the two Rxs equally - no preference either way. There is this hormone therapy or there is surgery and I play it equally. I never say no (to doing surgery).</p>	<p>Pros: You've removed the disease. Trips to the hospital less frequent. You're done and dusted. Most recover well. Cons: RTx means too-ing and fro-ing and being dragged around the countryside. Put their heart under strain - don't know how they'll come through it. Take longer to recover. You don't just operate and that's it, next day you're hunky dory.</p>	<p>The majority... who do have the surgery say "I'm amazed how well I feel". Single widows think surgery will cause inconvenience to their family.</p>	<p>Don't want to inconvenience their family. If they... do not want to have the op then I will accept their decision & put them on HT & I do also tell them if at any stage you change your mind... it's not a big problem. Warns them might run out of medical Rx.</p>	<p>If not fit for GA but adamant want surgery will bend over to find an anaesthetist to give her some form of anaesthesia so I can undertake the procedure. I have anaesthetic colleagues who would do vertebral blocks and I will put the LA and he will sedate them and we've done Mxs and WLEs under local so surgery is an option. I have done a Mx on a 96 y.o, under LA... & sedation, but it's been done so it's not impossible.</p>
<p>S32 Female High PET</p>	<p>I would always present surgery... as the first option. My preference would really always be surgery. I feel that the best chance of a cure is surgery. It isn't surgery vs tablets, it's surgery and further tablets vs further tablets. Been a sea-change more towards surgery. Now very pro-surgery here. Operate on more than we used to here.</p>	<p>Pros: Done and dusted, you're not bringing people back... easier on the pts and... clinic numbers. Up an about the next day... they're managing really quite well. Cons: Often these ladies are teetering on the edge of managing... having an op, having a GA, is actually going to impair them so much that they won't be able to manage. Mentions seromas.</p>	<p>Frightened of being admitted into hospital. Frightened of losing their independence. Worries about the GA... perception that a Mx is a very painful procedure. Generally they are very pleased. Haven't had anybody that's said to me "I wish I hadn't done that". They're surprised by how reasonably easy the surgery is.</p>	<p>"I don't want an op". They over-estimate how frail they are. Remember people being in hospital for a week. Surgery's moved on a lot but their perception perhaps of it hasn't. Bad experience. Frightened of losing their independence. I'll say "well, what is it that bothers you?" Happy to put them on to PET. Doesn't try and push them towards surgery as long as they understand.</p>	<p>I don't like doing wide locals and sentinel nodes under LA. He (anaesthetist) does lots of paravertebral blocks and bits and pieces. So we do have regional anaesthesia techniques that we can use as well... It's not common. Did a wide local and sentinel node under a regional block and local and it wasn't the most fun.</p>

S33 Female High PET	We try and offer surgery wherever possible. That's generally being promoted a lot more at all meetings in the last few yrs for surgery whenever possible.	<p>Pros: Older population report less problems than younger. Doesn't mean they don't have problems, they just don't report them. More resilient to the cosmetic effects and the pain effects.</p> <p>Cons: In the elderly... we've... got a high haematoma risk, and high complication risk. Complication rates are generally higher. Complication... causes a much bigger set-back and a much bigger impact on their QoL the older ladies.</p>	Much more stoical if they get some breast oedema or some breast pain post-treatment. They find RTx much more inconvenient. Modern surgery's maybe not what they perceive. Most of them are pleasantly surprised... that they've got through it so well. Has a bigger impact than they maybe perceived to lose their breast. Pleased to have just got rid of the disease.	Independence is what's most important to them. Previous experience of surgery. Inconveniencing their family... worry that they'll never... be able to look after themselves... might end up in a NH or lose their independence. "I definitely don't want a GA" - that's easy. Stress... they wouldn't be cured. If they've got concerns about... the anaesthetic, arrange for them to meet an anaesthetist.	For axillary surgery, I much prefer to do that with a GA. Can do wide locals with LA plus or minus sedation. Rarely (uses LA), because I think it's much more difficult to do the axilla. If they're not fit for a GA then we will often still offer resection of the primary with LA. One of our consultants does paravertebral blocks, but generally if he feels they're too frail for a GA he'd be reluctant to risk the complications of a paravertebral block and often it means they can't position ideally on their side for the paravertebral block.
G16 Male High PET	Surgery is best. I think people have seen that, I think the amount of surgery in the over 70s has increased.	Cons: Mentions that people die of surgery.	No comments.	"I'm not having an op whatever you say". Give them the confidence they're fitter than they thought. If you can get to the reason & you address that you can actually try to persuade them. People... are entitled to make decisions that don't make sense. Definitely people who will come in and do not want surgery. An experience that they... family or close friend has had. If they're a main carer. Read something in the paper.	No comments.
N09 Female High PET	I'm of the opinion that surgery is the gold standard.	Cons: Takes them out of their own environment, frightening.	Think operation and anaesthetic is something they put themselves & families through - cause worry. Might feel like a burden. Some just get on with it.	Pt indicates some sort of uncertainty, or they're frightened of surgery, or something that makes them feel very uncomfortable with having an op, then I would certainly flag it up (PET as an option).	No comments.

N12 Female High PET	Surgery is the best Rx - repeats this statement multiple times throughout. Surgery is the best option for these ladies. Surgery for elderly more common in recent years. Doctors getting better at steering pts towards the surgical options. Ladies in their late 90s and early 100s that have had GAs and have survived that and... are still F&W.	Pros: Remove the cancer. Very safe. Ladies in their 90s/100s have had GAs and survived and are still F&W. Cons: Mentions disfigurement, anxieties.	Pts worry about surgery. Historically... the elderly have been quite fearful of anaesthetics. Always a lot better than they anticipated. Think surgery is a serious thing and you have to stay in hospital for weeks. Pleasantly surprised... how they feel post-op.	They don't want to be bothered with it... want the easiest option. Don't have many pts refuse because they explain it's safe. Sometimes pts have such fearful pre-conceived ideas that they make that decision not to have surgery. Important to inform those ladies that its actually very safe and surgery is the best option.	Seeing more and more surgeons doing surgery to the breast under LA which again isn't optimal because we can't do surgery in the axilla to stage the disease.
N13 Female High PET	Surgery is the better option. All 3 consultants are pretty keen on surgery as a first instance. Very pro-surgery. Outer surface surgery so doesn't impact on older pts independence. Pro-surgery... whether that's right or wrong. Operate on people that... in the olden times... we'd have thought... that's too risky!"	Pros: Remove the cancer. They'll be in just one night with Mx. Recover very quickly. Better disease control. Cons: Harder to get over for an older person. Bleeding, infection, problems with the anaesthetic. It's quite disfiguring surgery. Mentions potential risks and complications. Some ladies... are absolutely distraught after surgery... it's gone... it's not them anymore.	Some pts think if they have surgery then they don't need tablets. Not everyone who's older wants something like a Mx. Some pts want to avoid RTx/travelling so opt for Mx. They're surprised at how F&W they are after it.	If they want to decline surgery... we could treat it with an ET. Explain effectiveness of PET is sometimes short-lived & we'd sooner catch them while there F&W... rather than... when their health might have deteriorated. It's about not judging that & just doing what they want you to do. We just support them doing it.	GA is far superior... we'll do a very straightforward lumpectomy with lots of LA but it's not our preference. Mentions can't do axilla.
N17 Female High PET	Want to treat it thoroughly, and 'thoroughly' is offering surgery. If surgery is safe then that's the route we will... go down. 20yrs ago would have said she's too frail for surgery but now realises that Rx should be equal despite age.	Pros: Not a major op in terms of we're interfering with any clockwork inside the body.	They just think about their age and would maybe, they're tired, they've lost some of their reserve in life, they just feel that they wouldn't be able to cope with an op. Feel they may be incapacitated after surgery. Think it might upset their QoL balance.	I'm too old. If I have an anaesthetic I'm going to die. Feel that they wouldn't be able to cope. Previous experience. Body image issues... turn around and say "no". Alternative Rx easier. Don't want to upset the balance... it's about QoL not quantity. Assessment so can make informed decision. Explain that it's not major surgery. Find out why they are refusing. She's saying she doesn't want to have surgery. Worry about the anaesthetic.	No comments.

<p>N19 Female High PET</p>	<p>The options usually would be a wide excision or mastectomy, sometimes reconstruction. Doesn't seem to personally have strong preferences for either Rx - choice seems most important.</p>	<p>Pros: Mx: it's all gone... done and dusted, they don't need any more surgery. WLE: keep breast which is very important regardless of age. Cons: May need further surgery. Pts are fearful of surgery and the recovery. Mx: small number... despite their age, still would feel a great sadness at losing their breast and having an altered body image. WLE: RTx and the journey.</p>	<p>Pts are fearful of surgery and recovery, feel that surgery will knock them back: I've heard people say they fear that they may never recover fully the level of activity.</p>	<p>Pre-fixed idea of what can be done or can't be done... "what's the point of doing anything?". Past experience. "I'm of a certain age... is it worth doing anything?" I'm looking after my sick husband I don't want to leave him. Fear of hospitals/ cancer/ surgery/ losing the breast. Understand why they're refusing: Informing pts correctly then hopefully you can influence or give them the info that would empower them.</p>	<p>Has limitations with axillary surgery. Is offered by all surgeons in the unit but don't do many. Offered mainly for local control.</p>
<p>N22 Female High PET</p>	<p>One or two (of the surgeons) will say 'we appreciate that surgery probably is ideal'.</p>	<p>Pros: The cancer's gone. Knowing psychologically it's gone. Reduces having to come up to the hospital. Get rid and they can move forward. Less uncertainty. Most will be doing things that they're doing, you know, 4 to 6 weeks afterwards really. Cons: Some pts think it will avoid another tablet - have to stress, 'you're not going to avoid the tablets. Have to factor a period of recuperation. Loss of breasts.</p>	<p>They are pleasantly surprised about how well they are afterwards. Feel that it's... going to stop them doing what they're doing now and limit what they can do. It's not to be feared now. You do get a bit of that, 'I don't need them (breasts) anymore'. People still think the only way to Rx BC is surgery.</p>	<p>Don't want to be bothered... elderly relative at home. They just feel... it's going to stop them doing what they're doing now and limit what they can do. E.g. of a pt who didn't want anyone to know she had cancer so was convenient to have PET. 'Is there any other way?'. Not many will try and avoid surgery. They've heard you can just take a tablet.</p>	<p>Techniques like SLNB are limited with LA. They do LA surgery. More of a palliative tool, but have been done where we need local control.</p>

<p>N31 Female High PET</p>	<p>Encourage surgery on all women... Surgery is the main and this is what we would rather do'. When they're in their 80s... as surgeons, all they're thinking is the quick fix, 'let's do this (Mx) and then they're sorted'.</p>	<p>Cons: Some people are traumatised by having their breast off. Travelling for RTx. Mentions a F&W 84 y.o. who ended up in a NH following surgery - I had no concerns about her having an op but she's in the NH now. Pts can deteriorate after surgery.</p>	<p>I've come across ladies who have had the surgery and some have regretted it. I had a lady... she said 'I wish I'd gone to the grave with two breasts'. Some people are traumatised by having their breast off.</p>	<p>Absolutely fed up. Some women you are not going to change. 'I've got to die of something, duck'. Wanted to leave her body to medical science. They've got a husband... they're nursing. Thought she'd be a burden. Misunderstanding or what their mates told them. Fear of GA. Tells them it might not work for very long. Surgeon encouraged her to have surgery... tell her the risks. They've got a right to choose. "I want to understand why... whatever you choose, I will support you".</p>	<p>Can't do axillary surgery. If they can't have a general... she doesn't do it that often but she does (use LA). Ladies with major heart problems that are desperate to have surgery. I had a lady...really obese, got horrendous COPD... when she met the consultant anaesthetist she was like 'under no circumstances I can put you under a general', so she's had a local.</p>
<p>N34 Female High PET</p>	<p>Majority... offered surgery... seen as being the best care, you know, the optimum care as it were.</p>	<p>Pros: Mastectomies as day cases. Better local control. They cope very well. Cons: There's some ladies where having the cancer isn't the issue, it's having a Mx because there's some very glamorous 75 y.o's. SEs and potential effects of anaesthetic. There's obviously a risk of not being... as well as they were before.</p>	<p>Most of our ladies are very surprised by how well they do cope.</p>	<p>Fear of dying on the table. Bad experience. It's too big a thing. They're not bothered about treating it. Fear of being flat. I don't want surgery. Fear of the unknown. When you... give them the info... they can view things very differently... "actually that's not that bad, I could cope with that". What are the issues... what's right for you. I'm not here to change anybody's mind.</p>	<p>No comments.</p>

S03 Male Low PET	Considers surgical option for over 70s. There is no BC pt who is not operable. May not be beneficial. Not really much disadvantages in that it's a quick procedure like a haircut; plays down risks - infection rate is minimal, I don't leave a drain and it's entirely pain free and I've never had an operative death.	Pros: Day case procedure, quick, home the next day so not apart from their partners, home environment, pets. You take the cancer and you bin it. Quotes less than 1% complication rate. Better local recurrence and QoL. Cons: Not really much disadvantages. Mentions infection rate, drain, pain and death but only to say they don't happen. Pts don't like going to theatre.	They don't like going to theatre, and nobody really does.	No comments.	I've done Mx under local or nerve block, it can be easily handled, if needed.
S24 Male. Low PET	Best Rx is surgery. Surgery was the gold standard. Drive to do more surgery for elderly pts.	Pros: Reassurance... the cancer's not there... don't have to keep worrying about it... don't have to keep coming to the clinic. Less pts in F/U clinic! Don't think there's an anaesthetic risk. In and out as a day case. Cons: Shakes them out of that comfort zone of being in denial. Coming into hospital & catching... MRSA. General deterioration... of the health of the pt having been in a hospital.	No comments.	People who don't really want an op that are saying "I'm not really fit enough". Wouldn't try and change their mind - I would say "Ok, let's put you on hormone tablets..." Get the BCN to... understand what it is about this lady that she's frightened about... and bring them into a place where they're more comfortable and relaxed about it. Doesn't happen very often.	E.g. of frail 90 y.o. I may have to do it but if I do it, I'll do it under local anaesthetic. Performs LA WLE surgery all the time, including SLNB, Mx not so often - the majority of my elderly pts will have their WLE under local.
N11 Female Low PET	Most people would want to have surgery. We're a unit that would promote surgery. It would be unfair not to offer it. Surgery is the primary way to get rid of a BC. In your best interest. We've operated on... centenarians. A joy to see older pts come through surgery - they've obviously got a lot from it.	Pros: Get rid of the cancer. Can be a day case. Joy to see older pts come through surgery: they've obviously got a lot from it. Older people... are very able and capable of getting through this. Cons: Body image being important no matter how old they are. Just part of the Rx plan, adjuvant Rx sometimes hits people harder, incl travel for RTx.	Most people would want to have surgery if they could have it. Am I too old to have surgery? Oh, I could do this. Will it impact on their lives. Relax when know it's day case. Worry about RTx but don't think people would stop themselves from having it because of where they've got to be. GA worries people of any age.	Don't get many refusing surgery as reassure them, give them confidence, they know they can change their mind, they've been fully assessed.	If they felt that this surgery is something they wanted to do, but a LA is the only way to have this done, it would be done that way. Important for some people to stay awake. Not common but has been done. Mentions use of nerve blocks to say they have been done.

N23 Female Low PET	Preferable option. We're thinking about surgery first. Only pts who are extremely unwell or coming to the end of their natural life who would not be offered surgery. Far more people go for surgery nowadays.	<p>Pros: Majority go home on the day, it's day case surgery. Not needing to come back for so many appointments.</p> <p>Cons: Mentions arm stiffness, lymphoedema. Mobility can be impaired due to arm stiffness if they walk with aids. Anaesthetic can make them feel their age, it can knock them. Can take you a little bit longer to get over an anaesthetic, the recovery of activity. Worry of surgery. Body image with Mx can be quite devastating.</p>	They worry about "will I get through an anaesthetic?". See it as a huge operation, worry about permanent changes, worry about surviving. Most say that it's (breasts) done its job, body image isn't so important but get some women where Mx is devastating for their body image. They're already old and they fear that it might just be the thing that tips the balance for them.	How would they recover when they've got absolutely nobody. They fear that it might just be the thing that tips the balance for them. Worried they'll become dependent. Reiterate they're fit, got a lot of natural life years ahead, it'll start to grow. So that I feel they're fully informed... "as long as you're aware then that's your decision, we will respect that decision". In a way it is about persuading and it goes against pt choice.	Suboptimal because if you can't get into the axilla, so that's not always the best way. We have done LN biopsies to the axilla but we knew that's not the best because it can be painful. Even if not fit for surgery we would offer LA surgery. The frailer ones, they feel comfortable with having a LA & S24 does LA more than most.
S04 Male Low PET	Standard Rx is surgery. Risks are very low. Difficult to avoid offering surgery. If they can be put to sleep they get an op. Indefensible not to offer surgery if fit for it.	<p>Pros: The benefit of surgery is there but it's not huge. Low risk. I haven't had a mortality to date.</p> <p>Cons: The risks of surgery are very low but the pts' perceptions about the risks are completely different from the actual risk.</p>	They're obviously concerned about the risks... but the pt's perceptions about the risks are completely different from the actual risk.	A pt who declines surgery, a lot of women in that age group have their own opinions and they can't be changed.	In general doesn't operate under LA. Only one anaesthetist who uses regional blocks as well as GA so not used often, positive about their use in this way. Their anaesthetist uses regional techniques with heavy sedation without GA.
S05 Male Low PET	Overall in favour of treating all women with surgery. Has to be surgery at some point. Result would always be to facilitate surgery as opposed to avoid surgery. Best practice and best for cure. 85 y.o. with recon: she's fine... she was up the next day and she was running around.	<p>Pros: Best practice and best in terms of cure. Well tolerated: she was up the next day and she was running around.</p> <p>Cons: We don't want it to make you unwell or give you prolonged hospital stay, HDU admission because of an anaesthetic. Loss of their independence. One pt said "the worst thing that can happen is that I have a flat chest".</p>	Gives an example of a recon on an 85 y.o. - she loves it, she's is really extremely pleased, she's very happy.	You do have some people with strong opinions, who don't want to have anything done. As a physician, if you tell them what's best for them they would eventually come around to your point of view. Uses PET for pts who don't want to have surgery but then says: I have yet to see a pt who has refused surgery.	LA surgery not an optimal thing to do. Mx under LA really uncomfortable for pts... they start jerking... the smell of cautery... bleeds more; not pleasant. Use of LA depends on how much local control is a problem or if progresses on PET. Offer LA if can't optimise for GA. One anaesthetist who does blocks, incl paravertebral and pectoral for pain control.

<p>S25 Female Low PET</p>	<p>I'm quite aggressive with managing these pts with surgery. Wouldn't deny them. By far the superior option. Definitive curative option than PET. Elderly pts are better with Mx - one definitive operation, one recovery, no RTx, F/U is easier. Not visceral surgery, it's superficial surgery so most of these pts actually do very well.</p>	<p>Pros: Can be curative. Not visceral surgery, it's superficial surgery so most of these pts actually do very well. Does not hinder their mobility, their GI function, does not hinder their ability to get up and go to the toilet... it's a breeze really. Cons: Complications happen... some of them end up going back to theatre. Mentions local recurrence.</p>	<p>A lot are reluctant to have surgery as don't understand the implications. They're afraid of surgery. Less concerned about disfigurement. Apprehension about post-op care and recovery. They're quite surprised how well they feel.</p>	<p>Who's going to look after the cat/house/drive me to appointments. Apprehensive about risk of complications. Made up their minds beforehand. Don't want to burden family. Prev experience. Don't understand implications of refusing. I say... there are tablets... but it's not as guaranteed... and let them choose. If you really think you might ever have surgery, have it now... before it advances and your health deteriorates. Duty to inform them but don't force them. Try talk them into it. "I'm not interested in an op at my age".</p>	<p>I do mastectomies under LA. Most are salvage procedures, wouldn't offer as a primary procedure because not curative. It's a sub-optimal Rx because you're not staging the axilla. Elderly pts tend to be small breasted so it's quite an easy operation to do, 20-30 min. If skin breach is an issue would do it under LA. We have one consultant who's started... to do a few... pectoral block.</p>
<p>S26 Male Low PET</p>	<p>Change in the management of these pts of a period of years- used to do more ANC, now SNLB/OSNA - used to do more Mx, now more WLE. My primary choice would be to do surgical intervention.</p>	<p>Pros: Know that margins are clear - you know it is all gone. Cons: Mentions complications under anaesthesia.</p>	<p>Pts don't want to stay in hospital. They think it's very mutilating surgery... they can't E&D & they're going to lie down in bed for many days... they are surprised after you do the surgery they sit up and have a cup of tea by the time you've finished the last pt.</p>	<p>It's the fear and... misunderstanding. I'm not going to twist that ladies arm. We just put it across the best scenario, the worst scenario... If ET doesn't work and that's how we put it across. I don't twist their arm but as much as possible. Some pts merely say "no, I don't want that".</p>	<p>Does Mx and lumpectomy under LA. It's not a question of if you can do the surgery it's a question of is this a realistic way to approach the whole thing. Mx in a real frail lady... can do that under LA. Not many anaesthetist of ours do regional blocks. Problem is... to do the axillary.</p>

S28 Female Low PET	My first choice is usually surgery. Surgery is considered as an aggressive Rx.	<p>Pros: If you remove the cancer, then a pt knows the cancer's gone. Don't have to drag pts back to clinic.</p> <p>Cons: You don't want... to render them dependent.</p>	surgery's viewed as a big thing. Pts worry surgery may tip the balance of their life - lose independence.	Surgery's viewed as a big thing. What are they going to gain by chopping parts of the body. "I don't want to be in a NH where I have a Mx scar and somebody else is dressing me, looking at my deformed body. They are the ones I would like to persuade towards surgery. If it becomes locally advanced how would you manage... most people come on board. We have a lower threshold to offer them endocrine.	Some pts you feel... they'd be best off having that area taken off under LA... because it'll be a problem for them to deal with the wounds. I haven't done very many (LA) in the last couple of years but I am not averse to it. Have a very active anaesthetist who will do pectoral blocks and things.
S29 Female Low PET	Primary surgery is better. Pts will get ET anyway. Uncommon actually that I wouldn't offer pts an op. Hope that that change in practice, has not only been peer-pressure, but it's been evidence-based as well.	<p>Pros: Relatively unusual for a pt actually not to survive anaesthetics. Better local control.</p> <p>Cons: Whether or not they survive. Longer-term effects of bringing somebody into hospital and giving them an operation affecting memory and mobility. Sailed through the anaesthetic but it's really knocked her for 6. Impact their QoL. More elderly... longer they will take to recover... physically and cognitively. More likely to have co-morbs associated with problems post-op (e.g. warfarin/bleeding). RTx - travelling for 3/52. Significant minority... sexually active, for whom how they look is still terribly important.</p>	"Oh, I thought I didn't have to have the tablets because I had the operation". Majority of the pts will use a phrase like "nobody's going to see me" or "it's done its job".	Sometimes prefer not to go down that route. Fear... elderly spouse and they're the primary carer. Don't feel they're worth treating. GP may have said... "they'll just give you a tablet". Bad experiences. Talk to them about why I'm recommending surgery. "ok... you're not very keen on surgery... why we don't we put you on a trial of HT. Would try and persuade younger pts. Encourage them to realise that they have potentially a long-term future.	Although if they weren't fit enough for a GA we may consider a LA as well. Not used often - mainly for pts with borderline fitness for GA, esp if they are ER -ve or imminent ulceration.

N06 Female Low PET	Surgeons will operate on pts if they can so most people have surgery. So if you're going to do the right operation, do it up front. Unit's policy is surgery is the best Rx. Almost everyone get surgery - only if the anaesthetist says this lady cannot undergo an anaesthetic.	Pros: Only a day case. Cons: Having surgery is scary. May "knock them" (i): lose some independence.	Having surgery is scary. Worry whether they will come round from the anaesthetic. See Mx as a big op. Older pts prefer to stay in hospital longer after an op. Worry about post-op recovery/ support. Surprised by quick recovery. They're not doing anything... take it off.	No comments.	Have used LA in the past although very rarely now because of anaesthetic advances.
N27 Female Low PET	We would always... say... surgery would be the optimum Rx.	Cons: Alludes to risk of surgery: there have been a few pts we've been relatively concerned about and actually have come through the anaesthetic... incredibly well. Frightening. Mentions wound break down.	Their feeling is: are they going to survive an anaesthetic? They are absolutely terrified.... what the implications will be, how will they manage at home if they live at home. If it goes well... they're relieved... If... they have problems, then I don't think they regret it, I think they just accept that.	Decline Rx based on that they're the main carer for another person. Tell them it may initially work but then it starts to regrow and might lose the window of opportunity to operate. They're unwilling to, then obviously then ET. We had a couple the other day, really didn't want to have surgery.	Surgery under LA is sub-optimum because wouldn't go into the axilla: would be intolerable under a local. Have done in the past. Couple of ladies who need to have a Mx and that has been done under LA. Especially if it's going to fungate or break through the skin.
N30 Female Low PET	Surgery is usually the first thing they're offered. The majority are treated with surgery.	Pros: Removes the area... can be curative. Greater information. Lump's not there... emotional benefits. People recover physically quite well. Recovery and length of stay generally quite short. Cons: Mx can be quite a devastating thought... it does disrupt their routine and it's an emotional and psychological hurdle to get over. Risk to anaesthesia.	Feel that it will knock their routine and they don't want surgery. Pts often perceive it to be a greater trauma than it necessarily is. People are often quite positive about it. They are a little bit anxious about anaesthetics.	Some pts... prefer not to have surgery... that has to be taken into consideration. They can't cope with surgery... feel that it will knock their routine. If they're looking after an elderly husband. It is their decision... as long as we've given good quality info and we feel that the pt has understood... it's important that that's respected. Explore their rationale... make sure that they know that if they change their mind... it's still an option.	It is done but it's not done on a regular basis. Might choose LA instead if the pt is not fit... for a GA.

Theme 3: Experience of Primary Endocrine Therapy as a treatment for older women with breast cancer

	3.1 Opinions of PET	3.2 Pros and cons of PET	3.3 Older women's views of PET	3.4 Practicalities of PET
S01 Female High PET	<p>OPINION: Reserved for people who will struggle to get through standard Rx. Do consider it (PET) for women in this age group. Inferior option. Equivalent mortality, inferior local control but not much.</p> <p>WHEN OFFERED: Won't tolerate or refuse surgery. Clearly not fit for a haircut. Choice in borderline women. Pretty frail... never get through an op in a million years.</p> <p>NEO: Start off as neo-adjuvant, give time to think: no harm... in starting them on the tablets and giving them some time to think. Trial of ET and if it's not really working... go down the road of anaesthetic assessment.</p>	<p>Pros: No Rx-related mortality. Give time to think. Reassured by tumour shrinking. Metastatic control the same. Shouldn't be any difference in mortality. No surgical risks. Well tolerated.</p> <p>Cons: May outlive response: you put them on PET and then they don't die of something else. Static response... might freak them out. Failed local control. Limited response. May not respond. Disturbed by palpable tumour. Inferior local control. 1/3 need change of management. Operate when older and frailer. Can just delay problems. Run out of Rx.</p>	<p>They all think that PET is great because it's the no risk scenario. Opinion is good when it goes well.</p> <p>Might freak them out if the lump doesn't disappear. Some women might find that a little disturbing... most women actually if the tumour is shrinking, found that very reassuring.</p>	<p>PET TYPE: Letrozole.</p> <p>TUMOUR ASSESSMENT: Clinical.</p> <p>F/U: Bring them back in 3-6m and reassess. Will control BC for an average of 2-3 years.</p> <p>RESPONSE: Variable response (1-10 years).</p> <p>REACTION: Change management. If it's not really working very well... go down the road of anaesthetic assessment. As soon as the disease starts to progress, you cut-and-run. 1/3 of them will need a change of management. Operate if fails, ?LA. If can't operate then palliative Rx.</p>
S02 Male High PET	<p>OPINION: I try not to set off with PET without having defined exactly why we're doing it. Needs to justify it's use? It's easy to sell it.</p> <p>WHEN OFFERED: I use it... in 3 situations... where the pt is clearly in a state of health where surgery is not going to be of significant benefit, 2nd... neo-adjuvant setting... and... where there is uncertainty about fitness for surgery to bide time while we make an assessment. Predicted life exp is 2 or 3 y.</p> <p>NEO: To downstage, just as we might use primary chemo in younger pts.</p>	No Comments.	<p>Pt opinion depends on how you put it:</p> <p>Majority... will say "Oh, well if I only need tablets, then that's great" vs. "we can just give you tablets because you're not well enough for an op, which would be best for you" then they have a different view.</p>	<p>PET TYPE: Letrozole</p> <p>TUMOUR ASSESSMENT: clinical</p>

<p>S07 Female High PET</p>	<p>OPINION: Unpredictable. Always be the right decision for people who really don't want an op. <i>Hope it works.</i> WHEN OFFERED: People who don't want an op. Offer choice to pts with medical issues. <i>These conversations (about PET) are generally over 80. Those who come, looking frail, with carers and they're 86 and we just go have this nice table.</i> NEO: Recent MI: <i>should be waiting 6/12, we'll put you on ET and then re-evaluate.</i></p>	<p>Pros: <i>They've missed out on an op.</i> No admission, no GA. Some have prolonged good response. Cons: Limited response, may be worse off 2y down the line. May fungate and require dressings. F/U may be upsetting.</p>	<p><i>Happy to take a tablet.</i> Seen as less hassle. Like that it avoids an op. A lot of those frailer older pts are accepting of the fact that you're not curing their disease. Lump generally not a factor: <i>as it's not bothering them... they're not too fussed.</i> F/U not an issue: <i>Most pts I think don't mind coming up to hospital every 3 or 4 m.</i></p>	<p>PET TYPE: Mentions Tamoxifen. RESPONSE: You see women who are on Tamoxifen for 10 years without a single sign of the tumour re-growing. Unpredictable response. <i>If somebody's going live >5 yrs then they're probably going to come to the end their endocrine... Rx.</i> REACTION: <i>If fit should have surgery: I keep saying to her "this isn't working very well - it's going to end up growing, you are well you should have" (an op).</i> F/U: Home visit instead of hospital appt.</p>
<p>S08 Male High PET</p>	<p>OPINION: Inferior Rx if pts <80. Don't use it much ~5% or 3 per month - <i>although actually in a high PET region.</i> WHEN OFFERED: Generally wouldn't consider PET <80. Would discuss it 80-85 and would tell pts he considers PET equal with surgery if 85+. Won't tolerate surgery. Big fungating ca PET not in their best interest unless so frail can't survive surgery. Would push for PET in very high risk elderly pt.</p>	<p>Pros: No surgery. Lack of other Rx like RTX, not coming into hospital, blood tests. Cons: May not work, suck it and see. SEs: joint pains, aches, risk of # (Letrozole). F/U can be difficult. Local control not as good. 20-30% will need surgery due to PD.</p>	<p><i>I have actually seen pts looking very gloomy, very depressed & soon as you've said "we don't need to do surgery, we can do tablets", they look like themselves and they're really happy.</i> Accept SEs fairly well. Like that they don't need surgery, doesn't alter their lifestyle. Lack of cure isn't an issue: <i>don't think it's a concept they understand.</i> Not had pt bothered by lump. Like it when lump shrinks, feel like success - <i>she was very happy... that I can't feel the lump anymore... they know that it's working.</i> Most have relative/carer to bring them to appointment. <i>seeing us is their social event.</i></p>	<p>PET TYPE: Letrozole then Tam. RESPONSE: Between 3m to death. A lot of progression occurs within the 1st year. 20-30% will run out of ETs. REACTION: <i>If it doesn't work, we can then consider surgery.</i> Swap ET from Letrozole to Tam, then surgery.</p>
<p>S10 Male High PET</p>	<p>OPINION: Variable response. Thinks a low % of pts Rx'ed with PET. WHEN OFFERED: Prefers PET if anaesthetist not happy with risk. Usually 85+. If recent MI.</p>	<p>Pros: <i>Most of them they tolerate it very well.</i> Few SEs. Cons: Hormone Therapy doesn't work all the time. SEs: joint pains, menopausal symptoms, osteoporosis.</p>	<p><i>They don't ask about cured. I think they just understand that we are controlling it.</i> Reassured by response, not bothered about residual lump - <i>They are reassured that it's not progressing. But they don't care whether it is disappearing or staying put.</i></p>	<p>F/U: Assess after 6m-1y, if no response would operate. If responding, see them in another yr & then we D/C them. RESPONSE: Starts working in 6m so have to wait 3-6m to see response. Variability of response: <i>If PET does the job, carry on, if not then surgery.</i> Believes it either works or doesn't: <i>they don't work and then they stop.</i> REACTION: Either changing tablets or offer them surgery (can be LA). Explain about very</p>

				high surgical risk and, if happy, will operate.
S14 Male High PET	<p>OPINION: Likely give control. It's not a cure - control is the operative word.</p> <p>WHEN OFFERED: Mentions PET to all older pts even if F&W. Mainly used for pts 77-90. Thinks about 30% older pts.</p> <p>NEO: Use PET as neo-adjuvant if not fit and reassess after a few months (i.e. recent MI).</p>	<p>Pros: Likely to give control. Can change it if not tolerates. SEs easily controllable.</p> <p>Cons: Don't know how long response will be. If PET fails. 30-40% chance they'll progress after 5-7yrs. May not respond. Compliance can be an issue. Risk of VTE, may need calcium replacement with. Might not tolerate. Not a cure.</p>	<p>Just want to avoid surgery. Some bothered by the lump but not all. Explain lump will get smaller but it will be there, modify pt expectations. Reassured when shrinks. Some find it difficult to travel but not much of an issue.</p>	<p>PET TYPE: Tend to start on Letrozole.</p> <p>TUMOUR ASSESSMENT: USS.</p> <p>F/U: F/U at 3m then 6m and then yrly for as long as they're on Rx.</p> <p>RESPONSE: Likely to give control over 5-6 years if they respond, 30-40% chance of progression after that. PET usually successful for 6,7 yrs.</p> <p>REACTION: You need to change or things.</p>
S15 Female High PET	<p>OPINION: Only 1/3 have PET. Survival can be comparable. Limited efficacy. Safely Rx BC with PET if life-expectancy 1-2yrs. Lack of cure not relevant as surgery will not cure BC either.</p> <p>WHEN OFFERED: If life expectancy <2-3 yrs. Pts with severe dementia.</p> <p>NEO: Pts who have had some recent serious illness... we use ET until they're well and then operate.</p>	<p>Pros: Most pts notice no SEs whatsoever. Avoids them coming into hospital, having an op, avoids RTx.</p> <p>Cons: Limited efficacy: whether ET alone would be likely to work for long enough. Issues with compliance but pretty uncommon. Bad thing about ET is that they have to come to the clinic.</p>	<p>Avoiding hospitalisation is a massive thing, they know if you come into hospital, something bad could happen. Some bothered by lump but a lot may not have noticed it themselves in the first place. Most people don't worry about the lump. They may ask is it getting smaller? Quite a lot of people like to be rid of the lump. I don't think that's as important as you might guess... Now I would have thought that that would be... quite a difficult thing to cope with but it doesn't seem to be.</p>	<p>TUMOUR ASSESSMENT: Calliper measurements, although not particularly accurate.</p> <p>F/U: Start off coming back every 3m. 3m, 4m, 6m. Much more active F/U than surgery. F/U for duration of Rx. Sometimes the GP says "really its so difficult for her, she's getting really upset".</p> <p>RESPONSE: Works for 2-3 years.</p>
S18 Female High PET	<p>OPINION: Feels uneasy about Rxing fit women with PET. PET alone probably long-term is not as good an option. Not serving pts well by using PET.</p> <p>WHEN OFFERED: If ER+ and pt enquires about PET would discuss it. In pts whose fitness is uncertain. NEO: Larger tumours or skin/chest wall involvement prior to WLE under LA. Lots of pts even when the tumour shrinks don't want LA surgery.</p>	<p>Cons: Resistance to AIs and the tumour grows. The cancer does sometimes come back and cause problems.</p>	<p>A lot of the pts... once you give them the tablet option, they're not interested in anything else. No they don't want the surgery, they'll just carry on with the tablets, thank you very much. Never found any pt worried about the lump, which amazes me. Feel quite reassured if they can feel it that it's not enlarging.</p>	<p>PET TYPE: AIs - Letrozole.</p> <p>TUMOUR ASSESSMENT: How they're doing in general, clinical exam, estimate size (don't always formally measure it), formal measurement with calipers/USS if enlarging.</p> <p>F/U: for duration unless pt refuses then GP. Interval depends on how they're doing, initially 6wk to ensure tolerance & compliance, then 3m then 6m or yearly.</p> <p>RESPONSE: Effects of AIs last longer than Tam. 5 yrs easily, but some way longer than that. We've still got some pts with good responses at 10 or 15 yrs.</p> <p>REACTION: Revisit GA surgery, offer LA. D/W oncologist re: switching AI.</p>

<p>S20 Male High PET</p>	<p>OPINION: Previously in 40% of >70s, less now. Extremely ER rich tumour that person's outcome is extremely good with PET so if quite old can be offered a choice. Wouldn't make a derogatory comment about PET. Unsure which Rx is more cost-effective. Strong supporter of PET... but I don't indiscriminately use it - I want to use it in the right context. WHEN OFFERED: Good option if pt has a minimal chance of surviving >4yrs, if H score approaching 300 then even if life expectancy is 10 yrs it might still be a choice. Pts w significant comorbs limiting their life expectancy to only a few ys or if you're going to kill her by doing surgery.</p>	<p>Pros: If properly selected, gives pretty good outcome. ET is quite easy. Cons: Issues with compliance. Mentions SEs (but get ET with surgery too). May be a bit more burden to the healthcare system in terms of F/U.</p>	<p>No comments.</p>	<p>TUMOUR ASSESSMENT: USS and clinical assessment every time: got a consultant radiographer who's very keen to do US. Unsure whether US has added value, more expensive. F/U: Burden on healthcare system in terms of F/U. Should F/U them up for duration of Rx. RESPONSE: Tumours with an ER H score >50 their average time to progression is 49m (4 yrs). Longest time to progression is 103m (8-9 years) with H score approaching 300. Maximum you'd probably get 10 yrs. REACTION: Pts who progress on PET could still have a salvage op.</p>
<p>S21 Female High PET</p>	<p>OPINION: Thinks >50% are Rx'ed with PET - I would probably say there are more in favour of hormone therapy than surgery. I do believe that the hormone therapy works.</p>	<p>Pros: Least disruption to their life. It's a little tablet to take. Doesn't have any dramatic morbidity. Cons: Might run out of medical Rx and the disease may progress.</p>	<p>"oh, I'm on a hoard of them (tablets), one more won't make a difference!". If they know that there are tablets then they feel "good, I don't have to have that op, there is another option". Lump doesn't tend to worry them because explains to them that if the tumour remains the same of reduces in size it's a positive response.</p>	<p>PET TYPE: Anastrozole 1st line. TUMOUR ASSESSMENT: USS or MMG if not longer visible on US. F/U: Designated PET clinic: seen in one room by radiologist and consultant. First appointment at 8-12wk, then 3m until good response then 6m until it disappears then yearly. On clinical judgement on how frequently. F/U until they don't want to come back or if goes to NH - then writes to GP to F/U. RESPONSE: If you see a response you'll see it within 1 yr. REACTION: "we have to think of other ways of treating this cancer". Advise surgery, doesn't have to be GA, could be blocks/LA. Try 2nd/3rd line HT and takes it back to MDT for discussion. Would have to run out of HT or imminently likely to ulcerate before operates.</p>

S32 Female High PET	<p>OPINION: Can be very effective... always a finite limit. Not against PET... got a foot in both camps. If well-informed and genuinely don't want surgery then I don't have any issue with that.</p> <p>OFFERED WHEN: Not fit or they expressed a desire to not to have surgery. High-risk for surgery. Recent MI or CVA.</p> <p>NEO: If undecided will put on PET and give time to decide whether want to proceed to surgery.</p>	<p>Pros: Can be very effective. Avoidance of surgery: avoid disfigurement and RTx.</p> <p>Cons: Finite limit (control). At that point (Rx failure)... you may well be less well and less able to tolerate surgery. SEs. Compliance is not particularly good. Uncontrolled local disease and getting into a situation where you convert a perfectly easily operable tumour into a fungating mass lesion.</p>	<p>Reassuring that they can see the lump shrinking so they know the Rx's working. Others are very anxious and whittle continuously about it. Surgery easier on the pt because you're not bringing them back every 3-6m.</p>	<p>PET TYPE: Letrozole 1st line.</p> <p>TUMOUR ASSESSMENT: Bi-dimensional caliper measurement, don't routinely use US.</p> <p>F/U: Same clinician sees the pt, easier to pick up progression. 6-8wk to assess SEs then 4m later to assess response. Then 6m and D/C to GP.</p> <p>RESPONSE: Pts on Faslodex for 12y. May work for 2y, 5y. Extremely variable. 2y, 2.5y period of control, I think that would be pretty medium-ish.</p> <p>REACTION: Expect to sequentially have to change Rx and we can have this discussion (re: surgery) again.</p>
S33 Female High PET	<p>OPINION: Very rarely here, I think we're using it less.</p> <p>NEO: start ET and get assessment (work-up takes a couple of months) and if anaesthetist think fit enough we'll proceed with surgery.</p>	<p>Pros: They just carry on with their life. Don't seem to have significant SEs.</p> <p>Cons: SEs: aches and pains (tend to ignore); hair loss with Letrozole, don't think about it... and actually they do worry about those things.</p>	<p>Happy not having had to have surgery. Love the fact that they can just carry on. Thinks pts are aware it's not a cure. Don't seem to be bothered about lump. Some of them say they get anxious a few days before the clinic appointment but most of them seem to be able to get on with their life.</p>	<p>PET TYPE: 1st line is Letrozole.</p> <p>TUMOUR ASSESSMENT: clinical measurement (calipers) or US if not palpable.</p> <p>F/U: Initially 4m then 4/6m, D/C with open-access if stable for a yr.</p> <p>RESPONSE: Variable, and I think that's the difficulty. Average, 4-5 yrs... my perception is they either fail within a couple of yrs or they seem to go on for a long time.</p> <p>REACTION: Switch to Tam or Exe.</p>
G16 M: High	No comments.	Cons: Failed endocrine Rx when they're frailer and everything's more difficult.	No comments.	No comments.
N09 Female High PET	<p>OPINION: Inferior options so doesn't mention it unless asked. Really low in their unit - uncommon.</p> <p>WHEN OFFERED: Frightened or uncomfortable with having op then would flag up PET as an option.</p>	<p>Pros: Don't see many progress.</p> <p>Cons: Issue of compliance. Don't see the PET pts as frequently in the initial period, not as supported. Mentions SEs - the idea of SEs can worry pts.</p>	<p>Easier. Idea of PET is more comfortable to them. Lump bothers some: "it's not gone, it's sitting in my breast still", Feel their lump all the time... touching it, checking it. BC remaining in the breast feels very uncomfortable for some pts. Is this her feeling, because she then says: But they would then probably plump for surgery - also never had a pt say "I'll have tablets" then say they "don't like the lump"</p>	<p>ASSESSMENT: Clinical exam.</p> <p>F/U: Initially 3-6 wks clinical r/v, check no SEs, taking the tablet. Then every 3m for 1yr then D/C. Not as frequently as surgical pts initially. Advise pt & GP to re-refer if progression. Doesn't know if GP regularly examines. Suspects only get flagged up as progression.</p> <p>RESPONSE: Doesn't take effect for at least 3/12. Don't see many progress.</p>

<p>N12 Female High PET</p>	<p>OPINION: Not optimal Rx. Number decreased over the years. Considers ET an adjuvant therapy. Very few only offered PET. Need to try to avoid giving PET as the only option for these ladies. WHEN OFFERED: Lots of co-morbs or senile. One pt because so anxious couldn't be admitted. NEO: Put on PET if they have a holiday booked but then surgery would be booked after that.</p>	<p>Pros: Where QoL most important. Avoid surgery. Cons: Seen a lot fail, they're 5/6 yrs on, more comorbs and surgery is the only option. Only keeps cancer at bay for a number of months.</p>	<p>Seen as the easier option. Happy to have steered clear of surgery. Not bothered by lump: <i>majority will say "I don't usually touch it"</i>. Often don't even know if it's responding.</p>	<p>TUMOUR ASSESSMENT: Clinical assessment, usually calipers (varies between clinicians). F/U: Only seen by BCN for 1st 6m then just by phone if pt needs them, F/U done by medical staff every 4-6m. RESPONSE: <i>Seen lots of women go through the ETs, fail, they're 5/6 ys on.</i> Mentions a pt who's been on PET a yr but not responded despite changing ET. Variable - some go a long time, others don't even get a first response. Only keeps cancer at bay for a number of months. REACTION: Swap ET. If still fail, <i>surgery is the only option.</i></p>
<p>N13 Female High PET</p>	<p>OPINION: Small % on PET. <i>Kept aside for people that are not fit. Minute you say "you don't need an op" they switch off. Fairly long-term good Rx, it's a good alternative sometimes. Fabulous Rx, however not for everybody and not forever.</i> WHEN OFFERED: PET is only... a first choice for someone who isn't fit for surgery or they've come knowing what they want. Don't offer it to people who are fit irrespective of age. NEO: Use ET as Rx while pts think about surgery - a bit like neo-adjuvant. Used while see if fit.</p>	<p>Pros: Safer than surgery. Whilst making decision. Cons: Effectiveness sometimes short-lived, health may have deteriorated, no longer fit for surgery. <i>Not a forever Rx. Run out of options. Relying on them to take it. Cancer's still there: while ever it's in your body you don't know what it's doing to you. Doesn't work over night. Not guaranteed effective for the rest of your life.</i></p>	<p>Easier option. Relieved they don't need an op. Pts think it's this magic thing that disappears overnight. Don't like the idea that they still have a cancer within the body. Mixed emotions. Majority aware it's not a cure. Become over anxious & over obsessed... <i>"before I never use to bother feeling but now I'm feeling every day & it's still there"...</i> it's a big worry for a lot of ladies. F/U: quite distressing, particularly older ladies with dementia... they don't want to come... families don't want to bring them.</p>	<p>PET TYPE: Letrozole as first option. TUMOUR ASSESSMENT: Don't scan unless concerned; clinical measurement. F/U: Periodically for duration, open access telephone clinic. <i>Sometimes their GPs will take over.</i> RESPONSE: Varies greatly... potential to work for yrs... See people at maybe at 4 or 5 yrs that all of a sudden this particular Rx now is not effective. At 3/12 may be no change at all... it may take much longer. REACTION: Change therapies, sometimes you run out of options.</p>
<p>N17 Female High PET</p>	<p>WHEN OFFERED: If not at all fit to have surgery. Short life expectancy, e.g. 2yrs. Severe dementia. If pt say surgery is not for me. Offered to all but emphasis on surgery. NEO: Some pts started on ET before going to clinic for assessment. <i>Many ladies that are treated with PET... to reduce the size not because of their comorbs.</i> Use PET to give time to think about choices.</p>	<p>Cons: Maybe a yr or so down the line, that ET is going to stop working, and they're going to be a couple of yrs older, maybe not fit for surgery at that point.</p>	<p><i>"I'll take tablets because that's going to be easier for me to cope with".</i> Tell them PET might only work for short time, they'll say <i>"well I don't mind if I just get another couple of yrs"</i>. Very aware the cancer is still there. Initially might find the lump disturbing but <i>after a few weeks they will notice the difference... so from that POV. then they are confident.</i> Majority reassured by F/U.</p>	<p>F/U: F/U in specialist clinic. NH residents who <i>may be really too frail to come</i> ask the GP to F/U and refer back if there is a problem. RESPONSE: Maybe a yr or so down the line ET is going to stop working. <i>Probably a couple of yrs, sometimes less.</i> May only work for 2 yrs.</p>

<p>N19 Female High PET</p>	<p>WHEN OFFERED: Even if it's deemed to be operable, HT would be considered an option, instead of surgery.</p>	<p>Pros: Avoids surgery. Easier. Cons: Mentions SEs but generally wouldn't be too unbearable. It's living with the fact that they've got something in their breast - cancer's still there. Can feel guilty, like they're letting themselves or their family down by not being brave enough to have surgery.</p>	<p>Some feel disappointed if they weren't having surgery, others are pleasantly surprised, they're relieved. Think taking a tablet is so much easier. Can feel guilty, like they're letting themselves or their family down by not being brave enough to have surgery. Aware it's not a cure. It's almost as though "can't I just keep taking this tablet? Why do I have to keep coming back?... Other people I think feel a measure of relief by coming back.</p>	<p>RESPONSE: Variable: number of yrs, some >5yrs, others <1yr.</p>
<p>N22 Female High PET</p>	<p>OPINION: Not many Rx'ed with PET. Contradiction: We do see quite a few on the Primary Endocrine now. NEO: Use ET while pts make a decision about whether to have surgery.</p>	<p>Pros: Suit their lifestyle better. Haven't got to worry... if they've got people at home, elderly partners, 'who's going to look after the dog?', the cat. Convenience... just carry on and no one needs to know. Cons: Potential SEs. Worry of having to come back every few months to get it scanned and checked and if it does grow. Inconvenience of F/U: wait for hospital transport.</p>	<p>Taking so much medication that they want to avoid another tablet. Lump bothers them until their first visit. Ones who would worry opt for the surgery, I think they're comfortable that they're having a tablet and it seems OK and 'I'm being checked out'. Some like F/U: it's a little trip out... look forward... to getting out and having a bit of company.</p>	<p>PET TYPE: Either Arimidex or Letrozole. TUMOUR ASSESSMENT: Clinical exam + USS. F/U: Every 3 to 4 months. Get to a point where it's stable so let the GP F/U, refer back if concerned. RESPONSE: Could be many years.... doesn't appear that we get many back who require surgery under locals. Longer now we use AIs. REACTION: If they don't work then there are other tablets, but then if they don't work then we may be visiting surgery at some point.</p>
<p>N31 Female High PET</p>	<p>WHEN OFFERED: Start introducing PET as a choice in 86+. Had a lady who was 101, but really actually endocrine was the main choice. 80% is pt choice, rest is because they're frail or unfit. NEO: We could look at starting her on endocrine for a while- if she had a chest infection...until they've got that sorted. Sometimes it's too big, so they're going to try and shrink it first. If it's shrinking they quite like the idea of staying on the ET.</p>	<p>Cons: Women are living longer so if you do endocrine, you're more likely to get them back when they're a lot older and frailer and surgery may not then be an option and you've only got RTx. Can never get rid of it with just endocrine alone.</p>	<p>They can be more anxious than the ladies who've had surgery. 'I don't like that in my breast anymore, it's making me worry all the time'. They quite like that (regular F/U)... they're being looked after and watched.</p>	<p>TUMOUR ASSESSMENT: Clinical and US every time they come. Subjective measurements. F/U: Regular basis. Initially at 3m. RESPONSE: 'It could work for 6m, 2 yrs, or for the rest of your life'. Might only work for 6m or she might... die from something completely different... very hard to predict. Some ladies it's carried on growing, but not many. Lot of the time it's yrs. REACTION: Surgery may not then be an option and you've only got RTx... you can switch your endocrine I suppose but there's only usually RTx.</p>

<p>N34 Female High PET</p>	<p>OPINION: Never take it away but it could keep it under control for as long as they need. Minority treated with PET. WHEN OFFERED: "I really don't want this surgery". Gives you another option when they can't always comply or understand. NEO: They can go on it initially to give them time to maybe have an anaesthetic assessment, or time to find out the info they need to decide what they want to do.</p>	<p>Pros: Could keep it under control for as long as they need. Well tolerated. Most... get on with it pretty well. Cons: if they don't get a good response... best option now is surgery but you could be a lot older. End up with an ulcerated, quite unpleasant malodorous wound. SEs:- flushes, arthritic pain, joint stiffness. Will never take it away.</p>	<p>Really struggling because they can't have surgery because they can't trust in the tablets. For some ladies it's very important that actually they're rid of it. Those who are bothered re: lump would probably opt to have surgery. Seeing it respond...is... quite reassuring. It's a bit of reassurance sometimes coming for clinic.</p>	<p>F/U: Initially and again at 6m, then a yr, the D/C to GP. RESPONSE: Varies, I've got one lady who's actually come off it after 20 yrs and had surgery because she got so fed up of taking it. Could last for life. Ladies that have been on it for 10 yrs but realistically you're looking at maybe 3-5 yrs before you need to change. REACTION: If they don't get a good response, then we might be saying "well, our best option now is surgery but you could be a lot older." Change ET.</p>
<p>S03 Male Low PET</p>	<p>OPINION: Considers for all over 70s. Sub-standard in terms of local recurrence and QoL. It is a good choice. Lazy surgeons use it without questioning the evidence. WHEN OFFERED: I offer both Rx's to all pts. If there's a bit of anxiety... I'm happy to keep them on the PE(T). NEO: Start them all on PET in view of bringing them to surgery to allow time for assessments.</p>	<p>Pros: Most likely to have good control. Pretty well tolerated. Cons: Sub-standard in terms of local recurrence and QoL. SEs well-known but minute, incl endometrial ca. Limited period of efficacy - then the cancer comes back.</p>	<p>No comments.</p>	<p>RESPONSE: We expect these tablets to work, on average 3 yrs and then the cancer comes back.</p>
<p>S24 Male Low PET</p>	<p>OPINION: Less now than used to <15%. Thinks survival is equivalent, main issue is QoL. WHEN OFFERED: Up until 3yrs ago was offering PET to all pts over the age of 70. Still offers pts PET but tells them surgery is best. Dementia is the one indication for PET in my book. NEO: Uses neo-adjuvant ET to shrink tumours to make them easier to operate on under LA.</p>	<p>Pros: Happy that they haven't had an op. Allows them to stay in the comfort zone of denial - don't have to face up to the fact that they've got something serious. Cons: Uncontrolled local disease. If I operate on her now, she probably will die. Continually watched. F/U reminds them they have cancer.</p>	<p>"I'm glad I didn't have an operation". They're not under the impression that it's going to cure it. Haven't told me they're worried about it (the lump). Feel comfortable it's not getting bigger. Can forget about it. Inconvenience of coming to clinic. Reminded they've got cancer. Most of them want to come.</p>	<p>TUMOUR ASSESSMENT: US the pts himself. F/U: Scan them every 6m. One-stop clinic, start with 3/12 F/U until knows they're responding then 6/12 if they're static or annual if they're in complete remission. Sometimes they say "can I not come?" and I say fine. RESPONSE: E.g. of a woman on PET for 9 years and now on Faslodex (had all the other drugs) with uncontrolled local disease. Works in about 80%, average response of ~10 yrs.</p>

<p>N11 Female Low PET</p>	<p>OPINION: Surprised if they jump straight into PET. Very few have PET - low % - maybe 10%. WHEN OFFERED: Would be discussed in a broad sense as in these are the options available. NEO: Tends to be started as neo-adjuvant to downstage with a view to surgery after 3-6/12 and pts leave knowing that. Some stay on PET with consent of surgeon if they think that's best.</p>	<p>Cons: If comes back in a few years, you'll be a few yrs older, perhaps with more co-morbidities. Not going to get rid of it.</p>	<p>Quite happy knowing they're leaving the hospital on Rx. Become anxious if the cancer grows. Know it won't get rid of it. Thinks it bothers pts: <i>every day they know... they have got cancer on board</i>. Can be reassuring when it shrinks. Reassured knowing <i>they're being assessed and checked... I can't say it's really going to make them feel worse</i>. Awkward if they're in a wheelchair or not very well - some say they don't want to come.</p>	<p>ASSESSMENT: US at 3-6m. F/U: Told to come back sooner if the cancer grows. 3m to start the 6m or yr. Won't see much difference before 4m. Another surgeon see them every month. F/U for quite a while and if health deteriorates ask GP to monitor. RESPONSE: 2-3 years you're seeing a regression, then tumour recurrence. REACTION: Surgery might be advocated.</p>
<p>N23 Female Low PET</p>	<p>OPINION: <i>We know we'd anticipate it to work.</i> WHEN OFFERED: If fitness for surgery was in doubt. Pts who are very immobile, bound to their own home, breathless. <i>If... they don't particularly want surgery... So it might be coming from the pt.</i> If extremely unwell. Pts coming to the end of their natural life.</p>	<p>Pros: Not having to go through an op. Cons: Not 100% effective in younger pts as going to be on it longer. Worrying about the cancer still being there - is it going to grow, it might stop working. May not be as fit for surgery when fail PET. <i>F/U: an effort to bring them here, because sometimes we've had them practically brought in on beds and it's so unfair for the pt.</i></p>	<p>Generally happy being Rx'ed that way. Some worry and are <i>forever touching it, thinking 'is it going down, is it going down?'</i> See it as an alien and they don't really want it in them. First appointment in particular gives them confidence and reassurance that it's working.</p>	<p>PET TYPE: Used to start on Tam but now Letrozole. TUMOUR ASSESSMENT: US, all team trained. F/U: Starts at 3m then 6m unless pts are confused/demented or really unwell them F/U by GP and re-refer. RESPONSE: Not common to have to change therapies at 6m, more like a year, <i>could have pts static for yrs. Variable: They were coming back 10 yrs later... and it's still shrinking, and then you have some that in a very short period of time relapse.</i> Some go through all of them within a yr or 2. REACTION: <i>We put you on to another tablet or we might have to go for surgery.</i></p>
<p>S04 Male Low PET</p>	<p>OPINION: <i>Only if there is a reason to consider it.</i> Inferior Rx. Doesn't offer it: I don't see them as 2 different options... I don't see it as a standalone Rx. Thinks only offering PET is not defensible in court if a pt is fit for surgery. WHEN OFFERED: Uses PET by default, <i>when they're not suitable for surgery.</i> Pts with other cancer, significant dementia or declines op. NEO: <i>Would offer it to pts who are not currently suitable for breast conservation, and who would become suitable.</i></p>	<p>Pros: <i>Keeps things at bay. Prevents the need for an op.</i> Cons: <i>Might not work.</i></p>	<p>Mixed views. Majority relieved they don't need an op but significant minority who are <i>not happy with the fact they are not getting an op, they feel uneasy about the fact they are on a medical Rx and haven't had the tumour removed.</i></p>	<p>No comments - doesn't really use it.</p>

<p>S05 Male Low PET</p>	<p>OPINION: Not recommended Rx if can have an op. Not optimal Rx. Doesn't consider ET as primary Rx: <i>has to be surgery at some point.</i> Offering PET a <i>slippery slope.</i> Negative attitude: <i>stick her on Letrozole and forget about her.</i> Fine for very frail old pts. Some benefit from <i>masterly activity.</i> WHEN OFFERED: can't have surgery, don't want surgery, time to get used to or optimise for surgery. If can't optimise. NEO: Uses more as neo-adj. <i>Result would be to facilitate surgery as opposed to avoid surgery.</i></p>	<p>Pros: Avoid surgery. Normally good response, have options if progress. Spare them the blade of surgery and the morbidity. Few progress. Cons: <i>May stop responding.</i> Local control may become a problem. SEs: bony pains, osteoporosis, DVT. Extra medication, e.g. adcal, bisphosphonates. Postponing surgery by 4-5 yrs <i>then you've postponed and you've got a frailer, older woman.</i></p>	<p>Pts see advantage of PET that they avoid surgery.</p>	<p>PET TYPE: Letrozole. F/U: Keep on very close surveillance so know if progresses. RESPONSE: 4-5 yrs. REACTION: Swap ET, go from Let to Tam. If she progresses then we would go in.</p>
<p>S25 Female Low PET</p>	<p>OPINION: Not as guaranteed an outcome. In some situations (eg dementia) may work equally well. About 7-10% of pts on PET. Does work very well. Not as definitive. <i>Uncertain Rx.</i> WHEN OFFERED: Not fit for surgery. Heart attacks in last 6m. Pts who refuse op, pts with dementia.</p>	<p>Pros: Works very well: <i>few... come back for volume assessments and they've got no residual cancer.</i> Cons: Failure of control, local problems: skin breach, fungating, ulceration. <i>Don't think we have major problems with the SEs or compliance. Might stop working... general health is that much poorer and surgery may not be an option then. Longer you wait, the more unlikely you are going to operate on them.</i> F/U disruptive.</p>	<p><i>Most of them are quite happy. Most not worried about lump. It's... a big deal bringing the up to hospital, disruptive.</i></p>	<p>PET TYPE: Letrozole (Tam if osteoarthritis) + Adcal D3, bisphosphonates in >75s. TUMOUR ASSESSMENT: Clinical + US. F/U: If they're F&W: <i>keep an eye on it because there may be a time to change the decision.</i> In 1st yr might do 3-4 monthly scans, when happy leave it 6m and some F/U by GP. F/U F&W pts for duration. May stop US if complete response and just clinical. RESPONSE: <i>About a couple of yrs. Average time... is about 8 or 9 m before you see any benefit. About a yr or 2... where you do see them under control... about a 25% group who come back with the increasing size and then we do switch them to something else. One on PET for 11 yrs (now has inoperable disease).</i> REACTION: Salvage operation.</p>

<p>S26 Male Low PET</p>	<p>NEO: Sometime people do start as a neo-adjuvant hormonal manipulation... at that point in time you may not be able to make a decision to say are you doing it as a “neo-adjuvant” setting or that’s going to be a definitive endocrine treatment. Use it to buy time - they gain confidence... nothing is lost... or sometimes somebody has had a MI only 2m ago, or a mild stroke.</p>	<p>Pros: Responds sometimes very well. No surgery, no admission. Cons: Two years down the line, other catastrophic events may happen and although we start the PET, not always the tumour responds to the level you want to respond.</p>	<p>They love it. They think no knife. They say “look, what I did was right”. Accept they’re not being cured. The reassurances when you do the ultrasound scan and tell them the volume loss... that gives them the happiness. There’s another group of people “I got a tumour, I don’t like it, take it out doctor”.</p>	<p>PET TYPE: If had thromboembolic events... we put them on Letrozole. If not Tamoxifen. TUMOUR ASSESSMENT: US + MMG. Extreme cases (wheelchair bound) just clinical. F/U: Initially every 3m, depending on the trend; if decreasing in size less frequent. F/U for as long as possible. RESPONSE: May live for yrs. Softening is the first thing to happen and then it shrinks. Variable response. Don’t come across many pts where you run out of ETs. REACTION: Switch the ET. It starts fungating... then we look at RTx. If small could use LA.</p>
<p>S28 Female Low PET</p>	<p>OPINION: Feels uncomfortable putting pts on PET. PET is writing somebody off. WHEN OFFERED: If they refuse surgery or they don’t have that kind of support, on the social side... we are relaxed enough to off them ET. 80+ lower threshold to offer them ET, 70-80 most people go through the knife. NEO: Give neo-adj ET while they go through assessment and optimisation, gives them chance to see if it’s responded - not delaying Rx whilst you get the assessments. You can leave them for 4-6 wks on ET and come back... by that time they’ve usually made up their mind.</p>	<p>Pros: If more likely to succumb to comorbs you don’t necessarily want to subject them to surgery. Don’t need hospital F/U, can be managed by GP. Cons: Non-responders... problematic, fungating cancers. Dragging pts back every 3-6m. Less fit in 5 yrs’ time, less likely to be candidates for surgery. If it becomes locally advanced.</p>	<p>Don’t seem to be bothered by the lump they don’t look at their breast, they don’t examine their breast, they don’t feel their breast.</p>	<p>PET TYPE: Letrozole, but used Arimidex in other centres. TUMOUR ASSESSMENT: Varies according to surgeon, don’t generally US unless neo-adjuvant. F/U: Just see them for 3-6m and make sure they’re not obviously getting worse on Rx and then just leave it to the GPs. RESPONSE: Often after 5 yrs they start to fail. Don’t know the proportion, you don’t know the denominator. If they fail, they tend to fail within 3-5 yrs.</p>
<p>S29 Female Low PET</p>	<p>OPINION: Uses it much less now than 5yr ago. WHEN OFFERED: If pt is reluctant to have surgery. NEO: Why don’t we put you on a trial of HT and see how you get on and see you again in 3 or 4m time and see if your tumour’s responding.</p>	<p>Pros: Avoiding surgery, I think that’s the only advantage, just trying to avoid the trauma of it. Cons: No disadvantages as pts will get ET if they have surgery anyway. Failure of local control can be quite a difficult clinical scenario to deal with, quite unpleasant. Mentions cognitive impairment that’s reported with Tamoxifen.</p>	<p>It’s something you have to explore with them because it is a disadvantage, if they’re going to be feeling their lump twice a day.</p>	<p>PET: AI, Letrozole. TUMOUR ASSESSMENT: Clinical +/- US, doesn’t use calipers, I measure it by eye. F/U: Initially 3 or 4m. I might arrange to see them again once more... and if they continue to have stable disease, I’d usually discharge them back to the GP. RESPONSE: Probably a year or so. REACTION: I would try a second line.</p>

<p>N06 Female Low PET</p>	<p>OPINION: In the minority. WHEN OFFERED: If not fit for surgery. NEO: Trying to avoid Mx by giving ET. May be used when close to breach date - particularly if needs assessment.</p>	<p>Pros: Can avoid Mx. Fairly easy Rx for an older pt. Quite an effective Rx. Good option without having too much impact on their life really. Cons: SEs.</p>	<p>If it's well tolerated pts like it. They deem it effective. It doesn't impact on their life, it's an easy Rx. When lump physically shrinks can be a positive thing.</p>	<p>TUMOUR ASSESSMENT: US + clinical assessment. F/U: Monitor them quite closely. Initially see after a month, 1st US @ 3m, if tolerating it see them at 6 months. Try and keep them on it for at least 6 m before doing surgery. RESPONSE: Usually wait 3-6 m for response before moving on to surgery. REACTION: It's not really working... let's move on to surgery.</p>
<p>N27 Female Low PET</p>	<p>OPINION: Maybe 20-25% treated with PET.</p>	<p>Cons: If PET doesn't work can lose the window of opportunity to operate.</p>	<p>They breathe a sigh of relief and think 'actually I don't need to go under anaesthetic'. Might feel that they're maybe abandoned: don't get as much contact time as surgical pts. If they can feel that it's resolving... they seem ok with the decision.</p>	<p>PET TYPE: Tamoxifen, Arimidex, Letrozole, Exemestane. TUMOUR ASSESSMENT: Clinical exam, if any discrepancy then repeat the US. F/U: See them within 3m, see if they're either receding or responding to Rx and then go from there. Have BCN number: 'if you have SEs or anything, ring in'... tend to lose a little bit of contact with them but... it's an open-door policy. RESPONSE: 9m window of opportunity for surgery. REACTION: If they're non-responders... would re-explore the surgical option. Go onto a different ET to try and maintain response... so we would switch.</p>
<p>N30 Female Low PET</p>	<p>OPINION: Low percentage... isn't uncommon. WHEN OFFERED: Pt feels that home circumstances are such that they can't cope with surgery.. feel that it will knock their routine and they don't want surgery. Will offer PET if felt it's in the patient's best interest. NEO: If there were comorbs or the tumour was sizeable might try neo-adjuvant to downsize and make surgery easier.</p>	<p>Pros: They've not had to go through surgery; for some people, it's the right thing. Cons: Run into problems later if they get resistance to it. Progress on ET, and if their health deteriorates, then that becomes far more challenging in treating the person optimally.</p>	<p>Older people cope with it being there, as long as they see it shrinking or they know it's not getting bigger.</p>	<p>PET TYPE: Generally Letrozole. TUMOUR ASSESSMENT: Use US to... compare the sizes. F/U: Review in 2-3m... see what response is. Usually kept in F/U. If getting to hospital is difficult often ask GPs to F/U. RESPONSE: Settled on it for at least 2-3 yrs, some people can go on it for a lot longer... but that's the point that I feel often they have to change Rx.</p>

S07 Female High PET	It will be personal experiences. Some... more prepared than others. If pts already suspect diagnosis conversation can be short if they just say "I don't want an operation".	Glazing of the eyes... only so much info that you can take in. Some more prepared than others. Sometimes conversation is brief if pt knows what you're going to say & they go "no I don't want an operation" so you don't get much chance.	Infers that pts influenced by what they think surgeons think is best but they get it wrong: they think you want them to have an operation - not really! Pts have their own reasons by choosing Rxs: wasn't the most logical reason but it was her reason... it was how she felt about it. Most women in Barnsley I think make up their own minds.	No comments.
S08 Male High PET	No comments.	Much less than younger women...that group of pts do not want to much info, can't cope with too much info. Discusses type of surgery, how long for PET, when see again, what to expect. It's purely dependent on the pt. Most Q&As from relatives rather than pts.	I would be pushing for PET and I suspect she will more than happily agree with that - infers they are easy to lead? 'Doctor knows best'. Elderly pts don't ask loads of questions, can't cope with too much info. Quite passive: Just say "do what's best for me". Contradicts this with: they'll know whether they want PET or surgery.	No comments.
S10 Male High PET	No comments.	I don't hide any facts from the pts. Mentions tablet SEs, failure, risks of surgery and anaesthesia, prognostic info. How the pt is accepting or digesting the info. Some of them are happy to accept everything, so I tell them everything. Some of them... they like just 'cancer' or 'not cancer'.	No comments - seems to be HCP-centred Rx decision. Mentions: QoL is important in this type of woman.	I'm happy to make a choice for them.
S14 Male High PET	Most elderly ladies accept the diagnosis much more easily than younger ones.	Tend to give the info to the pts and let them decide. Give them basic info, facts and figures. As much info as the pt wants. Some switch off and not listen to any more. Others will take more and so you give them more. Who comes with the pt, whether pt forgets. BCNs... reinforce what is being told.	There are pts who ask him to decide. Defer choice to family member: "let her decide, you talk to her because I forget". Some pts are quite happy to go along with whatever you recommend. I just find that the elderly ones accept things much more easily. Well not all of them like making their own decision, but a large proportion do.	Yes there are pts who ask him to decide. Some pts defer choice to family member - some of them will just say "let her decide, you talk to her because I forget". I think you take an objective decision as to what would give them more benefit. So that's what you decide for them.

S15 Female High PET	No comments.	Huge amount of info... info overload is a real issue. Incongruous to talk about everything if pt says doesn't want it. Depends a lot on what they're saying to me... don't talk about everything to everyone... need to be talking to each individual woman as an individual.	Commoner for older pts than younger to ask Dr to decide for them. The older woman who lives independently, they'd rather die than lose their independence... their priorities are very different... it's not about survival.	Commoner for older pts than younger to ask Dr to decide for them. Say "well, what is right in the way of Rx for you depends to some extent on what's important for you and what you would be most comfortable with. And since I'm not you, I can't tell what that is, I need you to tell me". Give time and usually will make a decision.
S18 Female High PET	They know of people who were in hospital with a Mx and then had horrible emphysema. Previous experience of surgery. Experience of friends/relatives. A lot of pts when they come already know what they've got. Elderly pts are usually quite switched on. Often already made up their mind.	Verbal info by her & BCN, also written info. Give them all the same info. As much as possible because I'd prefer them to be fully prepared. Pts need to be well informed to make a choice. Written info easier to understand and absorb than on a screen. BCN will then meet with them, usually at home, to go through everything again. BCN explains Rxs.	Some women actually do want choice and they accept that they might actually have poorer survival. They want to prioritise QoL over quantity of life. Usually quite switched on. They've often already made up their mind. Not well informed but still a decision. Difficult to change their mind once they've got a set opinion.	I weigh up all the info and then I feel it's my duty to, that if they ask me to decide, to most strongly recommend the Rx which gives them the best survival, so if they're fit for surgery, that would be surgery. Sometimes you're left with no choice because they insist that you make the choice - so fully inform them and document.
S20. Male. High PET	No comments.	Gives verbal info, draws pictures, tailor according to their needs. Have to provide them with the info to allow them to make a decision. Face to face discussion is probably better than several booklets. Older pts require less info than younger pts. Depends which Rx: approach would be a bit different in terms of talking to them. BCNs give out written info.	Require guidance... trust us... but once they've got the info, making a decision is not too difficult for them. QoL important, older pts don't view survival as important as younger pts. Some studies... indicate that older people... are more likely to listen to HCPs. They're not that anxious, they're realistic, so there is another myth out there that they can't make their own judgement. Require less info, they are able to make a decision and stick to it, still require guidance.	There is another myth out there that they can't make their own judgement so therefore you make the decision for them. Sometimes happens. Talks about other people - if they believe that older pts can't make decisions then you get extreme situations where some people always operate and some always use PET. Depends on which Rx group they're in, 2 groups he has already decided so group in the middle - If there is a clear choice... I would try my best to stick with the concept of a choice. Would try and explore why she can't make the decision, what is important to her, that would probably tell me which decision is better for her.

<p>S21 Female High PET</p>	<p>Majority make Rx decision before they come to clinic. Worried they have cancer before they've even had the biopsy.</p>	<p>Re-caps important points: 1) lump is cancer, 2) these are the two Rx options. Lot of written info too. Gives everyone the same info. Depends how much they take in: after she heard the word cancer she never heard anything. Elderly pts: how much they retain is debateable. Play it by ear. Inconsistent.</p>	<p>Majority made the decision before they come. Make up their minds quickly - Majority would be just say "yeah, give me the tablets or let me have the operation and let me get out of here".</p>	<p>If they ask me well what do I think, I will tell them... "You choose what is right for you, not what is right for me... or for anybody... It's not about us it's about you & what you want. This is the 1 time it is your decision." Even if they say "Well what would you choose" I would say "I'm not sitting in that chair, & the tables are not turned, & I don't know how I will choose if I was sitting where you're sitting so it really is your choice". Won't choose for dementia pts (unless ER-): we'll come to a decision as a group, not my decision. Gives them time. Tell pts they're not doing harm by choosing either Rx.</p>
<p>S32 Female High PET</p>	<p>Over-estimate how frail they are. They remember people being in hospital for a week with Mx's. Surgery's moved on but their perception hasn't. Known somebody who's had a bad experience. Previous experience if they have family members who've had surgery.</p>	<p>It's a little bit about starting to chat to the pt and get an idea of what I feel their... capacity to absorb info.</p>	<p>Few pts who will say "well you decide for me Dr, you just tell me what to do". "if it was your mum, what would you ask her to do or what would you tell her to do?".</p>	<p>You get... the few pts who will say "well you decide for me doctor, you just tell me what to do". "if it was your mum, what would you ask her to do or what would you tell her to do?". I find that very difficult... somebody who is clearly a high GA risk... I would say "well I feel that you have a good option in PET", if they're absolutely fine and well... I think you have to say to them, you know, "it's a very personal choice and the standard thing to do would be to do surgery in somebody of your age... but it's really something that you need to think about". The other thing that we'll sometimes do is you know, "why don't we just put you on some PET, give you a little bit of time to think about what you want to do".</p>

<p>S33 Female High PET</p>	<p>Pt's who've had other surgery it influences their decision. "Ooh I've not got too long to live".</p>	<p>Minimum you've got to discuss the diagnosis and the options available. Amount of info depends on partly how much they ask. "Do you want to have a drink instead" and take that, if they say "yes..." that's the place to stop... non-confrontation way of saying "have you had enough?".</p>	<p>Independence is what's most important. Pt's who've had other surgery it influences their decision.</p>	<p>I think deciding for them is uncomfortable for me. I would normally sit with them and try and go through why they're not keen on surgery and what the risks and benefits for them might be and try and bring them back with a member... someone else to support them, family or friend to talk it through and suggest that they meet some of our other ladies as well. if they're not keen (on surgery) at the start I would initially start them on endocrine therapy and keep discussing surgery with them because I think you're not going to cause complications with PET.</p>
<p>G16 Male High PET</p>	<p>"I'm not having an operation whatever you say"... they get the confidence that... they're a bit fitter than they thought.... When people hold such strong, seemingly irrational, views it's usually because of an experience. May have read something in the paper. Alternative sources to predict what dr is going to say, come with a view about what their diagnosis is and what the best Rx is.</p>	<p>Benefits and the risks of each of those choices in a way that allows them to make an informed decision. Talk you through the benefits and the risks of that and what else we could do.</p>	<p>It always worries me when people say "Yes I'll do anything you say, Doctor...". Most pts have an expectation that their dr will suggest to them what the best Rx is. Look to professionals to help them make what is the best decision. Life experience or family experience... will impact on their DM. Lot of older people who will not question the dr, "you don't ask the dr"... "you do what you're told".</p>	<p>It always worries me when people say "Yes I'll do anything you say, Doctor, I don't want any explanation". My approach is always "I hear what you're saying; I will talk you through the options. Yes I will tell you what I think the most appropriate option will be, but I'm going to talk you through the benefits and the risks of that and what else we could do". They probably don't listen, I don't know, they're probably going to do what you say anyway.</p>

<p>N09 Female High PET</p>	<p>No comments.</p>	<p>Risks and benefits of both Rx options. Overwhelm them. Check how pts feel with info and if they understand. What are you going to do with that info? Is it going to be a burden to you? Info on SEs. Amount dependent on clinician. Cloud people's judgement with too many options. Some say "I don't want a lot" but they're just frightened, others want everything & it scares them.</p>	<p>Some women... actually want direction from the clinician. Didn't expect to be given Rx options... they are doctor-pt led and... do not want to be involved in the decision process. Some women may indicate that they actually don't know how to make that decision. Some pts don't want a Rx but don't always voice it. Put pressure on themselves to make decision as don't want to burden their families.</p>	<p>Some women that actually want direction, from the clinician. Didn't expect to have a choice, feel uncomfortable having to choose - do not want to be involved in the decision process. Some women may indicate that they actually don't know how to make that decision. They are "doctor-patient led" - they are passive DM, prefer Dr to have a paternalistic style. Some clinicians will say "well, we'll make that decision for you". If don't want to be involved in DM: we accept that, and respect it too. Old school consultants more comfortable making decision for pts.</p>
<p>N12 Female High PET</p>	<p>Sometimes pts have such fearful pre-conceived ideas about surgery that they make that decision not to have surgery. See themselves at the latter end of their lives... pre-conceived ideas about... women in their 80s shouldn't be having surgery.</p>	<p>Important to inform pts that surgery is safe and the best option. Try to give the same info out whether a pts in their 20s or their 90s. Empower them with info. If not having surgery give them limited info. Older population I feel, don't want info because don't want to make the decision. They don't want to be empowered with info like the younger population. Give all the options and info for each.</p>	<p>Older population, if a doctor says jump, the patient will respond and say how high? They want the surgeon... to tell them what is the best option, they don't want to make decisions about their care. They will go with what the doctor says. They want the doctor to tell them what is best for them. The elderly... struggle with options for their Rx.</p>	<p>No comments.</p>

<p>N13 Female High PET</p>	<p>The diagnosis is devastating irrespective of the fact that often they came with a lump and they almost assumed that it was (cancer).</p>	<p>Written info about Rx and common SEs. Use info prescriptions: routinely the same things for sort of surgery or primary endocrine. Go through potential major problems with that Rx, that sometimes has to do if that's all they want. Tell pts PET's not guaranteed effective. Time affects amount of info given by doctors, BCN go through more. Patient-dependent: give them what they want, when they want.</p>	<p>Want you to make the decision for them. I'll do what you think's best. A lot of people want to please their families... with their decision. The older generation generally don't want to put people out so that has a big impact on the DM. Inconsistent: Not many older people come knowing what Rx they want then: Some ladies know what they want... and they will only go with their own choice... sometimes you have to compromise and I think that's what we do a lot of the time.</p>	<p>They almost want you to make the decision for them. We have quite a few... that say I'll do what you think's best. It's hard because no matter what we feel is the best for someone, that's our opinion. We always say "we can't tell you what we think's best... it's whichever's right for you" & we don't know what's right for them... you would hate to... coerce them into something and then they come back & say "you told me I needed that" so you've got to be so careful, you can only give them the information you've got and say "based on what we know so far these are the genuinely choices".</p>
<p>N17 Female High PET</p>	<p>If I have an anaesthetic I'm going to die. Feel that they wouldn't be able to cope with an op. Previous experience of major surgery. Philosophy of life as well, how they feel about their life. "I'm too old to have an op".</p>	<p>So much info they feel confident to make a decision. Everybody gets the same. Take into account what they can understand and read. Involve family/ carers/ learning disabilities team. Info for different languages. Dementia pts have to assess what they can understand & remember.</p>	<p>There are pts that can't make a decision, don't want to make a decision. Some have very fixed ideas: they still say "no, I don't want to have an op". Pts ask "what would you recommend?", "what would you do?". They don't want to upset the balance... it's about QoL not quantity.</p>	<p>There are pts that can't make a decision, don't want to make a decision no matter how much, so you don't want them to run away and not have any Rx. Quite often it can be about they're just really unsure about what's being said. You'll say "there's no 'best', it's what's safest" and that's the route that we tend to go down. Talk about the pluses and minuses. You have to go back over it again and explore those issues.</p>

<p>N19 Female High PET</p>	<p>Pre-fixed idea of what can be done or can't be done... "what's the point of doing anything?". Bad past experiences of somebody they've known. Think it's not worth Rx'ing because of their age. "I'm of a certain age, maybe there's not a lot of point in doing something for me"... "is it worth doing anything?" because of the age I am.</p>	<p>We (BCNs) go over the info and elaborate... explain more of the detail.</p>	<p>For some people it is such a very difficult decision. They're asking for guidance... as to really which one should they choose in view of the info that we know. It's quite difficult when people face that choice. "what would you do if it were me?". Some take a tablet because it's easier but sometimes there's a sense of guilt, not being brave enough, feel they're letting themselves or their family down. Some people may come with a pre-fixed idea of what can be done or can't be done, or might even think "what's the point of doing anything?".</p>	<p>If somebody asks, as many people do, "what would you do if it were me?", or "if it were your mum or grandma, what would you do?". I feel, when somebody is given a diagnosis and given the options, for some people it is such a very difficult decision. I think when people ask that question, really they're asking for guidance... as to really which one should they choose in view of the info that we know. I guess it's quite difficult when people face that choice (surgery vs. PET). I have known some people who say it's difficult to know unless you're in that position. I've known other people, perhaps even more helpful answer and actually answer it taking into consideration that person's circumstances, which might then influence a decision. Thinks it's ok to advise "if I was in your situation" - if it's done in a measured way and with consideration of that person's circumstances.</p>
<p>N22 Female High PET</p>	<p>Plant some seeds... so when they come back for the results, not many are totally knocked off their feet. Most have prepared themselves for the Dx. A lot of people have got internet access now... so they're not surprised when we talk about surgery. Often they've heard you can just take a tablet.</p>	<p>Written info: pack of info. Depends who's talking: Surgeons are pretty much... sing from the same hymn sheet regards the verbal info. Try not to flood them too much... can be overwhelmed.</p>	<p>It's QoL at the end of the day, and you see more of the importance of that really, quality rather than quantity sometimes. We do have occasionally ladies who go off to other countries for the odd spiritual need and sabbatical and they say 'I'll contact you when I get back'.</p>	<p>If they're not sure they're given written info and BCN will be in touch and we'll discuss it.</p>

<p>N31 Female High PET</p>	<p>They believe they're not going to live, or a lot of them will say 'I've got to die of something, duck'. Could just be a misunderstanding or what their mates told them.</p>	<p>Give it them in bits... what is relevant at that time. Ask if they want leaflets: don't just bombard them. Some ladies don't want any (but husbands/sister will read them). Can't give the same info to all pts: Could offend somebody... just go with my intuition and asking the woman herself.</p>	<p>What a Dr says is like God aren't they, to a lot of older people. Get women saying 'I can't make a decision' inconsistent: some are choosing surgery, some you cannot change. The surgeon encouraged her to have surgery... she went 'I am not having-...' some women you are not going to change.</p>	<p>You still get women saying 'I can't make a decision'. They would say 'I would rather do surgery'. If they were fit enough. We would rather take away the tumour and then treat with endocrine after. I'll say 'well, these are your options'. It's a personal choice, we don't know women well enough to help them make that decision. I'll say 'all I can do is give you the facts and then for us to discuss it more'.</p>
<p>N34 Female High PET</p>	<p>"I haven't got much longer to live anyway" so of course the tablet will be fine. Perceive it as a big open wound that they're going to be in for a week. Bad experience of a relative. Think it's too big a thing to have done. They're that old they're not bothered about treating it at all... & feel too frail for it, the thought of having an op... is quite an enormity.</p>	<p>Sometimes we will stagger that or it will be followed up. Need info about basic stuff. It's too much to do it on the day, they're too upset... so we would bring them back. It's titrated to them. Our role is... info giving, understanding the info they've been given. Laying out the facts... this is the pathway of this option, this is the pathway of that way.</p>	<p>Pts will regularly ask me what I would do. Perception that there's a lesser choice. Generation that think the doctors know best... that's a real struggle when you're talking about a choice. People make decisions on their past experiences. Lonely place to make that decision. These ladies have been making decisions all their lives & actually their DMing skills are actually pretty good & you give the info & time & take the crisis element out of it & actually they're very good at making decisions because they know what they want. They're pretty savvy.</p>	<p>Pts will regularly ask me what I would do. Happens quite commonly. When you're given choices, people have the perception that there's a lesser choice. It's a lifestyle choice at the end of the day it's not a medical choice. We've done the medical choice. you're still looking at a generation that think the doctors know best and sometimes that's a real struggle when you're talking about a choice. I quite honestly say I don't know what I'd do until I was sat in that chair. It's about laying out the facts. these are the pathways and we will support you to do whatever one's right for you. It's about... "tell me what the issue is for you here, what is it you're feeling, what is it your concerned about?". "You need to talk it through with the BCN but it's important that you make the decision for you". Explains: you've got two very good options. Tell me what you want out of this Rx... one of these options will fit that very nicely.</p>

S03 Male Low PET	No comments.	Enough info to make informed decision. Need to be told that non-surgical management is sub-standard. Advantages and the disadvantages, the risks and the benefits. Spend a good three quarters of an hour for every single such pt. Give full understanding of the clinical situation, progression of the disease, life-expectancy, the risks and benefits of each Rx.	No comments.	No comments.
S24 Male Low PET	GPs still tell their pts if they're elderly that they might just have tablets. Usually people who don't really want an op that are saying "I'm not really fit enough".	Gives them the diagnosis, tells them what the options are and hands over the BCN. BCN gives all info: She's with me at the consultation so she goes through it in more detail.	I could tell you the best way to treat your ingrowing toenail is to chop your head off and you know, if you're an elderly lady you'd say fine - infers that elderly are passive DMers. QoL is very important.	Never decides for pts (repeats this 3 times, feels very strongly) - I would say to them "go and talk to the Breast Care Nurse and have a think about it". I never tell pts what I think they should have, because I could tell you the best way to treat your ingrowing toenail is to chop your head off and you know, if you're an elderly lady you'd say fine.
N11 Female Low PET	A lot of older women think BC is a disease of younger women. "am I too old to have surgery?" .	Talk through practicalities. Asks if they like info. Tailor it, everybody's unique. Pts job can influence info-giving (teachers like info). "put their head in a sandpit" . Make sure understands, I often jump in with... and explanation of what's been said.	Pts obviously listen to their Dr. Being a carer or animals or grandchildren at home can have a bearing on Rx decision. Elderly pts less likely to question as much as younger, do less of their own research.	No comments.

<p>N23 Female Low PET</p>	<p>They're already old and they fear that it might just be the thing that tips the balance for them. The way people perceive themselves to be old is changed. "I thought I was too old to get cancer".</p>	<p>Prepare pts for surgery. Dr will say so much to the pt and then "[name] will go into a bit more detail about that", "[name] will cover that", so he sort of passes it on to me.</p>	<p>"what do you think, Dr?". A lot of people struggle when they're being given a choice... they say "what do you think I should do?". Want the advice... to be told what to do, but they still want the info to know that they're being given the choices. "you're the expert, you should be telling me what I should have done". Used to be 100% in elderly because they revered drs but that's gone now. Want to feel involved, but they don't want that decision... because they're too frightened of making the wrong decision. There's the DMers in life that want to gather info... and there's people that will never make a decision no matter what info you give them.</p>	<p>Still high numbers of pts that say "what do you think, Doctor?". I see a lot of people struggle when they're being given a choice... and that's when at the end of the day they say "what do you think I should do?". You also get... people that want all the info but they still want the advice, they still want to be told what to do, but they still want the info to know that they're being given the choices. I think it's a lot of confidence in people now saying "you're the expert, you should be telling me what I should have done". Used to be 100% in elderly because they revered doctors but that's gone now. I always put it back to them... "it's your decision, at the end of the day... by giving you a choice, one Rx is as good as the other"... then at least they know that they're not going to make a wrong decision. I emphasise... there's no right or wrong answer. So it's what you think is best for you.</p>
<p>S04 Male Low PET</p>	<p>A lot of women in that age group have their own opinions and they can't be changed.</p>	<p>Enough info so that I'm satisfied that they have the minimum amount of info, and beyond that as much info as they want. Clinician's judgement how much info pt needs. I don't feel the need to offload my info onto the pt.</p>	<p>Doesn't really comment as he selects the Rx and doesn't offer choice.</p>	<p>Doesn't offer a choice so no comments.</p>
<p>S05 Male Low PET</p>	<p>You do have some people with strong opinions.</p>	<p>Give info about what the surgery entails, importance of optimisation, risks of Rx, or what PET entails.</p>	<p>Pts will go with what the surgeon advises: if I want to take them down the endocrine route only then they'd go with it or if I said you need to have surgery, then they'd go with that. Sees them as passive DMers, easy to lead.</p>	<p>Doesn't offer a choice of the two treatments so no comments.</p>

S25 Female Low PET	I think they've made up their minds beforehand. Previous experience, them or family - don't want to go through all of that.	Can't give everyone the same standard info. Pt's intellect, how much they're absorbing. If they want info we always give it to them, if they don't want info we still give it to them but might cut it back a little bit... you can't force it on them.	Go with the clinician's recommendation. Pts can accept Rx risk (may go against advice): as long as the pt says "...I'll take the risk...". You tell them "well I think this is the best thing for you" they will do it. "oh, you're the expert, I trust you, I put myself in your hands, you do what you think is best". Independence is important to older pts. A lot of these older pts they would rather die of the cancer than lose that independence & end up in a home.	Is happy to decide in a borderline case e.g. Mx vs. WLE will choose Mx.
S26 Male Low PET	The ones who make up their mind the same day tend to be the ones who know it's cancer. People out there they think that surgery's evil, there are people isn't it who say "don't go to surgeons".	Surgeon can only do so much info-giving. Specialist nurse then gives info and explains a bit more.	"what would you do Dr, what is your advice?". The ones who make up their mind the same day tend to be the ones who know it's cancer, their decisions are a bit more easier. Some pts merely say "no, I don't want that". They take the choice and say "doctor, would you mind if I just take on to this and I don't want surgery".	They kind of ask you that question don't they "what would you do doctor, what is your advice?". If I honestly feel that surgery's the right thing, and if it is my mother and that's what I want for my mum, I tell them , I don't hesitate.
S28 Female Low PET	Surgery's viewed as a big thing.	This is a group where we do weigh and give the info because often they don't have enough social support or access to the internet or the ability to read the info.	They know if they're not fit, that it doesn't make sense to tip the balance of their life. They feel that they are at that part of life where what are they going to gain by chopping parts of the body.	Generally speaking I tend to make the pts decide... encourage them to discuss it with the family members... BCN... they can often tease their worries and their issues that is stopping them making the decision. Give them time. I don't tend to decide for them.
S29 Female Low PET	Think they're too old to be offered surgery, as if they don't feel they're worth treating. GP may have said "I think this is cancer, but don't worry, they'll just give you a tablet". Bad experiences of RTx... some elderly pts have very strong views that they don't want RTx. Widespread perception amongst the elderly that because we stop breast screening, it means they are no longer at risk.	Have written standard info. Have to make a pretty immediate judgement really, there and then in the clinic as to whether you feel it's appropriate for them to have that info or whether you think it might be scary.	If they can't make up their mind. This age group will be more likely to take on board what a consultant says simply because they're a consultant... less likely to be influenced by the media and by the internet... more influenced by what their relatives feel and wanting to do what they think their family wants them to do.	I think I've already told them what I think is the optimal Rx, which is surgery... I think if they can't make up their mind then I think then they should have time to think about it... I would probably rather they had a trial of endocrine treatment just to see whether or not they got a response. Rather than potentially twisting their arm to have an operation, in case anything happened.

<p>N06 Female Low PET</p>	<p>No comments.</p>	<p>Bombard pts with a bit too much info. Standard written info about all the Rxs, even if not relevant: <i>opens their eyes to what the other options are</i>. May seek further info to help DM. BCN gives extra info if feels something has been missed: <i>there's times where we might say "well actually, I might have thought about that"</i>. Some pts just don't want to read it, they're a bit panicked.</p>	<p>Pts may challenge Rx recommendation of MDT. Pts may seek for more info on options & DM based on written information given. <i>They don't want to know... they just go based on what we tell them - passive DMers because they're frightened?</i></p>	<p>No comments.</p>
<p>N27 Female Low PET</p>	<p>No comments.</p>	<p>Standard pack of written info. Ask if like to have lots of info. <i>If there's younger women you would look at sexuality, in older women you would try and give them the menopausal things. It is about informed consent, it is about giving them info.</i></p>	<p>They want to actually put the onus back on us to make the decision for them. They listen actually and they're much more compliant sometimes than our younger ladies.</p>	<p>They want to actually put the onus back on us to make the decision for them. We actually say 'no, the onus isn't with us, we can give you the info but we come to a decision as a joint between you and us or the team'. No, it's pt choice we can't have somebody coming back and saying 'You told me' or 'you said I should'.</p>
<p>N30 Female Low PET</p>	<p>Large proportion of pts that come with predetermined ideas. 'I would like to have this, my GP says I can have tablets'. A lot of people say 'but I am 86' or 'I am so-and-so' as though that's a barrier to them having Rx.</p>	<p>Enough info, the right info, and time to consider that info. Standard pack of written info + verbal. It's exploring what's right for the individual isn't it... sufficient info so that they can, in their own time when the shock lessens, consider things and perhaps then come back and say 'I've read this but what about for me?' because they can't all take it in at that time.</p>	<p>Some people have defined or definite ideas on what's right for them. Pts come with predetermined ideas. If they know there is a choice, they come and say 'I would like to have this, my GP says I can have tablets'.</p>	<p>They're given the pros and cons of both aspects and I think it's true to be said, if someone is struggling to make a decision then they're encouraged more so to do what feels right for them. Generally speaking, most people are guided but they're not told what to do.</p>

Appendix 16: Sample interview transcripts

Interview S01, on 29th January 2013.

- Jenna Morgan (J)
S01 I guess the first thing I should ask you is what treatment options you'd normally consider for a woman that presents over 70 with operable breast cancer – what would you, what would the options be for treatment?
- S01 OK, well firstly I think one has to try and treat them as well as you would treat a woman of any age. And make sure the treatment is adequate to deal with her cancer but also takes in to consideration her ability to tolerate the treatment. And that can sometimes be very straightforward because a woman of 70 may be as fit as a fiddle and need normal treatment as per the protocol for a woman of any age. It obviously has to take in to account her fitness for surgery, not necessarily surgery under general anaesthesia, fitness for chemotherapy, Herceptin and radiotherapy, and the appropriateness of those treatments.... It also has to take into account her preferences, which you know, she might be completely happy to have standard treatment but she may have things that she's not prepared to consider. So I think, you would ideally like to treat every woman in the most aggressive way that you possibly can, that she can tolerate. But you also have to recognise that for someone who is very frail, that treating her with, you know, full mastectomy, axillary node clearance, chemotherapy, etc, etc, may be more treatment than she actually needs. And if she's going to die in the very near future from her pre-existing lung cancer, or you know, the fact that she's got COPD and is forever in and out of hospital with pneumonia then you're not doing her any favours by treating her with that degree of aggression. So, unfortunately there are no hard and fast rules; there is no manual that says "if a person has this, then you shouldn't offer her chemotherapy". It's very much left in the domain of the physician's assessment of likely outcomes, and it's a very heterogeneous population, and very much where the art of surgery comes in to play. The art of medicine, rather than the protocol-driven, "this is the best research-driven, level one quality evidence", "This is what you do when you've got this".
- J So going on from that, we've talked about the normal what you would like to treat women under 70. Would you consider primary endocrine therapy for any patients or all patients? Is it something you would consider for everyone in this age group?
- S01 Primary endocrine therapy obviously is only appropriate for someone who has got an oestrogen-sensitive tumour, so that automatically rules out about 15 or 20% of the population in this age group. I think it's something that should be reserved for people who will struggle to get through standard treatment.
- J Right.
- S01 So if you've got someone who is clearly fit enough to have an operation then you should offer them an operation, and that doesn't necessarily just mean an operation under general anaesthetic. We know that primary endocrine therapy will control breast cancer for an average of 2-3 years. Some women that will be 10 years, some women it will be a year. And if that woman goes on to live for more years than that then you've got to change management. So I think, yes, I do consider it for women in this age group, but I try to base that decision on whether or not they will tolerate an operation, and also whether they want an operation. So there will be a group of women where, yes, they might tolerate the operation, they might have major problems or complications and the risks of surgery may be higher than they would be on average – and for those women you may want to offer them a choice of treatments. And then there will be other women who are clearly not fit for a haircut in whom you just say "I'm sorry, I don't think you'll get through an operation and I think we just need to treat you with tablets". So if you like, there are three categories, there's women who you are not even going to talk about PET to because

clearly they need an operation, it's the best thing for them, and you shouldn't really be messing around with anything less than that. Women who are borderline could be offered a choice and women who are clearly not fit for any form surgery who you should just offer primary endocrine therapy.

J Are there any other factors that you would think about that influence your decision. So we've talked about their level of fitness and their preference, and the ER status. Is there any other patient or relative factors maybe?

S01 I think patient views obviously have the primacy. Relative views become important if you've got a patient who's perhaps either not willing or not able to make the decision herself. So some women really don't want to make that decision, they think it's the sort of thing that a doctor should do, or they want to defer the decision to their relatives, carers, whatever, and they're quite passive and don't really want to get involved in thinking about things. Other women aren't capable of making the decision because they don't have the cognitive capacity to retain enough information to be able to make an informed decision. They may have a preference, even though they can't balance or weigh up the pros and cons, and you have to respect that. So you might get someone who, perhaps has got not such a good memory and can't really weigh things up but who says "oh, I don't want an operation" and again you can't ignore those views, even if you think that that's perhaps not the right thing for them. Other things would be, say, the Herceptin receptor status. We know that Herceptin sensitive cancers are less likely to have a durable and good quality response to anti-oestrogens, although some of them do. The type of tumour, mucinous tumours, whilst they are generally quite indolent and usually oestrogen-sensitive, don't usually get smaller on anti-oestrogens because it doesn't get rid of the mucin and they just sit there and are static response and so people sometimes feel or perceive that they haven't responded as well even though they have been inactivated they may not disappear which for some women might freak them out a little bit. Then you may have tumours where, say for example, they're locally advanced, and an operation might ulcerate and be painful and if they are on board that might be a better way of getting symptomatic control. And for some ladies surgery may be, if it's the sort of surgery where they need a mastectomy rather than a lumpectomy, you might be inclined to say well she'd probably be able to cope with a wide local for a small tumour under local but you wouldn't be able to do a mastectomy under local, or doing a mastectomy - I don't know if you've ever done any - trying to do a mastectomy under local on a large breasted woman is not a nice thing to do to someone.

J No I can imagine.

S01 The other thing is your anaesthetist because some anaesthetists are happy to put in epidurals and intra-pleural blocks and those kind of regional techniques which will permit you to do full surgery in an awake patient. Another anaesthetist not familiar with that won't do that sort of thing or aren't very good at doing it and also different anaesthetist have different thresholds for who's fit for a GA, some of them will anaesthetise anything that's breathing whereas others will send the patient home because they've got some minor problem with their blood pressure and "ooh no, not fit for surgery!". So, I mean usually most surgeons, I think, will be used to working with their anaesthetist and will know where their thresholds sort of lie. But obviously it's very much a team effort. The other thing would be breast care nursing, sometimes breast care nurses can be a little bit protective and maybe do have an influence on what women want and that may not be something that's said when the surgeon is there but when the surgeon goes out of the room the decision-making happens in consultation with the relatives and the breast care nurses and the patient. And the BCN may impose their views somewhat and maybe "do you really want an operation" or the reverse "you should really have an operation". So I think they do have a very important role to play and if they have a particular view what might be best for that particular woman then that can have an influence.

- J What are your feelings on formalised assessments; so anaesthetic assessments or these Geriatric Comorbidity Scores?
- S01 If I've got someone where I'm not sure about the risks of surgery for them, and these would be a lot of the people who would be in the borderline group, then I think having a formalised anaesthetic assess is very useful. Not necessarily using geriatricians to get involved but if they've got a treatable co-morbidity, for example if they've got uncontrolled hypertension then going along and seeing a physician to get that under control. If they've got badly controlled cardiac problems, say AF or something like that, then again that could be improved which could make surgery safer. We have a system here where they go pre-op assess and an anaesthetist will review them and flag up any issues and then refer them on for medical management and optimisation. And I think sometimes it's clear, you know, if you've got a very frail lady who's in a nursing home who's slightly demented, it's going to be fairly obvious, I think that that sort of person is probably better off with tablets. If you've got someone, who say, gets a bit of breathlessness going up stairs, gets chest pains doing certain activities you might want to have an anaesthetic assessment: "what is the risk" – let's put the actual risk of an anaesthetic into the mix.
- J Before you make that decision?
- S01 Yes. And so you have several consultations with them "OK, the anaesthetist says your risk of surviving an anaesthetic or not surviving the anaesthetic is 10%, your risk of surviving going on tablets is 100% but it may not work for very many years. So you've got to balance the immediate risks of an operation with the long to medium term risks of primary endocrine therapy not working for you", and you then have another discussion about it.
- J So it's sort of about providing all the information to make a balanced decision between you and the patient.
- S01 And sometimes going down that route. They may not want to go down that route because they may say "well actually I'd rather just try the tablets" and that's the other thing, there's no harm in most of them in starting them on the tablets and giving them some time to think. And see whether the tablets work, how they feel with the fact that they may have a tumour that's still palpable. Some women might find that a little disturbing, although from previous studies that we've done most women actually if the tumour is shrinking, found that very reassuring because they knew that the tablets were continuing to work. So you give them a trial of endocrine therapy and if it's not really working very well, say bring them back in 3-6 months and reassess, and then go down the road of anaesthetic assessment at that point. So, lots of different ways of doing it.
- J Specifically to surgery and PET, what do you feel are the risks and benefits balanced up against each other?
- S01 Well the risks of surgery are all the risks of surgery; the anaesthetic risks, pain, discomfort, hospitalisation – the fact that a woman who is brought into hospital out of their normal environment, which can result sometimes in a loss of function, which can last for quite some time. They often drop a level of functionality after an anaesthetic because it kills a few neurons. And there's a recognised thing that happens in older people where they can have a long term period of being knocked off after an anaesthetic, I've forgotten what it's called now, but they will often lose functionality after a hospital stay, they can become confused. The risks of surgery in terms of pain, disfigurement, lymphoedema, mutilation, haematoma, bleeding, blah-blah – the list goes on. Balanced against that, it's very good for treating the cancer in terms of local control. You have to also remember that the metastatic disease control is the same in both groups because they'll both be getting anti-oestrogens.
- J Yes.
- S01 So really what the surgery gives you is enhanced local control. The studies that have been

done, the RCTs that have been done, they show that local control is inferior with PET but metastatic control is the same because they've had the same level and so long as you're following the PET patients up and as soon as the disease starts to progress, you cut-and-run type of thing, then there shouldn't be any difference in mortality and if there is it's probably, I think with the RCTs that they did the difference in mortality was probably the patients who had ER negative tumours who'd been included inappropriately because they didn't test in most of the RCTs – so they were effectively a delayed treatment arm and nothing else because they were effectively going on placebo...

J Not getting treated...

S01 So it's very difficult because you can't go back and re-test those patients in the trials to take out the ER negative group. But the percentage difference in mortality was such that it could have been completely accounted for by the ER negatives included in the endocrine arm and so in terms of if you had a properly selected cohort, then I suspect the mortality between the groups would be identical and it's purely an issue of local control. So you've got the upfront risks of the surgical route, side effects of surgery, pain, disfigurement, blah-blah and the certainty of local control. On the PET arm you've got none of that but you've got the uncertainty of local control and you know that about 1/3 of them will need a change of management and that's in the trials, but they weren't very well selected. So I suspect if you selected them better for a frailer cohort than was included in the trials you would have potentially a much higher local control rate, much more similar to the surgical arm. Bearing in mind that in the surgical arm, even if you do a mastectomy, you would have a 10% recurrence rate at 20 years – 10% at 20 years following mastectomy – so if you've got a 30% failure of local control in the PET arm but 10-15% of them had ER negative tumours and therefore were on no treatment it's not much different in local control really.

J So by that logic then, just out of interest, had they selected better for the ER positive patients particularly in the PET arm, do you not think that actually the overall survival might have been higher in the PET arm because you've got the complications of surgery. S01 Might have been because some of them might have died as a result of surgery, but I don't think that any of the studies actually had any immediate deaths. Breast surgery is very safe and I think the reported mortality overall from the national mastectomy and reconstruction audit is something like 1 in 1000.

J So very low.

S01 Very, very low with modern anaesthetics and I think if you look at older studies doing mastectomies and clearances it was sort of 1%. So it's a very low mortality but it may be higher if you look at a subgroup who are elderly and frail but don't think we have that data but I did a review of surgical studies from a few years ago in older women and even in older women it was low. But it's not so much about the mortality of surgery it's the morbidity of surgery.

J Just a quick question, do things like cost and targets influence your choice of management at all...?

S01 No.

J Not at all?

S01 No. I don't think they do for many clinicians, or any clinicians to be honest. I think you try to do what's best for the patient. Targets will influence us in terms of the quickness of getting them in...

J But not that actual treatment they receive...

S01 But not the actual treatment decision. Costs again, never... it never enters my head to think about the costs.

J Ok.

S01 Other than a sly smile to think "this is expensive, snigger, snigger". Sorry.

J What sort of factors influence your strategy or have evolved your strategy – is it a mixture

of things like evidence base or personal experience, or – what sort have factors have culminated?

S01 Well in my case it's evidence based because I've read most of the papers on this subject...

J Indeed. Written some of them too...

S01 Yes. But I think it is partly experience as well and I think – the whole reason I got interested in this was because one of my colleagues used to put everyone on PET if they were over 70 and I just used to get fed up with seeing them come back with failed local control and then having to go for an operation, you know, several years down the line.

J And then of course they're much older and frailer at that point...

S01 When they're older and frailer. And that made me aware of the fact that this over 70s policy that was prevalent around 20 years ago was just rubbish. You know, it's just not a good way of doing it. Because it makes the surgery more difficult technical and less pleasant if they have to have a local anaesthetic operation when five years earlier they could have had a GA operation. And so that personal experience of seeing how it can be inappropriately employed was quite influential for me. And I guess you have a few patients where you see an old lady who is frail who is inappropriately had a major complication – I had one lady who had a stroke following breast surgery. She'd not been one that we'd considered for primary endocrine therapy and there were no risk factors or red flags but you suddenly realise that actually this kind of surgery can have major complications. I've also had a lady who had surgery as her choice and ended up having a significant hypotensive episode because she had post-operative bleed. She didn't die, but she might have done.

J Yes.

S01 So you realise that surgery has risks that can potentially be sometimes better avoided, and you realise that PET when inappropriately used can just delay problems. And I've had one or two patients where there has been failure of local control because they've been pretty frail and rubbish and you think they'd never get through an operation in a million years. And so you put them on PET and then they don't die of something else.

J They don't act the way you expect them to.

S01 You think "How can they possibly be alive?" And they keep coming back and then you're into palliative radiotherapy and all the hassle that that has because you've run out of endocrine therapies. So I suppose I've been around for long enough now that I've seen a few where we have lost local control and I've seen a few where we've had some major complications of surgery and so you see both ends of the inappropriate spectrum.

J What about the amount of information you would give to a patient or relative – would that again be based on the patient or.

S01 Yeah, I think the right answer there is as much as they want. And if that means you sitting down and talking to them several times over several hours and talking to the relatives and going over it all again when they've had a chance to think about it then that's what you give them. And if they just want "no doctor, you decide what's best for me, I don't know, I'm not the expert" I mean I've had that said to me many times. And in that situation you say "Well I'll tell you a little bit and let you have a little think about it and then if you want me to decide then I'll decide for you." So you try to give them information but you obviously have to be guided by them.

J And what do you think the patients sort of feel about either treatment, what do you think their main concerns tend to be?

S01 I think by and large, they both tend to be very well tolerated. Most of them are pleasantly surprised by breast surgery because usually it's better than they thought it was going to be. You'll have a few who have significant side effects who struggle with them – so I've had one lady who had lymphoedema after surgery and said "well if I'd known this was going to happen I wouldn't have let you do the operation"

J Sure, and hindsight being a wonderful thing.

S01 Hindsight being a wonderful thing. And they all think that PET is great because it's the no risk scenario in some respects, certainly to start with. And you know, we've done some research on it and the opinion is that both of them are good options for those where it goes well.

J Yes, right. The appropriately selected patients.

S01 Yes, that's right.

J Good. Well I've asked my main questions. Are they any sort of bits and pieces that you'd like to put forward about either treatments or treatment in general of older ladies with operable breast cancer?

S01 No. I think older ladies are changing though. I mean, when I was a newly qualified doctor, there was generally the view that anyone over 70 was too old to have anything. And I remember women of 70 coming in and having palliative treatments for cancers, like ethanol injections – rectal cancers, not breast cancer. And that was normal, you just wouldn't consider them unless it was, well desperation I suppose. But you know, nowadays 70 is not regarded as old.

J So the definition of old is changing, and broadening perhaps?

S01 I think the definition of old is changing. Yes, and so I think what used to be "70 is old" is now become "80 is old" and things have by-and-large moved with that. I mean my step-mother is 71 and she lives a completely full and active life, drives a car, drives to see friends down in Cornwall, you know, just does all the things a normal woman would. And you wouldn't think she was 70 and I would be horrified to think that anyone wouldn't treat her properly for cancer if she got it because she's as fit as a fiddle. And then I've got my husband's father who's in his mid-80s and is frankly, I wouldn't touch him with a bargepole for anything because he's so unfit. So I think things have changed – they've moved up by about 10 years in the 20 years I've been practicing and I suspect they'll continue to shift and we've got to keep moving the goalposts to match up with it.

J So do you think that this research that we do now will be still relevant in a few years' time.

S01 No, it will probably need to be continually revised every 10 years just to see where the cut-offs are. Although I think in terms of age they need to be modified but if we look at things in terms of the biology and fitness, and study that properly we won't need to take age into account. Then we can just base it on somebody's biological fitness rather than their chronological age, which is what we should be doing now.

J Do you think it would be useful to have a protocol, if you like, or a tool that would allow you to put these things in to help you to decide?

S01 I think it would, I think it would give useful guidance because I think everyone's got different thresholds for what is and isn't appropriate at different ages. So I think having a bit more formal guidance and maybe some screening tests that are fairly easy to use – that give you a good- and I think the things that come out will be the functional assessments, rather than disease-related, it will be "are you living independently", "can you wash", "can you dress", you know, something like the IDL and the ADL and I think you could do a very rapid screen on that and if you can live independently you should probably be having normal treatment and if you are not living independently then you should be considered for something else. And they're fairly quick assessments because they're only about 7 or 8 questions, very, very quick to do and I think that's probably one of the key things that will come out of this is to whether or not they're robust enough to use in normal practice, sensitive enough to make the right decision most of the time.

J Do you think it's important to try and standardise it or is it less about standardising and more about...?

S01 I think in terms of standardisation of practice, the patients are the variable, the clinicians should be doing what's best for the patient – and that should vary between surgeons. So yes, there should be a tool that's based on the characteristics of the patient not the

preference of the surgeon, and at the moment everything's based on the preference or the opinion of the surgeon as to their fitness and there's no guidance and everyone's got different thresholds and that means that people haven't got a clue what they're doing.

J Well, that's what we hope to investigate a little bit more here.

S01 Yes.

J Well I don't think I've got any more questions.

S01 No I think that's fine.

J Well thank you.

Interview N34, on 5th November 2013.

- Jenna Morgan (J) So this is Jenna Morgan interviewing N34 at "PLACE" on the 5th of November. So, N34, if I could just get you to tell me a little bit about you, your role, how long you've been practicing and that sort of thing.
- N34 Right, well I'm one of the breast care nurses, so really our role is to support patients, as they need, both emotionally and physically through all of their treatment and we don't disappear afterwards either, so it may be patient advocate, information giving, understanding the information they've been given, clarifying that maybe down the line they might come back and talk to us after they've seen the doctor. And ensuring they've got information they need they're having surgery so they're well prepared and supported them afterwards as well. I've been working 25 years probably about, I started as a ward nurse looking after breast patients among others and I worked my way up to being the ward sister so I've dealt with inpatient breast care for many years and I've done this role for about 5 or 6 years now.
- J Ok, and in this unit, how... what... let me just start by saying we're talking about older women, so we've got a general cut-off of over 70 but appreciate that older patients vary greatly, and we're talking about primary operable breast cancer. So when we have a patient presenting to this unit and they are elderly and they present with primary operable breast cancer, what treatment options are they usually offered here?
- N34 Well I would say, well what do you call as elderly really I suppose, I think any lady who's fit for surgery is initially offered surgery in the fact we look at age more medically than actually years if that makes sense? But there are some ladies who perhaps have a problem with surgery and then they can be offered sometimes oestrogen tablets, you know, hormone-based treatment. But that's very much for them to think about and they're given all the information and for us it's to make sure they've got that accurate information, to be able to make the decision that they need to. But I think also, often when you're talking about surgery, what they're perception of surgery is, is very different to how it actually is. They sort of perceive it as a big open wound that they're going to be in for a week, and you know, just because someone's 70-, I've got several 70 year olds that have had mastectomies as day cases because they're more than fit for it and when you actually give them the information that they actually need and sometimes talk to someone else who's had surgery they can view things very differently. So again it's for us about seeing, they might be saying no I don't want surgery but very much for us it's about well, what are the issues about that, what's right for you. So for me it's about finding, giving that information to the patient to make the right decision for them and it could be sometimes we use the hormone treatment so they can go on it initially to give them time to maybe have an anaesthetic assessment, or time to find out the information they need to decide what they want to do. And so, you know it's even though they might go on one treatment, it's not the be all and end all. So yes, they can be offered a variety but generally if they're fit for surgery, that's what they're offered.
- J Ok, are they offered a choice as well? Is primary endocrine therapy presented as an alternative?
- N34 Right then primary endocrine? Yes, as rule I mean basically, well yes because what we'd do, I think what – we tend to explain the difference. If having a cure, a potential cure is what they want then that's potentially what surgery will give them. But if they have the hormone treatment, it will never take it away but it could keep it under control for as long as they need. But they need to realise it's a cyclic treatment, and then the options could be that if they don't get a good response, then we might be saying "well, our best option now is surgery but you could be a lot older". So, yes, they're often given, I mean if someone's very keen for surgery, I mean ladies will often come in, know what they want so if they're keen for surgery then that's what they would have as a rule.

- J Yes, ok. What sort of factors, like patient factors, or you know, might prevent or might mean that they don't get offered surgery as sort of the first choice?
- N34 Medical fitness, fitness for surgery at the end of the day. If they're not well enough, you're going to kill them on the table, then there's no benefit giving them surgery. I think that would be the single most important thing. But if a patient really doesn't want it then another option, and you know, you might think just because someone's 75, the thought of having a mastectomy doesn't bother them but there's some ladies where having the cancer isn't the issue, it's having a mastectomy because there's some very glamorous 75 year olds.
- J There are.
- N34 And you know, if they really, really don't want it and they're saying "I really don't want this surgery" there's another option. But as long as they realise, you know, the restrictions of each then that might be another option to do it.
- J What about things like dementia, does that come into it?
- N34 It does, but then again, I've had the situation with a GP where we can't even get her to clinic.
- J Right.
- N34 And I've just had to advise her, I've gone through the consultant today and I've just rung them back and said, you know, she's going to start her on Letrozole as an option because she will comply to that. As she'll know, with a breast lump at 87, she's probably going to have an ER sensitive tumour.
- J Yes the likelihood is.
- N34 So they're going to treat her as opposed to doing nothing. And then I have had problems with dementia patients that won't even comply for having the biopsy and then I can think of one patient off the top of my head this year I think, or maybe the end of last year, where because she wouldn't have a biopsy, I mean it would have been difficult, it would have been dangerous to do the biopsy, she would have fought, we couldn't have got informed consent, that we took the risk and we started her on a tablet and she's still tolerating that really well.
- J Good.
- N34 So it gives you another option when they can't always comply or understand but on the other hand I have had ladies who had mastectomies and actually have come with daughters who have very fixed ideas about what they should be having, but actually can take that information in and the daughters saying, "look she demented she can't have any surgery" but then when we spoke to her she said "I actually do want to get rid of this, I need to get rid of it" and we brought her back again, I think a week later, and she could still remember the conversation and so she's had surgery.
- J Very mild dementia.
- N34 I think the daughter was quite miffed, but actually it was right for her and at the end of the day I'm here for patients to advocate, to make sure they get the right decision for them and they understand that and make sure it's a safe decision.
- J Yes. Ok. What do you think are the risks and benefits of surgery in this sort of, let's talk about the older, less fit patients?
- N34 Well, I guess it depends if they've have a breast cancer that's quite under the skin that potentially they don't have surgery or hormone tablets don't actually control it, they could end up with an ulcerated, quite unpleasant malodorous wound, which actually can be quite unpleasant for someone to have to manage. So it could be that actually for them the option that is the mastectomy is a far better option. Obviously the side effects and potential effects of anaesthetic but these days you'd hope generally if they've had a good anaesthetic assessment they're fit for it but there's always a risk with anaesthetic but ultimately I think the fact that women have choice is very significant because there's a lot of evidence now that women are involved in the choice of their treatment they will cope

and live with it better. And I think it comes down to at the end of the day if it's important for them to get rid of that cancer, and for some ladies it's very important that actually they're rid of it. Just because they're eighty something doesn't mean they feel any different to people who are younger and so it's about making sure that patient's able to give an informed choice and they are able to live with a choice that they feel is livable with. So there could be emotional impacts if you're not going to give treatment and I've got ladies that can't have treatment and have not been able to and are really struggling because they can't have surgery because they can't trust in the tablets. And that can be a lot of support that we need to give for these ladies. So yes, there's obviously a risk of not being able as well as they were before but I think in a majority of cases ladies have surgery because they're picked very carefully and then they are monitored very carefully so if they're fit for surgery they cope very well and most of our ladies are very surprised by how well they do cope. And we even have 70 year olds who have reconstruction believe it or not.

J Yes, I think that's happening more and more now. Still, it's in the minority but they're being offered it. Ok, how often do you think primary endocrine therapy is used here in the over 70s?

N34 I wouldn't know the proportions to be honest. I mean I've got a number of patients that are on it but I couldn't give you the actual statistics for that. I mean we have over 700 cancers a year so off the top of my head, I have a case load of about 200 a year, and they range from like 24 to 93 I think, so off the top of my head, I would say it's the minority because the majority are probably offered surgery because that is seen as being the best care, you know, the optimum care as it were so I couldn't give you, off the top of my head I couldn't tell you I'm afraid.

J Ok, those patients that are treated with it, how long do you think often it maintains control for, sort of on average?

N34 Well again that varies, I've got one lady who's actually come off it after 20 years and had surgery.

J Wow.

N34 Because she got so fed up of taking it. She'd been on Arimidex for 20 years.

J That's incredible.

N34 That's a huge thing for her to say, actually I tell a lie, she was actually on – she wasn't on Arimidex, she was on the injection -

J Faslodex.

N34 Faslodex injections and she'd been taking them for 20 years and she said "I'm getting fed up with this really" so we said "well, you can have surgery" so you know, it's difficult to tell isn't it really?

J Yes.

N34 I mean and that's what you say to ladies it could well be that it's going to last you for life, it's true I've got ladies that have been on it for 10 years but realistically you're looking at maybe 3 to 5 years before you need to change it but certainly, the chances are if you get a good response to one, you'll get a lesser but a good response to another, and vice versa obviously.

J And what do you think patients that are treated with primary endocrine therapy feel about the treatment – do you think they like it?

N34 I think generally most of our older ladies get on with it pretty well actually and I mean if they don't you hear about it because they ring us. And they're also good at self-monitoring, if they're worried about anything, you know we obviously give them the information that if you're worried it's getting bigger or it's harder or you're worried you ring us and we'll bring you back quicker and they will ring, without question. But most ladies get on pretty well. I mean I've got a lot of ladies 75, I mean if it's a flush or something I've never stopped getting flushes since I was 50 which is a bit worrying for those of us that have not had them yet. So I'd say it's tolerated pretty well to be honest and I think maybe they've perhaps got

a little bit of arthritic pain anyway so because they're lifestyle is slightly slower it perhaps has less impact for the majority of ladies than perhaps someone who's a bit younger who then gets the you know, side effects, bit of joint stiffness because it's something they've been coping with for years probably.

J And what about in terms of having the lump still there, do you think women are worried by that, bothered by that?

N34 I think there are some that are in which case they would probably opt to have surgery and that certainly is one of the issues for ladies, especially, I've got one lady at the minute, she wasn't actually fit for surgery but she had to go and get fitter, get her chest sorted out and things and she's had the best part of a year almost on hormone treatments, but it's not something we can feel so she couldn't see it, so we had to arrange for her to come back and have it scanned every time she came regularly. And although she couldn't feel the lump, the fact this was here was really bothering her so to see the scans and see it was actually shrinking, still needed a lot of reassurance for that but for her, surgery was always going to happen because that's right for her but at least she did it safely. And I think if ladies really are bothered by the lump then they opt for surgery if they can do but some ladies are on the other side of the coin, having the lump and seeing it respond to the tablet is also quite reassuring for ladies so, somebody says, "oh, it's gone and I can't feel it" and they feel quite comfortable with that. So it's each to their own really.

J What about the follow-up, do you think women are bothered by the intensity of having to come back?

N34 Well, I'm going to say yes and no to that one I suppose because we don't do as much follow-up now because we tend to follow them up initially, which obviously they're very relieved and again maybe at six months and then it could be that after a year we discharge to the GP, now some ladies have a real problem with that actually "how are my GPs going to know?" and "I'm not happy with it" and some ladies are quite happy to do that so I guess that's going to be different for everybody. I mean it is an afternoon clinic, with idea it's slightly easier for some ladies to get in if they're a bit slow getting up in the morning. But I think the issues more sometimes with relatives than it is with patients, particularly the old clinics of old when we first started were huge because we followed up everybody, there were horrendous waits, but now we've streamlined those now, they're in and out pretty quickly actually and I don't think a major... it's a bit of reassurance sometimes coming for clinic. So I haven't heard anybody really complain like they used to many years ago. And if they were finding it difficult then that might be something as a breast care nurse we'd be saying "can we get the Gp to do it" so there's flexibility within that.

J Yes. Ok. What about those patients then that say "I'd rather not have surgery" – what do you think some of the reasons are for patients refusing surgery or standard treatment?

N34 A lot of it can be fear, because they don't know, not enough information is often the case. Or they're fear of dying on the table. They might have a relative who's had surgery and had some adverse response to it. They think it's too big a thing to have done for them, usually. Or they just think they're that old they're not bothered about treating it at all sometimes they say "I'm too old for that to bother me" and feel too frail for it, the thought of having an operation and being put to sleep for anybody of that age is quite an enormity, you know. Well, I suppose not anybody, I've got 80 year olds that wouldn't think twice about it who are playing golf four times a week. So I think it's the enormity of surgery and their perception of that surgery. Could be fear of lying flat, I've got lots of ladies who will not have a mastectomy, and the thought of a mastectomy it is just not something that they will even entertain. So it could be the nature of the surgery, it could be the fact that a general anaesthetic seems like a huge thing to have and it's funny isn't it, I've had a lady quite recently, I think she's about 85, quite recently had major bowel surgery, had basically half her insides removed and yet was really worried about having a mastectomy and I was saying "in comparison, what you had nine months ago" and again you see it's the

anaesthetic, their perception of it, the mastectomy has a huge stigma in women of that age as well and her perception was that she would have a huge open wound. They can't see how it's going to close and she thought she'd have a huge open gaping wound on her chest and they can't envisage that. And that's quite common actually for people to think like that.

J Of course. I see.

N34 And when you actually talk through the surgery and talk about the recovery and you show them the picture of a mastectomy, or a photograph, they're actually quite surprised and think "actually, that's not that bad, I could cope with that". A lot of it is lack of information I think and fear of the unknown, although it may be a very definite "I don't want to have a mastectomy" and that's fine.

J Ok. And in those patients, particularly the younger, fitter end of the spectrum, where they sort of say "oh, I don't really want surgery" how is that approached, do you, obviously not try and change their mind, but do you try and you know...

N34 I'm not here to change anybody's mind.

J No, that's what...

N34 I think as a breast care nurse, that's what's pivotal to what I do. And sometimes you'll sit there thinking, you know, I guess we're all going to be prejudiced to some degree.

J Of course, yes.

N34 A patients will regularly ask me what I would do and I quite honestly say I don't know what I'd do until I was sat in that chair, what I think I might do and what I would really do might be completely different and so, you know, it's about laying out the facts, laying out you know, this is the pathway of this option, this is the pathway of that way. And some ladies say "well if I do nothing what's going to happen?" and these are the pathways and we will support you to do whatever one's right for you, but for us it's sometimes looking at "what is it that's making you think about that?" So, for us it's much more about the nice, the emotional aspects behind that. So it could be that someone's had a mother who's died gruesomely of breast cancer or someone who's had surgery and that didn't go well. So, for me it's about looking about "tell me what the issue is for you here, what is it you're feeling, what is it your concerned about?" Often if you ask ladies why their crying when they've been given the diagnosis. Well you might say, "well of course you know why they're crying" but often actually I will say "I can understand this is really distressful for you, it would be for anyone, but tell me what is it that's making you cry at the moment?" and it's hardly ever the cancer. It'll be something else that's happened.

J Oh really?

N34 Like my sister's died of breast cancer or I looked after my mother when she had breast cancer or how am I going to tell my children or you know, so it's very rarely about the cancer because probably they knew that was coming to be honest. And it will be some other, and basically people make decisions on their past experiences often, so for me it's very much about finding out what the underlying things are and that doesn't have to be done on that day, you know, we'll probably bring them back another day and discuss that. And sometimes when you look at those issues and you discuss them then things are not so frightening and they can make different decisions but if they want to make that same decision, then I'm part of an advocate, I'm here to help them do that, make that decision.

J What about the patients, so the opposite, and you briefly mentioned it, those patient's where they're offered a choice of the two treatments and they go "I don't know doctor, you decide" and they try and make the doctor decide, they try and make you decide...

N34 That happens quite commonly actually.

J How is that approached, both by your surgeons and by yourself?

N34 The surgeons tend to say "well you need to talk it through with the breast care nurse" but it's important that you make the decision for you.

J Yes.

N34 And again, a lot of the things, again I think when you're given choices, people have the perception that there's a lesser choice.

J Well there's a right and a wrong answer, yes.

N34 Yes and it's very much for us to explain the rationale behind that choice and actually you've got two very good options depending on what you want out of it. So forget the options, tell me what you want out of this treatment. You know, if you come in, where do you want to be in two years' time sort of thing regarding your breast cancer? And they may say "well I want to keep my breast and I don't want to have gone through surgery", well, "then let's look at the two options again and you'll probably find that one of those will fit very well". And other ladies say "well actually I want to be alive as long as I can" although we can guarantee that of course, but you know, "I want to be rid of this, I don't want to have anything there". You know, it's about what do you want out of this because one of these options will fit that very nicely.

J That's a really nice way of thinking about it.

N34 So you almost take the complexity out of it.

J Yes, nobody's ever said it like that before. That's a really nice way of thinking about it.

N34 Well we do this with every choice because everyone gets choice in breast cancer.

J Of course.

N34 It's like well actually you've got two right choices – you've got to be careful not to do that (Participant was gesticulating) – you've got too right choices, the right one can only be...

J Why not that (copies participant)?

N34 Because it's balancing breasts

J Oh balancing breasts, ok!

N34 So you've got two right choices

J Right ok.

N34 So, but it's very much about that and ultimately it is a lonely place to make that decision because the evidence says if you are involved in that decision, you'll live with it better but actually it's you that's got to live with it.

J Yes.

N34 And the other thing is you often have a lot of other people's opinions, particularly with the older patients and you have to cut them a bit and say at the end of the day, people ask me what I might do and I would say I don't know until I'm in that situation and lots of people have opinions about what people should do but if they were in that position and I've had people who have been in that position and made a very different decision because at the end of the day you live in your body not anybody else and it's you that has to be there in a years' time living with your decisions so it is something that you have to do but you're not going to make a wrong choice. It's a lifestyle choice at the end of the day it's not a medical choice. We've done the medical choice, you've got to work out what's right for you, your personality and it's a lifestyle choice so we sort of take the medial bit out of it to help them choose really.

J Ok. What about, what affects the amount of information that you give to patients after a new diagnosis of breast cancer?

N34 Well I think they all have a deal of information but sometimes we will stagger that or it will be followed up. Interestingly actually, quite interesting, we have a woman recently who seemed absolutely lucid. Came on her own, kept her son outside the office and there was just something that I wasn't sure about this woman. She was going to go on tablets, she definitely didn't want surgery and I don't know whether you just get an instinct but she seemed to take it all in, she took the information in, she took the leaflets, she took everything, including my contact number and I rang her up at the end of the week and she had no recollection of who I was. Claimed she'd never had any conversation and been told she'd got breast cancer and knew nothing and hadn't got in contact with her GP, and had no paperwork. So I said "just do me a favour, just go and look in your bag and see what you

can find” and she suddenly found these leaflets and then remembered everything, absolutely everything, and I said “I’m Claire the breast care nurse” and she said “oh yes, I did meet a nurse and she was called Claire” so then what I did then was to ring the GP – I’ve forgot what the question was now.

J About information giving.

N34 Yes, so I actually rang the GP, had a long chat with the GP. She called her in, sorted her out her tablets and said “I’ve obviously got some concerns whether you’ll take it” and I’ve just followed up with calls and she’s been absolutely fine since. So whether it was shock or stress or some degree of both and I’ve got a feeling that the shock maybe has exposed a very early stage of perhaps something

J Yes, gosh.

N34 But then I would follow that up with a phone call which obviously, and I think instinctively sometimes you know, or sometimes patients will come back to see me. Often we see a patient maybe even after surgery when they’ve had results or even at diagnosis, it’s too much to do it on the day, they’re too upset or they’re too – it’s just too much – so we would bring them back and they have what we call a nurse appointment where we have an hour aside with time in the counselling room. So it’s just that hour for them and it’s their time to fire at everything and maybe I’m giving information or filtering the information that they need from the conversation. It’s titrated to them.

J So it sort of varies on what they need.

N34 Certainly, obviously they need information about the tablets they’re having and basic stuff but if there’s other issues for them some of them will need some counselling to sort out, some of them might need a bit of information or red cross or we’ve got boots macmillan support that we can tap into as well which is really useful.

J What about sort of information needs of family and things like that, does that sort of impact on...?

N34 Well we treat everybody. I mean if a patient wants us to, I wouldn’t talk to anybody without that but I’ve got several patients where I’ve got daughters all over the place and it’s all written in my notes, please speak to daughter who rings up and she had a choice to make for her surgery, because sometimes they’ve not only got a choice of hormone tablets but they’ve got a choice of surgery too.

J Which surgery to do, yes.

N34 And a real mess, so yes, I’m talking to daughters all around the country so, because she was saying “I’m not having this because there’s no one to take me for radiotherapy” but the family are saying “of course we’ll take you, it’s no issue at all”. So we got them all in a room together and said “right then” and she made a decision, they made it as a family, I think for her it was important. Yes, and often family come and it’s very important that they’ve got somebody who’s perhaps, we always encourage them to bring somebody because they need that support anyway, another pair of ears.

J Yes.

N34 But that can sometimes, they can have very strong opinions, you know, about what that person should do and that’s very difficult sometimes but on the other hand, family are family and they’re going to support that patient so they’re key. And I’ve had twelve people in a room before now, a whole family.

J And in terms of making these sorts of decisions, is things like life expectancy, is that sort of discussed?

N34 Well I think it always is when you’re talking of potentially of...

J Outcomes?

N34 Yes, if someone’s medically fit for surgery then you’re saying, you know, you’re life expectancy is relatively good and I think when you’re talking about what the evidence is with hormone tablets, in many cases these tablets will last as long as they need to but you don’t know that for sure, and I guess now people are living longer and longer, what was 70

- ten years ago may not be quite what 70 is now.
- J Yes.
- N34 And so, yes, you're obviously looking at life and ladies will often raise that on their own and will get it and say "well, I've only got five, I haven't got much longer to live anyway" so of course the tablet will be fine, I'll not be here, you know, whatever and you suggest to these ladies that they might live to 100 "oh, no I don't want to ever be that old" you know, so I think a lot of these age group have looked at that themselves and might volunteer it to some degree.
- J Yes, ok. And what about things like decision making tools, or aids, do you think they can be helpful when making this sort of decision?
- N34 Yes, I mean, often, sometimes it depends, sometimes you get to know your patient and sometimes just writing things down, you sort of say "just get a list put your pros and cons, pros and cons and you'll find that all of a sudden one of those columns becomes..."
- J Really long.
- N34 And to actually see it on a piece of paper, becomes visually "well of course that's what I want to do", you know so yes, and we can, we will pull in some of those if we feel it's necessary. Having said that, you know what, these ladies have been making decisions all their lives and actually their decision-making skills are actually pretty good and you give the information and time and take the crisis element out of it and actually they're very good at making decisions because they know what they want at the end of the day. These ladies have gone through big things in their lives and often have got their lives very much in proportion and I think you learn a lot from these ladies actually.
- J Do you think it's more the younger ladies that struggle in comparison?
- N34 Perhaps. It can be, sometimes. I think it comes down to the individual, greatly so. But they've got a lot of, you know, when you get older, they've got a lot of living experience to fall back on, they might have lost a spouse and in the greater picture, having breast cancer is not the biggest thing in their life and that might sound silly.
- J No it doesn't.
- N34 But they've developed skills, you know, they're pretty savvy these ladies actually. I take my hat off to them, they're a fabulous group of patients actually, so yes.
- J I think one of the reasons that we're doing this is because of the amount of variation across the country so if you look at say, London and Oxford, 90% of women over 70 get operated on but in comparison to our units like Sheffield and Derby, where only about 60% of over 70s get operated on – what do you think might cause a variation like that in the way older women are treated?
- N34 Choice? I mean ultimately I would say it comes down to choice, where it's suitable, and obviously you get women who aren't fit for surgery, and I guess it depends how many of those ladies are coming for screening, because some will pick up from screening. And if your uptake for screening at that age is not as good then you're not going to pick up so many ladies maybe. And again it depends what level you're picking up, perhaps the bigger lumps are not so operable, I don't know. But certainly I think we treat our ladies like anybody else, it's about choice and it's not about – perhaps ladies are not given the choice I would have to argue. Or it's not given in a way, in a non-biased way possibly. And that's something we all, you know, sometimes you sit there and I'll say "I'm not telling you that one's better than the other" because you think you've perhaps done that and so I say "I'm telling you now there's no right or wrong here, I'm here to give you the facts, ultimately it's what you feel's best for you" and I sometimes hear myself saying that and think "am I sounding a bit biased to one or the other" and ultimately it is, I think, we treat our ladies with autonomy and their given the choices that they want and I think we give them information to make a choice. They've got the information and I guess the information is given differently or whether it's a cultural thing, I don't know.
- J Because that's my next question is about how much impact you think we as clinicians and

- you are breast care nurse have on the decisions that these patients have to make?
- N34 I think massive in that group, I think they're very much in awe of medical staff still, and we tell them not to be!
- J Yes!
- N34 And I make it clear, I tend to say "I know I wear uniform but at the end of the day, have no doubt about the side of the fence that I sit on, it's very firmly on your side". And I try to de-medicalise everything, but there's very much in, you're talking about a generation still that think basically they come in they'll be told what to do and treat doctors in an ivory tower. I think in 20 years' time that's going to be extremely different.
- J I was going to say, I think that will have gone.
- N34 It will do yes, I think the nature of that epidemiology will be very, very different. But at the minute I think you're still looking at a generation that think the doctors know best and sometimes that's a real struggle when you're talking about a choice – "actually do you know what? You know best because it's your body"
- J Particularly if you've got a doctor who says "I will not make a choice for you, it's your decision" that can be hard for them as well.
- N34 They think that they're making them make a medical choice and the minute you say "no, actually, we've made the medical choice, we're never going to offer you a lesser choice, the route you get there might be slightly different but actually those choices are just as safe" and we're saying "we're experts in that, we can offer you this, but actually the expert about you is you" so, you know, I think once you actually clear that it's, you know, but it's a complete turning about of how they view the medical profession and everything, so yes, I do think that does impact greatly on this generation still. Lesser so, but still quite greatly so. And I think there is an element about some ladies will do what their husbands want them to do still.
- J Really?
- N34 On the other hand, you know, on the other hand not the case, most of my ladies are having very active sexual lives and it's a very important part to them.
- J Yes. Right, I've not really looked at my paper so I'm just going to have a quick squidge to make sure I haven't missed anything.
- N34 The term I guess I haven't used and I guess I ought to put in somewhere, for me it's all about quality of life really. And when I talk about quality of life, it's not just about physical state, it's about a mental and emotional state.
- J Right.
- N34 So that's really what we're looking at when we're offering surgery and making sure they're making the decision that's right for them.
- J Ok. What sort of factors have influenced your personal strategy for dealing with these sort of patients, you know, giving the advice you give. Is it the literature that you've read, your past experience, the unit's policy, what sort of?
- N34 All of the above I suppose.
- J Anything else?
- N34 Yes, I mean my mother had breast cancer but very differently so I guess from my experience talking to women and what they, and I've been a ward sister for many years you see, so I sit at the back and see what women actually worry about and so I guess I use all the above to actually focus on that one patient, or person should I say. And we're very much see women as people and not as patients, I think that's the beauty of this job actually, as being on the ward, to make the decision that's right for them. And I'm still learning now.
- J Yes. I think that might be all of my questions. Have you got anything else that you'd like to add that I have talked about, either about this group of patients, or women, or about the two treatments that we've talked about?
- N34 I don't think so actually, not that I can think of off the top of my head. I didn't have much

time to focus before I came in, because it was just in the middle of clinic will you do this, yes, ok, you know, whatever it is I'll do it.

J I know thank you so much.

N34 I don't know if it's been useful

J No very useful.

N34 It's a pleasure.

J Thank you and thank you for taking the time to speak to me, I really appreciate it and I shall stop this.

Appendix 17: Letter to participant in questionnaire study



The
University
Of
Sheffield.

Miss Lynda Wyld
Senior Lecturer
Academic Surgical Oncology Unit
Room EU32, Royal Hallamshire Hospital
Glossop Road, Sheffield, S10 2JF

Telephone: +44 (0) 114 271 2510
Email: l.wyld@sheffield.ac.uk
24th October, 2012

Dear Colleague,

Clinician Preferences for the Treatment of Older Women with Operable Breast Cancer.

We would like to invite you to participate in the above research study that has been funded by the National Institute for Health Research and is being undertaken by researchers from The University of Sheffield, Sheffield Hallam University and the University of Leicester.

There is wide variation in UK practice relating to the treatment of older women with breast cancer, with some areas demonstrating much higher rates of Primary Endocrine Therapy (PET) compared with others. Studies have shown that primary endocrine therapy is an effective treatment for breast cancer in older women but there is uncertainty about the age, fitness level, disease biology and stage for which it is indicated. The 4 fold variance in UK practice is testament to this lack of guidance. This research project is part of a larger study to try and define best practice for this age group of women by helping to define the characteristics of older women that suggest they may benefit from either surgery or PET. We want to establish the views of health care professionals across the UK about their own criteria for each treatment.

We are writing to you because you are a specialist health professional to ask you to consider taking part in this study by completing the attached questionnaire. We anticipate that it should take you about 15 minutes to complete. Taking part is completely voluntary. If you wish to take part in the study, then please complete the attached questionnaire and return it to the researchers in the FREEPOST envelope provided.

If you would like to find out more about the study before deciding whether or not to take part please contact myself, Lynda Wyld, Senior Lecturer and Consultant Breast Surgeon, at the Royal Hallamshire Hospital, via e-mail, l.wyld@sheffield.ac.uk, or Miss Jenna Morgan, a researcher on the project, at the Royal Hallamshire Hospital. Telephone 0114 2620174 ext 13611 or email j.morgan@sheffield.ac.uk

Many thanks for considering taking part.

Yours faithfully,

A handwritten signature in black ink that reads 'L Wyld'.

Lynda Wyld, Senior Lecturer and Consultant Surgeon

Appendix 18: Final questionnaire

Sheffield Teaching Hospitals 
NHS Foundation Trust



The
University
Of
Sheffield.



Variation in Clinician Preferences for Treatment of Older Women with Operable Breast Cancer

Health Care Professional Questionnaire

All information that you provide will remain strictly
confidential

When you have finished please post the questionnaire back
in the FREEPOST envelope provided. You do not need a
stamp.

If you have any queries about this questionnaire or the study,
please contact Lynda Wyld (Senior Lecturer and Consultant
Breast Surgeon), EU36, University of Sheffield Medical
School, Beech Hill Road, Sheffield. Telephone 0114 2268640.

This sheet is intentionally blank.

Section One

This section requires you to give brief information about your professional background

1. What is your age in years?

2. What is your gender? (please tick appropriate box)

Male

Female

3. What is your profession or speciality? (please tick appropriate box)

Breast Surgeon

Oncologist

Breast Care Nurse Specialist

Other (specify).....

4. Which area do you currently work in? (please tick appropriate box)

Eastern

North West

Northern & Yorkshire

Northern Ireland

Oxford

Scotland

South West

Thames

Trent

Wales

West Midlands

Other (specify).....

Section Two

The table below contains factors that may be considered when discussing treatment options with an older patient with operable breast cancer. Please rate the importance of each of these factors in shaping your advice regarding treatment options in an older woman (≥ 70) in whom you are considering the choice between surgery and primary endocrine therapy.

For each factor place your tick in the relevant box that best describes how important you think each factor is. Please only tick one box per question.

Patient Characteristic	Very important	Important	Some importance	Not important
Patient age	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Breast cancer ER positivity	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Breast cancer Her 2 receptor status	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Size of tumour (e.g. suitability for WLE)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Presence of axillary nodal disease	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Suitability for surgery under local or regional anaesthesia in a frail patient	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Estimated life expectancy of the patient	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's preference for operation or PET	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Functional status (level of independence, ability to perform	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Cognitive function (dementia)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Co-morbidity (are they fit and well or do they have multiple health problems?)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's anxiety level about breast cancer	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Patient's anxiety levels about an operation	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
Family member/carer preference for operation of PET	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄

Section Three

The following questions relate to your views about the choice between surgery and primary endocrine therapy.

For each of the statements below please circle one box to indicate your views about the validity and accuracy of the statement:

- 1) All women ≥ 70 with operable breast cancer should be offered an operation, regardless of age.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

- 2) All women ≥ 70 with operable ER+ve breast cancer, who have multiple co-morbidities such that anaesthesia may carry an increased risk of morbidity and mortality, should be treated with PET.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

- 3) All women ≥ 70 with operable ER +ve breast cancer, who have significant dementia, (unable to give informed consent) should be treated with PET.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

- 4) Primary endocrine therapy may be offered to any woman ≥ 70 with ER+ve disease as there is no proven survival disadvantage.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

- 5) Surgery is almost always possible for older women ≥ 70 with operable breast cancer under local or regional anaesthesia.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

- 6) Most older women ≥ 70 , if given a choice of treatment would prefer to have non-surgical treatment for their breast cancer.

STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
------------------------------	-----------------	--------------	---------------------------

Section Four

The following questions relate to your experiences with treating older women ≥ 70 with operable breast cancer. For each of the questions below please tick the box of the answer that is most similar to your experiences.

1) What percentage of women ≥ 70 receive PET in your unit?

- | | | | |
|---------------|--------------------------|-----------|--------------------------|
| Less than 10% | <input type="checkbox"/> | 10 to 20% | <input type="checkbox"/> |
| 20 to 30% | <input type="checkbox"/> | 30 to 40% | <input type="checkbox"/> |
| More than 40% | <input type="checkbox"/> | | |

2) In your experience, how long on average does PET maintain local control?

- | | | | |
|-----------|--------------------------|-----------|--------------------------|
| 6 months | <input type="checkbox"/> | 12 months | <input type="checkbox"/> |
| 18 months | <input type="checkbox"/> | 24 months | <input type="checkbox"/> |
| 3 years | <input type="checkbox"/> | 5 years | <input type="checkbox"/> |

3) What action would you take if your first line anti-oestrogen failed to achieve a response in a patient being treated with PET?

- | | | | |
|----------------------------------|--------------------------|-----------------------------|--------------------------|
| Start second line anti-oestrogen | <input type="checkbox"/> | Advise operative management | <input type="checkbox"/> |
| Advise radiotherapy | <input type="checkbox"/> | Other (specify)..... | <input type="checkbox"/> |

4) In your experience, are anaesthetists in your unit happy to perform regional blocks to allow you to undertake surgical excision in women ≥ 70 who have multiple co-morbidities where a general anaesthetic may carry increased risk or morbidity and mortality?

- | | | | |
|---|--------------------------|--|--------------------------|
| Never perform regional blocks in this group | <input type="checkbox"/> | Rarely perform regional blocks in this group | <input type="checkbox"/> |
| Regularly perform regional blocks in this group | <input type="checkbox"/> | | |

5) In your experience, is surgery under general anaesthesia well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

6) In your experience, is surgery under local anaesthesia well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

7) In your experience, is PET well-tolerated in women ≥ 70 with operable breast cancer?

- | | | | | | |
|-----|--------------------------|----|--------------------------|----------|--------------------------|
| Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | Not sure | <input type="checkbox"/> |
|-----|--------------------------|----|--------------------------|----------|--------------------------|

Section Five: Introduction

This section comprises a series of 20 clinical scenarios on which you are asked to make a hypothetical decision. They are concerned with the importance that you place on various factors influencing your preferred option for surgery or PET in individual women ≥ 70 with operable breast cancer. **PLEASE NOTE:** the option for surgery may include operations under General, Regional or Local anaesthetic if this is how you would treat the patient. Please tear out this double-sided sheet to use as a reference when working through the scenarios

1. Patient age (years) Divided into the following age bands:

70 – 74	75 – 79
80 – 84	85 and over

2. Co-morbidity

Divided into the following:

- 5) No co-morbidity
- 6) Mild co-morbidity, e.g. arthritis, hypertension
- 7) Moderate/well-controlled co-morbidity, e.g. diabetes, coronary heart disease, moderate COPD
- 8) Severe co-morbidity, e.g. disabling stroke, congestive cardiac failure, severe COPD

3. Cancer Stage

Divided into the following:

- 5) Small tumour, no nodal involvement
- 6) Small tumour, nodal involvement
- 7) Large tumour, no nodal involvement
- 8) Large tumour, nodal involvement

4. Cancer Biology

Divided into the following:

- 4) ER++/HER2- (ER strongly positive, HER2 negative)
- 5) ER+/HER2- (ER moderately positive, HER2 negative)
- 6) ER+/HER2+ (ER moderately positive, HER2 positive)

5. Functional Status

Divided into the following:

- 5) Fully independent
- 6) Mild dependence; requires weekly help for domestic activities, e.g. shopping
- 7) Moderate dependence; requires daily help with washing, dressing, continence management, etc.
- 8) Severe dependence; requires 24 hour care, e.g. resides in a residential or nursing home

6. Cognitive Function Divided into the following:

- 5) Normal cognitive function
- 6) Mild cognitive impairment; functions normally in society
- 7) Moderate cognitive impairment; unable to cope without help
- 8) Severe cognitive impairment; requires daily social services input or lives in residential or nursing home

Section Five: Patient Scenarios

For each of the 20 scenarios below, based on the information provided, please indicate your preferred choice of recommendation for treatment (i.e. in favour of operative treatment or primary endocrine therapy (PET), by placing a tick (✓) in the relevant box below the scenario description. If you prefer both options equally, please tick both boxes. Please assume that each hypothetical patient has asked you to advise them on what treatment option they should choose.

Scenario 1

PATIENT AGE (YEARS)	85+
CO-MORBIDITY	NONE
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE
BREAST CANCER BIOLOGY	ER++ / HER2-
FUNCTIONAL STATUS	MODERATE DEPENDENCE
COGNITIVE FUNCTION	SEVERE IMPAIRMENT
For Operation	<input type="checkbox"/>
For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>

Scenario 2

PATIENT AGE (YEARS)	70-75
CO-MORBIDITY	SEVERE
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE
BREAST CANCER BIOLOGY	ER+ / HER2+
FUNCTIONAL STATUS	MODERATE DEPENDENCE
COGNITIVE FUNCTION	NORMAL
For Operation	<input type="checkbox"/>
For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>

Scenario 3

PATIENT AGE (YEARS)	70-75		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 4

PATIENT AGE (YEARS)	70-75		
CO-MORBIDITY	MILD		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 5

PATIENT AGE (YEARS)	75-80		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 6

PATIENT AGE (YEARS)	75-80		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	MODERATE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 7

PATIENT AGE (YEARS)	80-85		
CO-MORBIDITY	MILD		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 8

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	INDEPENDENT		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 9

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	SEVERE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 10

PATIENT AGE (YEARS)	75-80		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	NORMAL		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 11

PATIENT AGE (YEARS)	80-85		
CO-MORBIDITY	NONE		
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2+		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 12

PATIENT AGE (YEARS)	70-75	
CO-MORBIDITY	NONE	
TUMOUR STAGE	LARGE TUMOUR, NODE POSITIVE	
BREAST CANCER BIOLOGY	ER+ / HER2-	
FUNCTIONAL STATUS	MILD DEPENDENCE	
COGNITIVE FUNCTION	NORMAL	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 13

PATIENT AGE (YEARS)	85+	
CO-MORBIDITY	MILD	
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE	
BREAST CANCER BIOLOGY	ER+ / HER2-	
FUNCTIONAL STATUS	INDEPENDENT	
COGNITIVE FUNCTION	NORMAL	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 14

PATIENT AGE (YEARS)	70-75	
CO-MORBIDITY	SEVERE	
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE	
BREAST CANCER BIOLOGY	ER++ / HER2-	
FUNCTIONAL STATUS	MILD DEPENDENCE	
COGNITIVE FUNCTION	MILD IMPAIRMENT	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 15

PATIENT AGE (YEARS)	80-85	
CO-MORBIDITY	NONE	
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE	
BREAST CANCER BIOLOGY	ER+ / HER2-	
FUNCTIONAL STATUS	MILD DEPENDENCE	
COGNITIVE FUNCTION	NORMAL	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 16

PATIENT AGE (YEARS)	70-75	
CO-MORBIDITY	MODERATE	
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE	
BREAST CANCER BIOLOGY	ER+ / HER2+	
FUNCTIONAL STATUS	INDEPENDENT	
COGNITIVE FUNCTION	NORMAL	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 17

PATIENT AGE (YEARS)	80-85	
CO-MORBIDITY	MODERATE	
TUMOUR STAGE	SMALL TUMOUR, NODE NEGATIVE	
BREAST CANCER BIOLOGY	ER+ / HER2-	
FUNCTIONAL STATUS	MODERATE DEPENDENCE	
COGNITIVE FUNCTION	MILD IMPAIRMENT	
For Operation	<input type="checkbox"/>	For PET <input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>	

Scenario 18

PATIENT AGE (YEARS)	70-75		
CO-MORBIDITY	MILD		
TUMOUR STAGE	SMALL TUMOUR, NODE POSITIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	MILD IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 19

PATIENT AGE (YEARS)	70-75		
CO-MORBIDITY	NONE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER+ / HER2-		
FUNCTIONAL STATUS	SEVERE DEPENDENCE		
COGNITIVE FUNCTION	SEVERE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

Scenario 20

PATIENT AGE (YEARS)	85+		
CO-MORBIDITY	MODERATE		
TUMOUR STAGE	LARGE TUMOUR, NODE NEGATIVE		
BREAST CANCER BIOLOGY	ER++ / HER2-		
FUNCTIONAL STATUS	MILD DEPENDENCE		
COGNITIVE FUNCTION	MODERATE IMPAIRMENT		
For Operation	<input type="checkbox"/>	For PET	<input type="checkbox"/>
Prefer both equally	<input type="checkbox"/>		

If you have any additional comments, please write them on this page.

Use additional sheets if necessary.

If you would like to receive a summary of the research findings please provide your name, position and either a contact telephone number, address or e mail address so that we can contact you to arrange for this to be sent to you. The results may take up to a year to be produced.

If you wish to remain anonymous, please leave this blank: the results may still be available to you via publication in peer reviewed journals.

If you would like to have your results sent back to you with a comparison of your answers to the rest of the sampled population please tick the 'Feedback' box.

Name:

Profession:

Contact telephone number:

E mail

Address:

I would like to receive Individualised Feedback please:

Thank you for completing this questionnaire and for taking part in the study.

Please return the completed questionnaire in the FREEPOST envelope provided.

Miss Jenna Morgan, EU25, University of Sheffield Medical School, Beech Hill Road, Sheffield.

Email: j.morgan@sheffield.ac.uk