Making Treatment Decisions for Older Women with Cognitive Impairment and Breast Cancer

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Declaration

I, the author, confirm that this thesis represents my own work, and that where materials owned by a third party have been used, copyright clearance has been obtained. Where any work has been completed with others, this has been stated at the beginning of the relevant section.

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Abstract

Background

The UK population of older people is expanding due to increasing life expectancy and the arrival of the 'baby boomer' cohort (born 1945-1964) now reaching 70 years of age. Many diseases are linked to older age, including dementia, and a range of common cancers, which means that inevitably these two diseases will co-exist in some patients. The management of cancer in the presence of premorbid dementia is often non-guideline concordant and data shows that cancer outcomes are sub-optimal. Making decisions about cancer treatment in this setting are therefore often complex. Where a patient lacks the capacity to make their own decisions, a 'proxy' decision maker will take on the role of navigating treatments and care. This is usually based on the best interest principle or guided by formal legal arrangements such as lasting power of attorney or an advance decision. Often, family and caregivers are involved in this decision-making process. Few studies have explored the experiences of caregivers for older patients with dementia and breast cancer, and there is little evidence of how they make decisions, the issues that influence them, and the factors that underpin their decisions.

Aims

1. To determine the oncological outcomes for older women with early breast cancer when also affected by cognitive impairment.
2. To determine the role of informal caregivers in making cancer treatment decisions for patients with cancer and dementia.
3. To determine the support needs and wishes of informal caregivers in the breast cancer care setting.

Methods

1. A systematic review of the wider literature relating to the role of caregivers in cancer decision-making and supporting patients with dementia and cancer.
2. Analysis of data taken from a prospective observational multi-centre cohort study of older women (>70) with early breast cancer to determine the baseline

cancer characteristics, treatment, and survival outcomes of women with breast cancer and cognitive impairment.

3. The design and application of a bespoke quantitative questionnaire to a sub-group of caregivers involved in treatment decision-making for patients with dementia recruited to the Bridging the Age Gap trial.
4. Semi-structured qualitative interviews with caregivers for older patients with dementia to explore the experience of decision-making and caring for a relative with dementia and breast cancer.
5. A mixed methods synthesis of quantitative and qualitative findings to gain an in-depth understanding of the challenges facing caregivers and patients with dementia and breast cancer.

Results

1. The systematic literature review identified six relevant studies. The key findings were that caregivers feel inadequately supported both during decision making and other phases of the cancer journey. Three themes were identified: HCP dementia awareness and knowledge in the clinical consultation; Treatment decision-making discussions, information and communication needs; and the caregiver role and caregiver relationship.
2. A diagnosis of cognitive impairment was identified in 478 of 3416 (14%) patients recruited to the Bridging the Age Gap trial. Cognitive impairment was significantly associated with non-standard care. For women with normal cognition the rate of surgery was 84.9%, compared to women with mild (73.8%) moderate (61.0%) and severe (39.8%) impairment ($p=0.001$). Overall survival rates at median 5 year follow up were worse for women with cognitive impairments (35.7%) compared to women without dementia (18.8%) ($p <0.001$), however cause-specific survival was similar between the two groups.
3. The quantitative questionnaire was completed by thirteen caregivers. Three themes were identified: Information needs, treatment decision-making and support needs. Caregivers reported that the level of information received was satisfactory and enough time was allocated to making the decision, although the process was highly stressful.

4. Eight caregivers took part in a semi-structured interview. The key findings were that caregivers had unmet needs in respect to information, continuity and cancer support services. Four themes were identified: clinical interactions; accessing information and support; decision-making involvement; and treatment influences.
5. The mixed methods synthesis of the systematic review, cohort analysis, questionnaire and interview findings highlight the nuanced role of the caregiver in making cancer treatment decisions. Three over-arching themes were developed: caregiver role in making decisions; expert knowledge; and influence of dementia diagnosis.

Conclusions

Older patients with dementia and breast cancer are currently treated at variance from national guidelines, with significant variation in practice and inferior cancer outcomes compared to patients without dementia. The role of the caregiver is central to making treatment decisions, including gathering information on behalf of the patient and communicating their preferences to the treating clinician. Caregivers were happy with the level of information they received, although this information was rarely tailored towards the needs of breast cancer patients with pre-existing dementia. Improvements to the provision of services were highlighted by caregivers as an area in need of attention.

Publications and Presentations

Publications

Bridging the Age Gap in Breast Cancer: Impact of chemotherapy on quality of life in older women with early breast cancer.

Battisti NML, Reed MWR, Herbert E, Morgan J, Collins K, Ward S, Holmes G, Bradburn M, Walters S, Burton M, Lifford K, Edwards A, Robinson TG, **Martin C,** Chater T, Pemberton K, Shrestha A, Brennan A, Cheung KL, Todd A, Audisio R, Wright J, Simcock R, Green T, Revell D, Gath J, Gosney M, Hatton MQ, Thompson AM, Wyld L, and Ring A, on behalf of the Age Gap TMG. European Journal of Surgical Oncology, 2021. doi: 10.1016/j.ejca.2020.11.022

Treatment outcomes for older women (>70) with breast cancer and dementia: Results from a prospective, multicentre cohort study.

Martin C, Shrestha A, Morgan J, Bradburn M, Herbert E, Burton M, Todd A, Walters S, Ward S, Holmes G, Reed MWR, Collins K, Robinson T, Ring A, Cheung KL, Audisio R, Gath J, Revell D, Green T, Lifford K, Edwards A, Chater T, Pemberton K, and Wyld L. Journal of Geriatric Oncology, 2020. doi: 10.1016/j.jgo.2020.12.006

Bridging the Age Gap in Breast Cancer: Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer. A risk stratified analysis of survival outcomes and quality of life.

Wyld L, Reed MWR, Morgan J, Collins K, Ward S, Holmes G, Bradburn M, Walters S, Burton M, Herbert E, Lifford K, Edwards E, Ring A, Robinson T, **Martin C,** Chater T, Pemberton K, Shrestha A, Brennan A, Cheung KL, Todd A, Audisio R, Wright J, Simcock R, Green T, Revell D, Gath J, Horgan K, Holcombe C, Winter M, Naik J, Parmeshwar R, Patnick J, Gosney M, Hatton M, Thomson A. European Journal of Cancer, 2021. doi: 10.1016/j.ejca.2020.10.015

Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: the Age Gap Trial.

Todd A, **Martin C**, Morgan J, Herbert E, Bradburn M, Burton M, Reed MWR, Chater T, Pemberton K, Walters S, Cheung KL, Audisio R, Ring A, Robinson T, Green T, Gath J, and Wyld L. Journal of Geriatric Oncology, 2020. doi: 10.1016/j.jgo.2020.10.015

Observational cohort study to determine the degree and causes of variation in the rate of surgery or primary endocrine therapy in older women with operable breast cancer.

Morgan J, Holmes G, Ward S, **Martin C,** Burton M, Walters S, Cheung KL, Audisio R, Reed MWR, and Wyld, L on behalf of the Bridging the Age Gap Trial Management Team. European Journal of Surgical Oncology, 2020. doi: 10.1016/j.ejso.2020.09.029.

Breast Cancer Surgery in Older Women: Outcomes of the Bridging the Age Gap in Breast Cancer Study.
Morgan J, George J, Holmes G, **Martin C**, Reed MWR, Ward S, Walters S, Cheung KL, Audisio R, and Wyld L. on behalf of the Age Gap Trial Management Team.
British Journal of Surgery. 2020. Jun. doi: 10.1002/bjs.1167. Epub 2020 Jun 02.

How are caregivers involved in treatment decision making for older people with dementia and a new diagnosis of cancer?
Martin C, Shrestha A, Burton M, Collins K, Wyld L.
Psychooncology. 2019 Jun;28(6):1197-1206. doi: 10.1002/pon.5070. Epub 2019 Apr 24. Review. PMID: 30908755

Quality of life versus length of life considerations in cancer patients: A systematic literature review.
Shrestha A, **Martin C,** Burton M, Walters S, Collins K, Wyld L.
Psychooncology. 2019 Jul;28(7):1367-1380. doi: 10.1002/pon.5054. Epub 2019 May 15. Review. PMID: 30838697

Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial.
Collins K, Reed M, Lifford K, Burton M, Edwards A, Ring A, Brain K, Harder H, Robinson T, Cheung KL, Morgan J, Audisio R, Ward S, Richards P, **Martin C**, Chater T, Pemberton K, Nettleship A, Murray C, Walters S, Bortolami O, Armitage F, Leonard R, Gath J, Revell D, Green T, Wyld L.
BMJ Open. 2017 Jul 31;7(7):e015133. doi: 10.1136/bmjopen-2016-015133. PMID:28760787

Submitted for publication

Caregiver experiences of making treatment decisions for older women with breast cancer and dementia.
Martin C, Burton M, and Wyld L. Manuscript submitted to Health & Social Care in the Community, 2020.

Bridging the Age Gap in Breast Cancer: Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer on quality-of-life outcomes.
Shrestha A, Morgan J, Reed MWR, Herbert E, Bradburn M, Walters S, **Martin C,** Collins K, Ward S, Holmes G, Burton M, Lifford K, Edwards A, Ring A, Robinson T, Chater T, Pemberton K, Brennan A, Cheung KL, Todd A, Audisio R, Wright J, Simcock R, Thomson, A, Gosney M, Hatton M, Green T, Revell D, Gath J, Horgan K, Holcombe C, Winter M, Naik J, Parmeshwar R, and Wyld L. Manuscript submitted to British Journal of Surgery, 2020.

Bridging the Age Gap in Breast Cancer: Cluster randomised trial of the effects of two decision support interventions for older women with operable breast cancer on quality-of-life, survival, decision quality and decision choices.

Wyld L, Reed MWR, Collins K, Burton M, Lifford K, Edwards A, Ward S, Holmes G, Morgan J, Bradburn M, Walters S, Ring A, Robinson T, **Martin C**, Chater T, Pemberton K, Shrestha A, Nettleship A, Murray C, Brown M, Richards P and Wyld L.

Manuscript submitted to British Journal of Surgery, 2020

Published abstracts

Bridging the Age Gap in Breast Cancer: An analysis of the decision-making preferences of older women with operable breast cancer in the UK.

Morgan J, Holmes G, Ward S, **Martin C,** Burton M, Audisio R, Cheung KL, Ring A, Reed MW and Wyld L. European Journal of Surgical Oncology. 46(6): e28. Jun 2020. doi: 10.1016/j.ejso.2020.03.104.

Bridging the Age Gap in Breast Cancer: optimisation of survival and quality of life outcomes in older women with early breast cancer.

Wyld L, Reed MWR, Collins K, Ward S, Holmes G, Morgan J, Bradburn M, Walters S, Burton M, Lifford K, Edwards A, Ring A, Robinson T, **Martin C,** Chater T, Pemberton K, Shrestha A, Cheung KL, Todd A, Audisio R. Breast Cancer Research and Treatment. 180(2): 594-594. Apr 2020.

Bridging the Age Gap in Breast Cancer – Analysis of the influence of age, comorbidity and frailty on the types of surgery performed in older women with operable breast cancer.

George J, Morgan J, **Martin C,** Shrestha A, Ward S, Holmes G, Bradburn M, Burton M, Chater T, Pemberton K, Nettleship A, Walters S, Ring A, Robinson T, Cheung KL, Audisio R, Reed MW and Wyld L on behalf of the Bridging the Age Gap Trial Management Group. European Journal of Surgical Oncology. 46(2): e22. Feb 2020. doi: 10.1016/j.ejso.2019.11.476.

Bridging the Age Gap in Breast Cancer – Analysis of the complication rates of surgery in older women

George J, Morgan J, **Martin C,** Shrestha A, Ward S, Holmes G, Bradburn M, Burton M, Chater T, Pemberton K, Nettleship A, Walters S, Ring A, Robinson T, Cheung KL, Audisio R, Reed MW and Wyld L. European Journal of Surgical Oncology. 46(2): e47-e48. Feb 2020. doi: 10.1016/j.ejso.2019.11.089

Bridging the Age Gap in Breast Cancer – Analysis of the impact of comorbidity, dementia and frailty on the rates of surgery in older women

Morgan J, George J, Ward S, Holmes G, Burton M, Chater T, Bradburn M, **Martin C,** Shrestha A, Cheung KL, Audisio R, Reed, MW and Wyld L. European Journal of Surgical Oncology. 45(5) May 2019. doi: 10.1016/j.ejso.2019.01.191

Comparison of quality of life of older women treated with surgery or primary endocrine therapy for early breast cancer: propensity score matched analysis of a large prospective multicentre cohort study

Shrestha A, **Martin C,** Burton M, Collins K, Holmes G, Ward S, Audisio R, Chater T, Pemberton K, Robinson T, Cheung KL, Ring A, Walters S, Reed MW, Gath J, Green T, Revell D and Wyld L. European Journal of Cancer. 92(3). April 2018. doi: 10.1016/S0959-8049(18)30261-2

Preference for quality of life versus length of life in older women making treatment decisions in early breast cancer.
Shrestha A, **Martin C,** Collins K, Burton M, Audisio R, Chater T, Pemberton K, Robinson T, Ward S, Cheung K, Walters S, Reed M, Green T, Revell D, Gath J, Wyld L. *European Journal of Surgical Oncology*, 2018 44. doi: 10.1002/pon.5054

The impact of cognitive impairment on treatment allocation of elderly women with early breast cancer.
Martin C, Shrestha A, Collins K, and Wyld L on behalf of the Bridging the Age Gap in Breast Cancer Team. *European Journal of Surgical Oncology.* Nov 2017. Volume 43, Issue 11. pp. 2238. doi: 10.1016/j.ejso.2017.10.183

Quality of life versus length of life in cancer patients: literature review
Shrestha A, **Martin C**, Collins K, and Wyld L.
European Journal of Cancer, Vol 72, Supplement 1. February 2017. doi: 10.1002/pon.5054

Quality of life of elderly women with early breast cancer following surgery.
Shrestha A, **Martin C**, Collins K, Burton M, Audisio R, Chater T, Pemberton K, Robinson T, Ward S, Cheung K, Walters S, Reed M, Green T, Revell D, Gath J, Wyld L. EJSO. doi: 10.1016/j.ejso.2018.01.234

Impact of dementia on treatment of older patients with breast cancer. An interim analysis of the bridging the age gap in Breast Cancer Study.
Zaman O, Ward S, Collins K, Cheung KL, Robinson T, Audisio R, Oscar B, **Martin C,** Reed MW, and Wyld L. EJSO, Vol 42, Issue 11, S232–S233, 2016

Conference posters

Making Cancer Treatment Decisions for Older Women with Breast Cancer and Dementia.
Martin C, Burton M, and Wyld L. University of Sheffield SiTRAN *Dementia Futures Conference*, Sheffield 2019.

The impact of cognitive impairment on treatment allocation of elderly women with early breast cancer.
Martin C, Shrestha A, Collins K, and Wyld L. NCRI Cancer Conference, Liverpool, 2017

Quality of life versus length of life in cancer patients: literature review
Shrestha A, **Martin C**, Collins K, and Wyld L. ECCO (European Cancer Congress), Amsterdam 2017

Proxy decision making for older women with cognitive impairments and breast cancer.
Martin C, Burton M, Collins K, and Wyld L. University of Sheffield Medical School 12th Annual Research Meeting, Sheffield 2016.

Research Awards

Early Career Researcher Prize: *Excellence in research and/or impact*.
September 2018. The University of Sheffield.

Abstract Selection Prize Award.
August 2017. National Cancer Research Institute (NCRI) Cancer Conference.

Contents

Figures

Tables

Abbreviations

ACP – Advance Care Planning

BPSD – Behavioural and Psychological Symptoms of Dementia

CGA – Comprehensive Geriatric Assessment

CI – Cognitive impairment

DLB – Dementia with Lewy bodies

DSM – Diagnostic and Statistical Manual of Mental Disorders

ECOG – Eastern Cooperative Oncology Group

ER – Oestrogen Receptors

FTD – Frontotemporal Dementia

GPCOG – General Practitioner Assessment of Cognition

HCP – Healthcare Professionals

HER2 – Human Epidermal Growth Factor Receptor 2

IADL – Instrumental Activities of Daily Living

ICD – International Classification of Diseases

IHC – Immunohistochemistry

LPA – Lasting Power of Attorney

MCA – Mental Capacity Act

MDT – Multidisciplinary team

MMSE – Mini Mental State Examination

NICE – National Institute for Health and Care Excellence

NHS – National Health Service

PET – Primary Endocrine Therapy

PPI – Patient Public Involvement

PR – Progesterone Receptors

R&D – Research and Design

RCT – Randomised controlled trials

SNLB – Sentinel Lymph Node Biopsy

U.K. – United Kingdom

WHO – World Health Organisation

Study Scope

This PhD was undertaken as a part-time staff candidacy alongside my role as the Bridging the Age Gap Trial Monitor **(2012 to 2015)** and Trial Manager **(2015 to 2020)**. The idea for a sub-analysis of the dementia cohort within Age Gap was mine, the protocol for analysis was developed by myself and the literature review and mixed methods components were conceived, designed and delivered wholly by me. **Figure 1** shows the study timelines for this PhD.

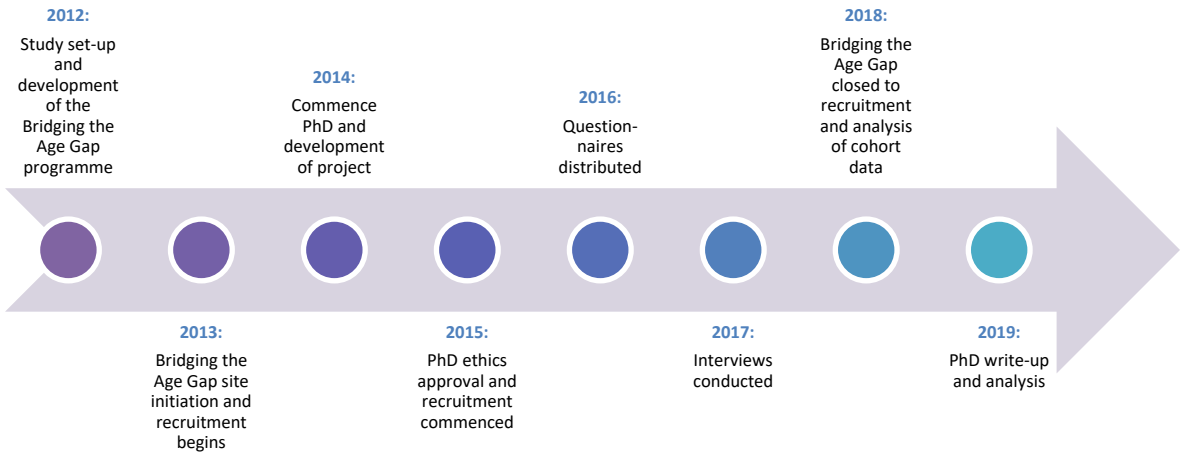


Figure 1: PhD study timeline

2012: Study set-up and development of the Bridging the Age Gap trial

2013: Bridging the Age Gap site R&D set-up and recruitment start date

2014: **Start of PhD and development of project**

2015: Ethics approval to begin recruitment to the mixed methods component

2016: Postal questionnaires distributed

2017: Interviews conducted

2018: Bridging the Age Gap closed to recruitment and follow-up

2019: Analysis of Bridging the Age Gap data, PhD write-up and analysis

2020: Submission of thesis

Bridging the Age Gap in Breast Cancer Trial

This thesis includes work undertaken as part of the Bridging the Age Gap in Breast Cancer programme, which was conducted between 2012 and 2020. The study was funded by the National Institute for Health Research (NIHR) and sponsored by Doncaster and Bassetlaw Teaching Hospitals.

Bridging the Age Gap recruited women aged 70+ with early-stage breast cancer from 56 centres, including women both with and without cognitive impairments. This PhD study sampled the caregiver consultees who had assented a patient with cognitive impairment and breast cancer to the trial **(Figure 2)**.

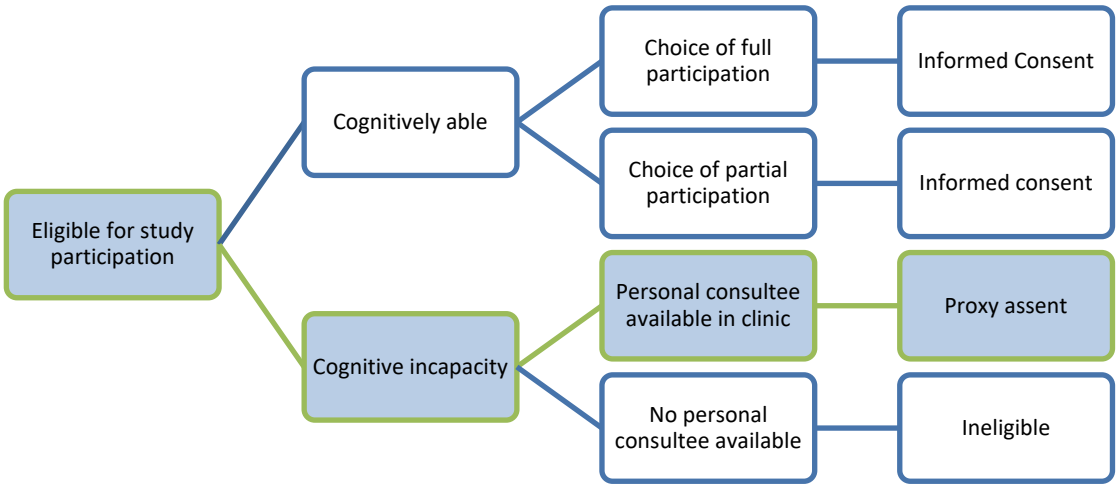


Figure 2: Bridging the Age Gap participation levels

The Bridging the Age Gap trial closed to recruitment in June 2018, enrolling a total of 3456 patients (478 of whom had cognitive impairment). A detailed overview of the Bridging the Age Gap programme can be found in **Chapter Six**.

PhD Study Schema

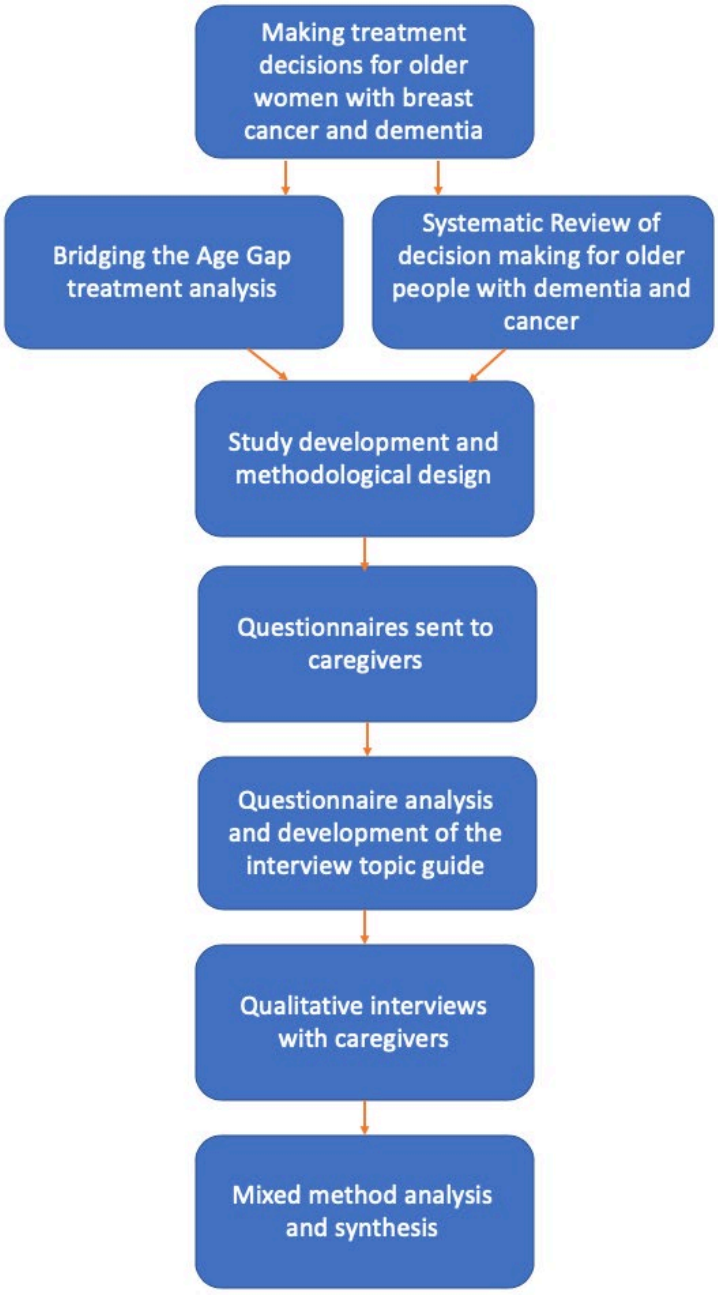


Figure 3: Study schema

Chapter One: Introduction

1.1. Society and Age

The definition of what is meant by 'old age' varies between cultures and countries, which in turn makes reaching an absolute classification problematic. According to the World Health Organization (WHO), the most widely accepted chronological age of an older person is 65 years old (1). This social construction of age approximates with the age of retirement in England and Wales, which currently hovers around 65-68 years. In the United Kingdom (U.K.), 1 in 6 people are aged over 65, with an average life expectancy of 79.2 years for males and 82.9 for females (2). The last census data taken from 2011 showed that the over 65's accounted for 16% of the U.K. population, approximately 9.2 million people (3). This population increase is partly a side effect of the baby boom that followed the Second World War; generally defined as those born between 1946 and 1964. The increased life expectancy of this population is complex and multifactorial, with major contributions seen from the rise in modern living standards, medical treatment advances, and the improved management of chronic diseases. The U.K. population itself has experienced a rapid demographic change in the last 25 years, with the fastest increases seen in the 85+ group, which is set to make up 7% of the total population by 2066 (4).

Age classifications are an arbitrary way of demarcating the old from the young in society, with most research stratifying the elderly into sub-populations such as the young-old (65-74), middle-old (75-84) and old-old (85 and over). Within these three categories there is much variation in terms of health, fitness and independence amongst people of the same age. While age stratification can be particularly useful when considering the needs of different age subgroups, 'old age' has increasingly become associated with a set of negative social and cultural perceptions (5). While these roles and behaviours vary markedly between societies and cultures, it is argued that age constructs and subtypes have led to negative stereotypes of older people and ageism (6).

1.1.1. Biological Ageing

Ageing of the body is a complex process triggered by accumulated cellular changes in the organs and tissue, which affects the body's ability to function over time. The rate at which this occurs is highly variable and dependent on both polygenic hereditary factors and environmental factors, which is why biological and chronological age are often mis-matched (7). Most human organs degenerate as we age (senescence), with a reduced functional reserve seen in the kidneys, lung, heart and immune systems amongst others. There is also a gradual accumulation of genetic mutations due to the cumulative exposure of key genes to internal and external carcinogens, and age-related 'wear and tear' of DNA over time (8). This, when combined with reduced efficacy of immune surveillance, is one of the key reasons why some cancers are more common in older people. There is also an increase in the number of comorbid diseases such as peripheral and cardiac vascular atherosclerosis, arthritis and osteoporosis seen in older age groups, in addition to a loss of skeletal muscle mass with age, sarcopenia, resulting in muscle weakness and physical frailty (9).

1.1.2. Ageing and Co-morbidities

The association between old age and comorbid diseases may have an impact on the range of treatments that are available to older people who go on to develop cancer, as this will mean they are more susceptible to the risks of mortality and side effects. In a study by Louwman et al (10), the primary treatments received by patients with breast cancer and comorbidities were less extensive compared to the treatments of those without comorbidities. Similarly, the presence of comorbidities in older patients are associated with a poorer prognosis and decreased survival in breast cancer patients (11). It is recommended that health care professionals and breast clinicians should not deny treatments to patients on the basis of age, but there is evidence that this does happen (12-14). To guide clinicians, there are several integrated care assessments which can be used to assess the suitability of older adults for treatments, such as the Comprehensive Geriatric Assessment (CGA), although these are rarely used and clinician opinion is highly variable (13, 14).

1.1.2.1. Assessment Tools for Older People

The Comprehensive Geriatric Assessment (CGA), (also sometimes known as Geriatric Evaluation and Management), is a multi-dimensional assessment which is used to inform shared decision-making for older people (15). The CGA is made up of four components: a physical assessment; functional, social and environmental assessment; psychological; and medication review **(Figure 4).**

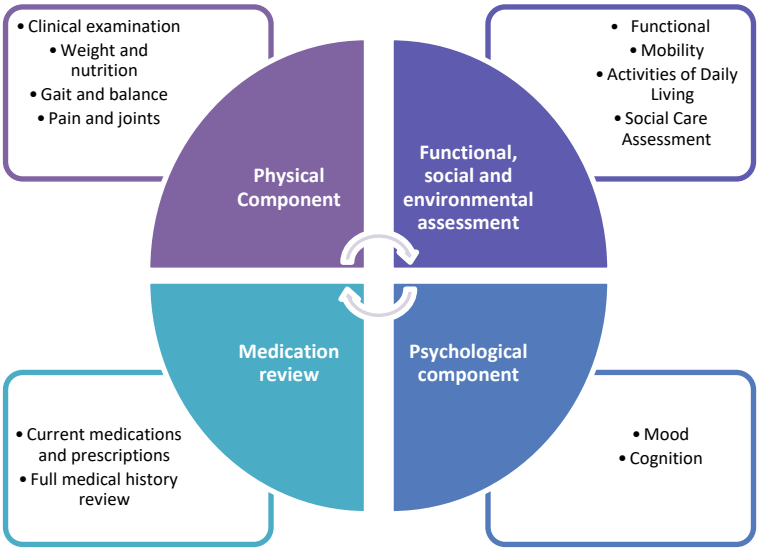


Figure 4: The four components of the Comprehensive Geriatric Assessment.

The use of the CGA in older patients is recommended by the National Institute for Health and Care Excellence (NICE) (16), and is widely used in the National Health Service (NHS) (17), although not widely applied in breast surgery clinics. The CGA goes beyond the single parameter of chronological age (18) by evaluating factors that include predicting treatment tolerance (19), the psychological ability of the patient to cope with treatment (20) and risk for mortality and morbidity in older patients (21). One limitation is that the CGA can be time-consuming to complete, often taking up to two hours, and some aspects are difficult to administer without specialist training. Assessing patients who lack capacity, such as people living with dementia, may pose challenges if they were unable to give consent to physical assessments. Similar less complex tools that can be used in older populations include the Charlson Comorbidity Index (22), which predicts probability of mortality in patients with co-morbidities, and

the Adult Comorbidity Evaluation-27 (ACE-27), which is used in cancer patients with co-morbidities (23).

1.1.3. An Ageing Population

As a result of the issues covered thus far, the U.K. (and many other developed countries) are experiencing a significant growth in the older age groups. This fundamental demographic change has resulted in an ageing population, which is set to increase; the worldwide population of over 60 year olds is set to reach 1.6 billion in 2025, and increase further to 2 billion by 2050 (24). The implications of ageing populations are that many people are now living longer than ever before into their older years and facing numerous health challenges. This includes managing complex co-morbidities, such as dementia, and the potential risk of developing age-related disease, such as breast cancer. This will be explored in the following section.

1.2. Dementia

1.2.1. Definition

Dementia is a neurodegenerative disease that affects the brain, which is the most complex organ in the body. Dementia is an umbrella term used to describe a syndrome characterized by a long-term (>6 months) loss of cognitive capacity in someone of previous normal intellectual function (25). It may be static or progressive, and of variable severity. In the International Classification of Diseases (ICD-10) (26), it is F00.0 to F03 with the sub-classification depending on aetiology.

The cellular structure of the brain is made up of neurons connected by numerous synapses, which enable the neurons to communicate signals to one another by means of axons. In a person with dementia, this function is impaired, and the ability of neurons to transmit signals is limited by, for example, neurofibrillary tangles and plaques, or in the case of vascular dementia for example, by loss of neurons due to ischaemia (27). The syndrome has numerous manifestations including loss of memory, impaired reasoning and understanding, the inability to learn, a progressive deterioration of language function, social disorganization and disinhibition (28). In its mildest stages, individuals may function relatively well in daily life, while at its most severe, 24-hour personal care may be required. Since the incidence of dementia is known to increase with age, what this means for the future is an older demographic with varying levels of incapacity. Age is a primary risk factor for dementia, however it is a misconception that dementia is a normal side effect of the ageing process (29).

1.2.2. Epidemiology

The World Health Organisation estimates that the global incidence of dementia is approximately 7.7 million new cases each year (30), presenting dementia as a global public health challenge (31, 32). In 2015, it was estimated that around 850 000 people suffer from some form of dementia in the U.K. (33) with this figure set to continue increasing.

Longitudinal data from the past 20 years indicates that the prevalence of dementia varies demographically by age sub-group and gender. A review of dementia in the over 65 population suggests that the prevalence of dementia increases exponentially with age; with late-onset dementia (in the over 65s) being the predominant dementia type in the U.K. (34). Analysis of prevalence from a major U.K. cohort study, Cognitive Function and Ageing (CFAS) II (35), found that dementia prevalence in the 'old-old' category (>90 years old) was significantly higher in women compared to men **(Figure 5)** and almost doubles in 5-year increments.

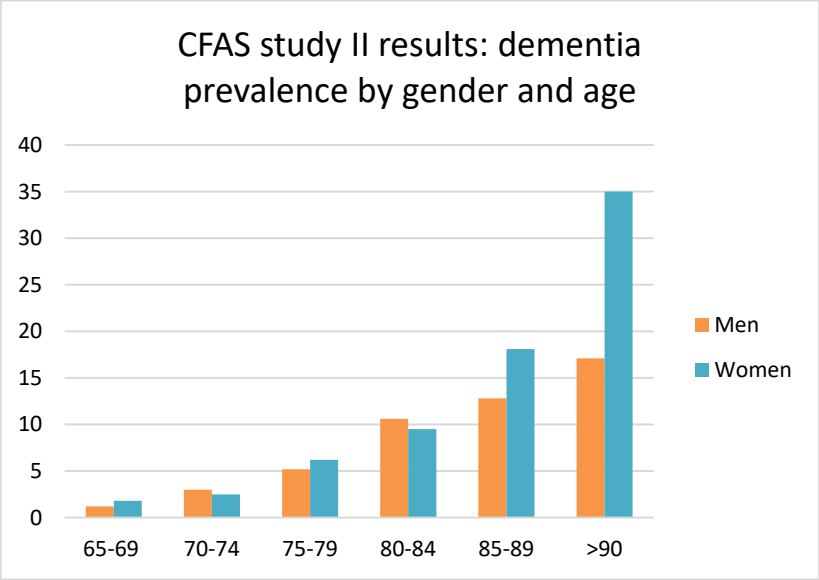


Figure 5: CFAS 2 study - dementia prevalence in men and women.

Source: Adapted from Matthews et al (35) "A two decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results from CFAS".

Explanations for this gender disparity point towards a combination of environmental and genetic factors; with one study associating the high risk and susceptibility of dementia with PCDH11X (Protocadherin 11 X-linked gene), of which women have two copies, as it is on the X chromosome (36). This gene is important for cell-cell recognition and neurological function and has been linked in some studies (but not all) to late onset dementia. Other studies suggest that the prevalence of dementia is more closely linked to social deprivation (37) and the complex set of aetiological factors this engenders. Figures taken from Quality Outcome Framework (QoF)

indicators show that the percentage of people diagnosed with dementia is higher in the North of England compared to the South (38).

1.2.3. Diagnosis of Dementia

The International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) are primarily used as diagnostic criteria for dementia subtypes in the U.K. The diagnostic process will usually begin in primary care, when patients present to their general practitioner (GP) with early symptoms. Following an assessment and examination, it is often a referral to specialist services, such as a Memory Clinic or Neurology clinic, where a specific diagnosis will be made.

Having an early diagnosis may be beneficial as this can mean the individual is able to plan ahead for future care and treatment options. However, since the early symptoms of dementia can be associated with, or mimicked by, other conditions, such as depression, hypothyroidism or stress, this can significantly delay a diagnosis. To rule out these causes, a range of interventions will be carried out, such as blood tests and scans of the brain. As dementia cannot be diagnosed from one single test, screening tools may be used to make an initial diagnosis, such as the General Practitioner Assessment of Cognition (GPCOG), Abbreviated Mental Test Score (AMTS) and Mini Mental State Examination (MMSE) (39). Specialist tests can later involve magnetic resonance imaging (MRI) and computed tomography (CT) scans of the brain to differentiate dementia from a range of other conditions with clinical similarities (such as delirium for example).

Following a diagnosis, NICE (40) recommend that treatment and prognosis is discussed with the patient, alongside any wishes for future care planning (this will be discussed later in the thesis). Diagnosis will also involve assessing the stages of dementia, although it is important to note that the way in which an individual experiences dementia can vary from case-to-case, with some stages overlapping.

1.2.4. Stages of Dementia

The clinical symptoms and signs of dementia are wide ranging, and it is a misconception to confine these to memory loss. Some symptoms may present earlier in some individuals and later in others; varying by the stage and specific type of the disease (for example, stroke-like symptoms are often a feature of vascular dementia). The commonality is that most types of dementia are progressive, and so it can be useful to understand the condition by thinking of the disease as a series of stages – mild, moderate, and severe – as summarized in **Table 1.**

Table 1: Summary of dementia by stage (mild, moderate and severe)

Dementia Stage	Symptoms
Mild Dementia (early stage)	Small changes in an individual's behaviour or cognitive abilities. May include disorientation, recall difficulties, forgetfulness and mild confusion.
Moderate Dementia (middle stage)	Progression of earlier symptoms and an increase of support needed to manage daily life (may include reminders to eat, wash and dress). May begin to show signs of behavioural symptoms such as becoming upset or angry, and a loss of confidence.
Severe Dementia (late stage)	Symptoms will become more challenging to manage, an increase in help required, and in some cases becoming dependent on others for care. Physical symptoms may affect walking and gait.

In the early stages of dementia, the symptoms associated with the condition may be very mild and as such may not formally be diagnosed as dementia. Quite often, however, symptoms will gradually worsen over time and require higher levels of care and support. The next section will describe the stages of dementia in further detail.

1.2.4.1. Early-Stage Dementia

Many of the biological changes in the brain that are associated with dementia begin to occur long before the onset of symptoms. For some individuals, mild cognitive impairment (MCI) is a 'pre-dementia' condition, which represents a range of symptoms rather than a disease. This is often the initial stage where an individual (or their friends and family) may begin to notice some subtle changes in respect to their cognition, reasoning or changes in mood. These symptoms are often not formally defined as dementia unless they start to reach a stage that impacts on daily activities,

but it is known that having MCI means there is an increased risk of going on to develop dementia – around 10-15% each year (41). A faulty APOE4 gene can also increase this risk. Assessment will involve a review of the patient's physical health and medications to rule out the possibility of other conditions that sometimes present with dementia-like symptoms, which could be treatable. Following a diagnosis, the patient will be routinely monitored by either their GP or Memory Clinic. Currently there are no approved treatments for MCI, although health and lifestyle changes to avoid the risk of developing dementia are advised in respect to smoking, diabetes, diet and exercise. This may be a stage where older adults start to think about putting plans in to place for their future health care, such as appointing a lasting power of attorney (LPA) for health and welfare.

1.2.4.2. Moderate Dementia

Also known as *middle stage* dementia, this is often the point where a patient begins to exhibit more pronounced symptoms associated with dementia such as forgetfulness, the need for reminders to undertake daily tasks, and confusion. Guidance from Alzheimer's UK notes:

> *"Changes in behaviour tend to be most common from the middle stage of dementia onwards and are one of the most challenging aspects of dementia for carers"*
>
> **Alzheimer's Society (42)**

The middle stage is often the point at which treatment is considered for the patient (**Section 1.2.6.** outlines the different types of treatment for dementia).

1.2.4.3. Severe Dementia

Also known as *late-stage* dementia, this is the point in the dementia trajectory where symptoms will often become much more severe, alongside the need for care and support from others, such as a caregiver or family member. Advanced dementia at this stage would affect the patient's memory, communication, mobility, behaviour and mood.

1.2.5. Dementia Types

The management and progression of symptoms will vary from person to person and be dependent on a whole range of factors such as early detection, the start of treatment and presence of any other co-existing health problems. Dementia can present in different forms, known as subtypes, which manifest distinctive symptoms in the patient, for which numerous treatments are licensed. The four most common subtypes of dementia are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and Frontotemporal dementia (which is more often associated with young-onset (under 65s) dementia) **(Table 2)**.

Table 2: Overview of dementia subtype, tests and % of cases in the UK

Dementia Subtype	Assessment Criterion setting body	Further tests	% of cases diagnosed in the U.K. (43)
Alzheimer's Disease	National Institute on Ageing (NIA) criteria for Alzheimer's disease	Computerised tomography (CT), Magnetic resonance imaging (MRI), examination of cerebrospinal fluid.	62% of cases
Vascular Dementia	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et L'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia	MRI, CT.	17% of cases
Dementia with Lewy Bodies	International FTD criteria for frontotemporal dementia and International Frontotemporal Dementia Consortium criteria for behavioural variant frontotemporal dementia	Single photon emission computed tomography (SPECT), cardiac scintigraphy.	4% of cases
Frontotemporal Dementia	International FTD criteria for frontotemporal dementia and International Frontotemporal Dementia Consortium criteria for behavioural variant frontotemporal dementia	MRI, Fluorodeoxyglucose positron emission tracer (FDG-PET) scan, perfusion SPECT,	2% of cases

Mixed Dementia	A combination of assessments used for Alzheimer's vascular, dementia with Lewy bodies and frontotemporal dementia.	MRI, CT, SPECT.	10% of cases
Other	-	-	5% of cases

The detailed aetiology of dementia is outside the scope of this thesis; a summary of each subtype is described below.

1.2.5.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, accounting for 62% of cases diagnosed in the UK **(Table 2).** Mild cognitive impairment (MCI) is an intermediate state of cognitive decline and a known precursor to AD in the elderly (44, 45). Some symptoms that are more characteristic of AD include:

- Loss of memory and forgetfulness
- Ability to undertake daily living tasks may become challenging and require reminders, support and planning
- Difficulties in communicating ideas, thoughts and feelings
- Changes in mood, such as depression and anxiety

The aetiology of AD is associated with genetic mutations. Familial AD is caused by a single-gene mutation linked to the amyloid precursor protein (APP) gene on chromosome 21, and two presenilin genes - the PSEN1 gene on chromosome 14 and the PSEN2 gene on chromosome 1. Both gene mutations are known to cause early onset dementia (46). The second genetic aetiology is polygenic inheritance, with over 20 genes identified which can determine the chances of developing the disease. These genes interact with other factors which increase the likelihood of an individual going on to develop the disease, such as the apolipoprotein E (APOE) on chromosome 19. The underlying pathology of AD is linked to a malfunction of 'misfolding' protein structures that cause amyloid fibrils (protein deposits) to form in the brain, which results in memory loss and other associated symptoms (47).

1.2.5.2. Vascular Dementia

After AD, vascular dementia is the second most common dementia subtype (34). It occurs when the blood vessels which feed the brain become damaged (atherosclerosis), often caused by a stroke or small vessel disease, resulting in subcortical vascular dementia (48). The symptoms for this particular subtype of dementia vary, but can include:

- Symptoms which are associated with strokes, depending on which part of the brain is affected, such as muscle weakness
- Coordination problems (walking, change in gait)
- Impaired cognition which affects reasoning ability
- Changes in mood, including anxiety and depression

No single gene mutations have been discovered for this subtype yet, but there may be risk genes involved, such as the APOE gene. A family history of heart disease or strokes can also increase the risks of developing the disease. An acute stroke may result from either the blockage of a cerebral blood vessel (ischemic stroke) or bleeding from a blood vessel (haemorrhagic stroke) causing brain damage. This not only impairs sensorimotor functions (the classical perception of a stroke) but may also cause intellectual impairment and therefore dementia. If the white matter is predominantly damaged, this is called sub cortical leukoencephalopathy. More chronic vascular occlusion caused by atherosclerosis will cause progressive vascular dementia (49). The risk factors for this are generally those of atherosclerosis (hypertension, diabetes, smoking and hypercholesterolemia) (50) and stroke-related (51).

1.2.5.3. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is the third most common subtype, symptomatically presenting in a similar way to both AD and idiopathic Parkinson's disease. The symptoms for this subtype can include:

- Tremors and hallucinations
- A fluctuation in cognition and confusion
- Sleep disturbances

- Coordination problems – falls are a common risk

As with other subtypes of dementia, memory impairment is also a hallmark of DLB (52). Research suggests an overlap in underlying pathology linked to how the brain processes the protein alpha-synuclein; whereby protein deposits build inside the nerve cells within the brain (53, 54). This results in damage to the way in which nerve cells (particularly those responsible for movement and memory) send signals and communicate. Research to date has not identified any single gene mutations so far, but the APOE e4 variant is a strong genetic risk factor (55, 56). Some genes are also involved in Parkinson's disease, which accounts for the overlap in some symptoms, and most patients will go on to develop both conditions. There are no exclusive tests for DLB, however scans of the brain can be used. This accounts for about 4% of all dementia cases in the U.K., however there is evidence that strongly suggests this type of dementia is under-diagnosed (57).

1.2.5.4. Frontotemporal dementia

Also known as Pick's disease, frontotemporal (FTD) is a form of presenile dementia that accounts for around 2% of cases in the U.K. **(Table 2),** and is most common in the under 65 population (58). It is caused by cerebral atrophy, due to nerve cell damage in the frontal and temporal lobes of the brain. There are a number of complex genetic aetiological theories underpinning this condition, with familial frontotemporal dementia linked to mutation in the C90RF72 gene, and protein genes tau (MAPT) and progranulin (GRN) (59). The symptoms of this subtype manifest clinically in personality and behavioural difficulties and vary depending on which area of the brain lobes (frontal and temporal) are most affected. The two variants of FTD:

- **Behavioural variant frontotemporal dementia**
    - Loss of inhibition
    - Apathy and loss of motivation
    - Loss of empathy and social interest
    - Compulsive behaviours

- **Language variant (progressive non-fluent aphasia and semantic dementia)**
    - Slow, hesitant and slurred speech
    - Impaired understanding
    - Loss of vocabulary and understanding of words

In the later stages of FTD, the symptoms progress in a similar way to AD (and is often misdiagnosed as atypical AD). Blood tests, mental ability tests, CT and MRI are often used to rule out other possible causes, and measure brain activity.

1.2.5.5. Mixed Dementia

Mixed dementia is typically a combination of more than one type of dementia, although usually AD and vascular. This accounts for around 10% of dementia cases in the U.K. (43), although the exact prevalence is unknown as it is often diagnosed post-mortem (60). A range of symptoms such as those previously described and depending on which part of the brain is affected, can characterize this. It is usually treated according to the predominant cause of dementia.

1.2.6. Treatment for Dementia

The treatments that are available for people living with dementia will depend on the stage, subtype and speed at which the disease is progressing. This will vary as dementia affects individuals in different ways. In its very early stages, the symptoms of dementia may be manageable, and individuals may be capable of maintaining their independence with minimal treatment. This might involve taking a practical approach, such as keeping mentally active, physical exercise and memory training. In the later stages of dementia, where symptoms are much more advanced or severe, pharmacological treatments and social care will be needed to support the patient. At present, there is no known cure for dementia, but there is evidence that some treatments are able to slow the progression of the disease and help to manage its symptoms (61).

1.2.6.1. Pharmacological Management

The two main types of pharmacological treatment for AD are Acetylcholinesterase (AChE) inhibitors and N-Methyl-D-aspartate (NMDA) receptor antagonists **(Table 3).**

Both treatments will initially only be prescribed by a specialist HCP, with routine management either followed up by the patient's GP or a specialist care team. Regular assessments are important to ensure the effectiveness of the treatment and to monitor any untoward side-effects.

Table 3: Overview of treatments for dementia available in the U.K., recommended for use by NICE.

Drug	Subtype treated	Starting dose/ administered	Potential improvements	Potential side effects
Donepezil *(brand name Aricept®)*	Mild-moderate and severe AD	5mg or 10mg once daily. Tablets.	Reduced anxiety, improved motivation, memory and concentration, improved ability to continue daily activities.	Loss of appetite, nausea, vomiting, diarrhoea, muscle cramps, headaches, dizziness, fatigue, insomnia.
Rivastigmine *(brand name Exelon®)*	Mild-moderate AD	3mg up to 12mg daily, as tablets, oral solution or patches.		
Galantamine *(brand name Reminyl®)*	Mild-moderate AD	8mg, increasing up to 16-24mg daily. Oral solution or slow-release capsules.		
Memantine *(brand names Ebixa®, Maruxa® and Nemdatine®)* ***Licensed since 2002.***	Moderate-severe AD	5mg, increasing up to 20mg daily. Oral drops or tablets.	Slow progression of symptoms including disorientation and difficulties carrying out daily activities, delusions and agitation.	Dizziness, headaches, tiredness, raised blood pressure, constipation.

Source: NICE TA217 (61)

1.2.6.1.1. Acetylcholinesterase (AChE) Inhibitors – Donepezil, Rivastigmine and Galantamine

Guidance from NICE (61) recommends the use of AChE inhibitors for the management of mild to moderate AD. It may also be offered to patients with dementia with Lewy bodies and mixed dementia types (where AD is predominant or involved). Cholinesterase inhibitors work by blocking the cholinesterase enzyme from breaking down acetylcholine in the brain, which is a chemical that helps the brain send signals between nerve cells. By helping to increase the communication between nerve cells in this way, some the symptoms of AD can be stabilised and improved, such as memory and levels of concentration.

The three main types of AChE inhibitors work similarly, but can vary in side effects, which will be experienced differently depending on the individual. The NICE guidance on the use of these drugs for AD recommend Donepezil initially. Randomised controlled trials (RCTs) have shown that Galantamine can significantly improve cognitive function for patients with vascular dementia (62, 63), however the drug is not currently licensed for this use. Rivastigmine is licensed for dementia related Parkinson's. In cases where a patient's symptoms are exacerbated, or where there is an intolerance to AChE inhibitors due to side effects, the use of Memantine can be considered.

1.2.6.1.2. N-Methyl-D-aspartate (NMDA) Receptor Antagonists – Memantine (Ebixa)

Memantine is one of the main NMDA receptor antagonists licensed for the management of moderate to severe AD (61) . Memantine works by blocking NMDA receptors and elevated levels of glutamate in the brain, which is a chemical that can damage brain cells if released excessively (a side effect of AD). By blocking these effects, the drug helps to protect the cells from further damage. In terms of its efficacy, Memantine is not particularly effective in mild AD, but is known to be effective in halting the progression of AD symptoms (behavioural and psychological) (64, 65).

1.2.6.1.3. Antipsychotics Treatments

The behavioural and psychological symptoms of dementia (BPSD), anxiety and agitation are common non-cognitive symptoms which manifest in people living with dementia (66). These behaviours are often caused as a result of chemical changes occurring within the brain, pain as a result of the condition or treatment, and distress (67). The use of antipsychotics in this context is not recommended for mild non-cognitive symptoms in vascular or mixed dementia, and should only be considered in severe cases if the benefits to the patient outweigh the risks (68). Where non-pharmaceutical approaches have been unsuccessful, antipsychotics can be used to reduce some symptoms. For behavioural control, Lorazepam, Haloperidol or Olanzapine are recommended at the lowest effective dose for the elderly and frail

patients, particularly in circumstances where an individual may place themselves or others at risk as a result of their behaviour (69). This is because some of these treatments can have serious side effects, including:

- Risk of infection, blood clots and stroke
- Can exacerbate some dementia symptoms, increasing their severity
- Increased risk of death

For this reason, antipsychotics should only be used in the short-term with supervision and regular review.

1.2.6.2. Social Care Provision and Support

Social care planning is essential for assessing the needs and level of care for individuals with dementia. NICE guidance (70) recommends that care coordination should begin by:

- Involving the views of patients, caregivers and family members in respect to the individual's ability to cope and their needs
- Advising the patient and caregiver on how to access support and specialist services
- Ensuring that patients and their caregivers are aware of their rights and advocacy services, in line with the Mental Capacity Act (71).

In the U.K., the Care Act (72) outlines the law around providing care for adults and carrying out health needs assessments. This act also sets the threshold for whether the individual or local authority is responsible for any care home fees. Some adults with dementia can be eligible for NHS continuing health care, dependent on an assessment of needs undertaken by a clinical commissioning group (CCG). Where patients are not eligible, support may be provided by local authorities, or in some cases a joint package of care, which may be part-funded by the NHS (such as NHS-funded nursing care) and the patient. The main care settings for people living with dementia are:

1. Living at home independently or with caregiver support (family or professional)
2. Sheltered housing
3. Residential Care

1.2.6.2.1. Living at home independently

For people with mild-moderate dementia, it can be possible to continue living at home, as individuals may wish to live within an environment that is familiar to them. Many are able to do this with the help of caregivers or by adapting their home to be dementia friendly (73). In situations where a patient is visited at home by a caregiver, respite care (also known as replacement care services) can be accessed, which may include the individual attending a day centre or having a short stay within a residential care home. This can be arranged via local authorities or care agencies, with varying levels of costs involved.

1.2.6.2.2. Sheltered Housing

Sheltered (or supported) housing may also be considered in situations where a person with dementia still wishes to live independently but with on-site support available if needed. Often these dwellings are built with older adults in mind and adapted towards those with extra care needs, such as wider corridors for those with reduced mobility issues and emergency alarms in toilets. Living in sheltered housing often includes services such as scheduled visits from wardens and help with daily living. The costs of this can vary, with most sheltered housing funded by councils and housing associations, or private renting.

1.2.6.2.3. Residential Care Homes

For some patients with moderate-severe dementia, it may be in their best interests to live full-time within a residential care home. This is often the case where individuals require high levels of care, or if their health needs can no longer be met by living independently at home. This can be a difficult decision for family and caregivers to make, especially if the person has expressed a wish to remain at home (74). The behavioural and psychological symptoms of dementia (BPSD) are known to expose caregivers to the greatest degree of stress, and this is often a reason for seeking

respite care or moving the person living with dementia to residential care. The benefits of moving into residential care is that continuous support can be provided, alongside offering some social benefits from living with other residents. The majority of residential care homes operate under a 'person-centred' principle, allowing input from both patients and their caregivers in their care and treatment plans (75). Within this domain, HCPs are able to assist with a wide range of physical and personal support, depending on the level of care needed. This can involve washing, dressing and feeding. The costs for this provision of care can be self-funded, funded by the local authority or the NHS.

1.2.7. Dementia Caregiving

The caregiving provision for people who are living with dementia is often discussed as part of the patient's care coordination plan and routinely reviewed as the disease progresses. Specific recommendations for care coordination are outlined in NICE guidance NG97 (40). The two main forms of caregiving in this context are formal (paid/funded) and informal (unpaid) care.

1.2.7.1. Formalized Care Provision (including Admiral Nursing)

Formal care provision for people living with dementia involves the use of paid health and social care professionals, who will either visit the individual at home or provide care in a residential care home. The advantage of this form of care is that it is provided by people who are dementia-trained, and as such will have specialist knowledge of how to address the specific needs of a person living with dementia (such as BPSD symptoms). Admiral nurses are specialists in dementia care and work within a variety of local care settings (both community and residential). Admiral nurses are involved in developing tailored care plans that can help people with dementia to live independently, including modifying the home environment and providing assistive technology (76). This also involves helping both caregivers and people with dementia access services, such as memory clinics, occupational therapy, and speech and language services.

1.2.7.2. Informal Care Provision

Informal care provision is typically unpaid, with an estimated 700,000 unpaid caregivers for people with dementia in the U.K. (77). Family caregivers are often the main source of informal provision, usually assuming the caregiver role for older relatives as they become less able to function independently in their later years. Adopting this role can in some cases be a complicated transition; such as suddenly taking on a range of complex responsibilities with little preparation, support and experience (78). Depending on the individual's health and level of need, some family caregivers may be required to take on this role full-time, particularly where a person with mild-moderate dementia wishes to continue living independently at home. The scope of duties can include managing medications, coordinating appointments and care, managing finances, housework, and personal care such as bathing and feeding.

As the disease progresses, the need for higher levels of care may place a huge financial and psychological burden on caregivers, meaning that this form of care is no longer feasible. This can result in caregivers facing difficult decisions such as the transition of a person with dementia to residential care (79), weighing up their relative's preferences with what may be in their best interests, and the financial implications of such decisions.

Caregiver burden is well-documented in the literature (80-82), and described as a "multidimensional response to physical, psychological, emotional, social, and financial stressors associated with the caregiving experience" (83). This burden and increased demand in caregiving can become increasingly intense and complex where a person with dementia receives a new diagnosis of cancer (84). The next section will explore this in more detail.

1.3. Breast Cancer

1.3.1. Epidemiology

Breast cancer is predominantly a disease of middle aged and older women, with a median age at diagnosis of 62 (85); with one third of cases occurring in women over the age of 70 years (86, 87). This represents approximately 12,000 women per year across the UK. In this age group of women, the prevalence of dementia is around 10.5% (34), meaning that each year approximately 1260 women with cognitive impairment are likely to present with breast cancer.

There are some potential risk factors associated with breast cancer, the strongest of which is age (88, 89). This may be attributed to a number of causes, such as a lifetime of exposure to carcinogens, environmental factors and lifestyle choices such as obesity and alcohol consumption (90), alongside age-related genetic wear and tear **(Table 4).** Family history is also a risk factor, with certain potent genes (BRCA1, BRCA2 and PALB2), weaker genes (ATM, CHEK2 and up to 70 others) and single nucleotide polymorphisms (SNPs) predisposing women to developing breast cancer (91). However, these gene mutation carriers usually develop their cancers at a relative early age and so hereditary causation is less relevant to the older population.

Table 4: Overview of breast cancer risk factors for women

Biological Risk Factors	Environmental
Gender – more likely in women than men	Diet
Age – increases with age	Obesity and alcohol
Previous History of atypia or DCIS	Older age at first pregnancy
Family history – genetic risk	Oral Contraceptives
Dense breast tissue on mammography	Use of combined HRT

1.3.2. Diagnosis of Breast Cancer

Breast cancer care and treatment involves input from a multidisciplinary team (MDT) made up of specialist breast care nurses, breast surgeons, radiologists, oncologists and pathologists. Two thirds of women present with symptoms in the breast, the most common of which is a breast lump, but may also have noted nipple discharge,

indentation of the skin, nipple inversion or a range of less common symptoms. After referral to a breast clinic, the diagnostic process for most women involves triple assessment consisting of a physical examination, imaging with mammography and ultrasound, and a biopsy. These three sets of findings are then reviewed at an MDT to determine if they concordantly indicate a diagnosis of cancer. If results are non-concordant, further tests may be arranged to clarify the diagnosis. NICE guidelines (92) recommend that patients should be informed of their results within one week. If cancer is diagnosed, normal clinical practice involves a consultation with a consultant and breast nurse specialist who will explain the results and discuss the next steps for treatment **(Figure 6).**

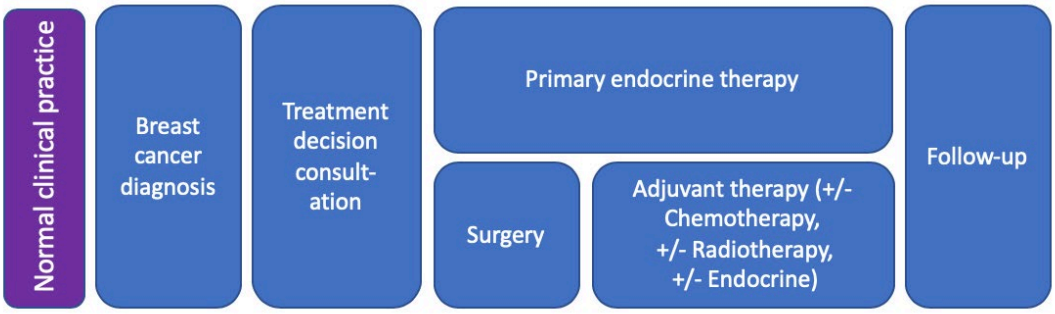


Figure 6: Clinical pathway for breast cancer treatment.

The type of treatment offered will depend on a range of complex factors including disease stage and biology (grade and receptor subtype) and the patient's treatment tolerances and preferences. A full discussion of the management of breast cancer is beyond the scope of this thesis, so the following is a simplified overview.

1.3.3. Histopathology

1.3.3.1. Grade, Staging and Receptor Status

Grading is used to interpret how differentiated the abnormal cells are from normal cells in the breasts. This ranges from being well differentiated (low grade), moderately differentiated (intermediate grade) or poorly differentiated (high grade). This has prognostic implications for the patient, and also influences treatment decisions regarding use of adjuvant therapies. The most common system for grading used in the U.K. is the Elston and Ellis modification of the Scarff-Bloom-Richardson grading system

(93). Breast cancer staging uses the American Joint Committee on Cancer (AJCC) TNM system (last updated in 2018) to classify the tumour size (T stage), lymph node spread (N Stage) and any metastasis (M stage). The prognosis of the patient may be determined from disease stage, combined with the grade and biological subtype (oestrogen, progesterone, HER-2 and Ki 67 expression levels of the cancer) using complex algorithms such as PREDICT (94).

Immunohistochemistry (IHC) is always used to determine the receptor status of the tumour, assessing for the presence of progesterone receptors (PR), estrogen receptors (ER), and human epidermal growth factor receptor 2 (HER2). In addition, the proliferation index (Ki67 score) is sometimes measured, which also gives prognostic information. This will guide administration of certain adjuvant therapies and the likelihood of the cancer cells responding to specific treatments. The receptor type also has a powerful influence on prognosis; with HER2 positive cancers being the most aggressive sub-type with the worst prognosis, and strongly ER+/PgR+, HER2 negative, low Ki-67 cancers the best prognosis. There are also more complex classifications based on aggregation of these receptor profiles classifying cases into luminal A or B, triple negative and HER2 enriched (95). There are now even more complex methods of breast cancer phenotype classification available using assays of multiple genetic characteristics such as Oncotype DX® (96, 97), Breast Cancer Index (BCI) test (98) and MammaPrint™ (99); the former of which can be used for patients with ER+, node negative, and intermediate prognosis cancers where the case for chemotherapy is unclear.

1.3.4. Treatment for Breast Cancer

In England and Wales, the NHS is guided by the National Institute for Health and Care Excellence (NICE); a non-departmental governmental body which publishes evidence-based treatment protocols and guidelines for treating patients. The key guidelines for early and locally advanced breast cancer is NG101 (92) and quality standard 12 (16). NICE guidance for early locally advanced breast cancer states:

"Treat people with invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than just endocrine therapy, unless significant comorbidity precludes surgery"

NICE Guidance [NG101] (92)

The suitability of treatment for breast cancer depends on a combination of disease related factors (mainly the stage, grade and biotype of cancer) and patient related factors (patient preferences, patient fitness). Standard treatments for breast cancer are categorized as local and systemic treatments, which can be used in combination, before or after each other (92). The standard local treatment for operable breast cancer is breast surgery, combined with a lymph node sampling procedure (sentinel lymph node biopsy (SLNB)) or full node clearance if the nodes are clearly involved at presentation. Surgery is then followed by adjuvant therapies (chemotherapy, radiotherapy or endocrine therapy) **(Figure 7).**

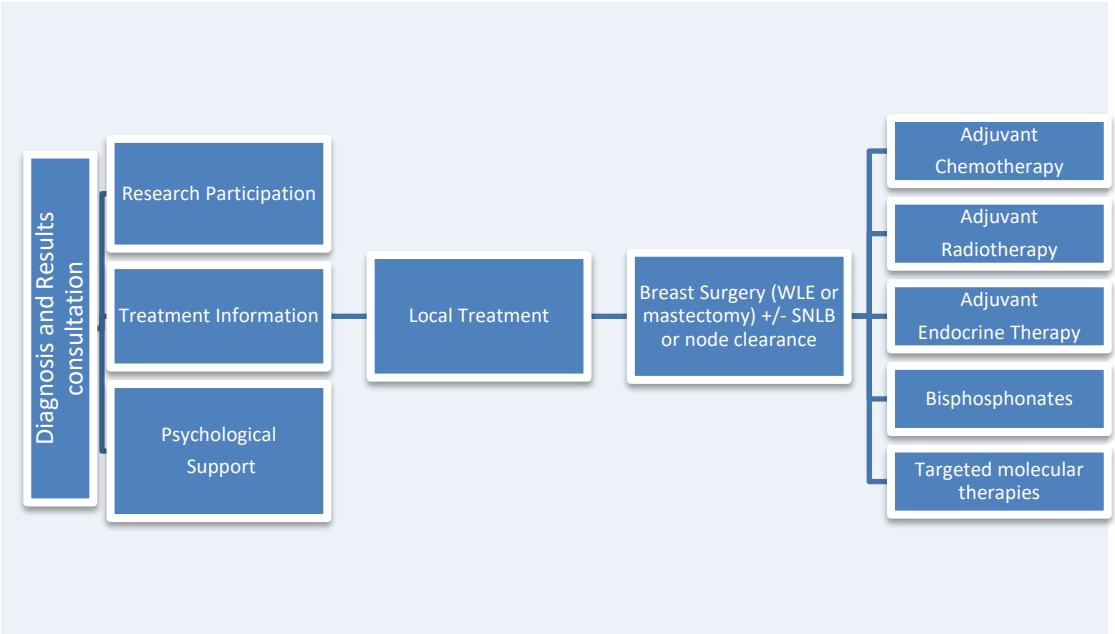


Figure 7: Local treatment pathway for breast cancer

The next section will give an overview of the local and systemic treatments for breast cancer.

1.3.4.1. Local Treatment: Surgery and Radiotherapy

1.3.4.1.1. Breast conservation surgery and mastectomy

The two main surgical approaches to treating breast cancer are breast conserving surgery (wide local excision or lumpectomy) and mastectomy. Wide local excision (WLE) involves removal of the tumour and some of the surrounding normal tissue, whereas mastectomy is the removal of the entire breast. In some cases more complex surgery may be offered such as mastectomy and reconstruction, or breast re-shaping after WLE (oncoplastic surgery/therapeutic mammoplasty) (100). These surgical approaches are combined with stage appropriate axillary surgery and followed by adjuvant or neo-adjuvant therapies.

1.3.4.1.2. Axillary surgery

In women who have no clinical evidence of node involvement at the time of diagnosis and a negative axillary ultrasound, limited axillary surgery to sample between 1 and 4 axillary nodes is performed. Selection and identification of the most 'at risk' nodes are aided with either radioisotope, blue dye or paramagnetic iron (SPIO) suspension, which are used to identify the nodes draining the tumour (a sentinel node biopsy). This operation has a minimal morbidity and high accuracy (101). If the nodes are affected (either at the time of initial diagnosis or after SLNB), an axillary clearance operation to remove the rest of the axillary nodes is performed, although increasingly more conservative strategies are being applied based on research showing that omission of completion clearance (+/- axillary RT) is oncologically safe and reduces morbidity (101, 102).

1.3.4.1.3. Adjuvant Radiotherapy

Radiotherapy is often used as an adjuvant therapy following surgery (103) to reduce the risk of local recurrence by destroying any remaining cancer cells in the breast. This is regarded as obligatory in women who have had breast conservation surgery and depends on the stage of the disease following mastectomy (usually given to women with node positive or locally advanced cancer) (92, 104). Radiotherapy is achieved by externally targeting the area with radiation from a linear accelerator, although

research is currently evaluating local application directly in the breast (intraoperative radiotherapy) (105, 106).

1.3.4.2. Systemic Treatments: Hormone Therapies, Adjuvant Chemotherapy, Bisphosphonates and Targeted Therapies

1.3.4.2.1. Hormone Therapies

Hormone therapies can be used as an alternative to surgical intervention for ER+ breast cancer (in frail older women) and as an adjuvant therapy following surgery where they reduce the risk of recurrence by approximately 25-30%. Hormone therapies work by blocking oestrogen from stimulating the growth of cancer cells either as direct receptor antagonists or by reducing oestrogen synthesis. Having a HER2 positive cancer can also guide treatment. The main hormone therapies used for treating primary breast cancer are Aromatase Inhibitors (AI) (Anastrozole, Exemestane or Letrozole) (107) and Tamoxifen (92). Treatment is usually for 5 years, or 10 years for women with high-risk disease (108, 109). The side effects include hot flushes, bone density loss and joint pain with AI's (110). Hot flushes, endometrial hypertrophy and rarely endometrial malignant change, and deep venous thrombosis are frequent side effects of Tamoxifen.

1.3.4.2.2. Adjuvant Chemotherapy

Chemotherapy, which is a combination of cytotoxic drugs given concurrently, is usually advised for women with poor prognosis breast cancer as an adjuvant therapy. Side effects can be severe, and in some cases, may result in death from neutropenic sepsis, and so is rarely used in women over the age of 80 (111). Chemotherapy may also be used as a neoadjuvant therapy to reduce the size of the tumour enough to make surgical intervention easier. Chemotherapy is also widely used in the palliative setting in women with metastatic disease.

1.3.4.2.3. Bisphosphonates

Recent evidence from a range of trials has shown that post-menopausal women with breast cancer may benefit from taking bisphosphonates (112, 113) which are primarily used to treat osteoporosis. In trials with breast cancer patients, it was found that bisphosphonates improve survival and reduce the rate of bone metastases (114).

Bisphosphonates have recently been approved in the adjuvant setting for post-menopausal women with moderate or high recurrence risk breast cancer (115).

1.3.4.2.4. Targeted Therapies

One of the main targeted therapies for breast cancer, Trastuzumab, is a monoclonal antibody, which inhibits cancer cells that over express the HER2 receptor (116). These cancers have the worst prognosis, however, the use of Trastuzumab (and some other targeted anti-HER2 directed therapies such as Lapatinib, Pertuzumab and TDM-1) (117) improves prognosis in these cases (118, 119) and can prolong survival in patients with HER2+ cancers.

1.3.4.3. Surgery versus Primary Endocrine Therapy in Older Women

In practice, it is recommended that older women older than 70 should be considered for the same surgery as younger patients, and that Primary Endocrine Therapy (PET) should only be offered as an alternative to women who are unsuitable for surgery with ER positive tumours, a short estimated life expectancy, or who are considered too frail for surgery (120). Before making a choice between surgery and PET, patients will discuss with their doctor what type of operation they will need (WLE or mastectomy and axillary surgery) and weigh up the risks and benefits of each type of treatment.

Primary endocrine therapy offers the advantage of allowing older women to avoid the risks associated with surgical complications, such as seroma formation, haemorrhage/bleeding, wound infection and lymphedema (121) as well as more serious systemic complications from having a general anaesthetic such as chest infections, cardiac arrhythmia, stroke and post-surgical confusion. Patients are also able to avoid hospitalization (122) and loss of independence while recovering from surgery. There are also psychosocial effects to consider in terms of body image for women who choose surgery (123), as both WLE and mastectomy will result in scarring and mastectomy will profoundly change cosmetic appearances. Studies generally present PET as an effective alternative for patients with co-morbidities (124, 125), or those that choose to refuse surgery based on personal preference. Some women

treated with PET, however, may need surgery later due to disease progression, at which point they will be older and more vulnerable to surgical complications.

Surgical options are summarised in **Table 5** and techniques are briefly discussed below, although detailed discussion is outside the scope of this thesis.

Table 5: Summary of Surgery and PET comparison

	PET	**Surgery** *(plus endocrine therapy)*
Regimen/what it involves	Patients take a tablet each day.	An operation under local or general anaesthetic. Axillary glands may be removed and tested. Patients then take a tablet every day.
How the treatment works	The tablet blocks oestrogen, which controls the tumour (can shrink or stop its growth)	Removal of the tumour by either a lumpectomy (to remove the breast tissue containing the tumour) or a mastectomy (complete removal of the breast).
Risks and side effects	Common side effects include fatigue, hot flushes, aching joints.	Risk of infection, swelling (lymphoedema), or bleeding from the operation.
Recovery	Most women can continue with daily activities.	Recovery varies depending on WLE or mastectomy. Some women can return home the same day, others may need to stay in hospital overnight. It may take up to 6 weeks to return to daily activities.
Chances of recurrence	In 3-5 years, the risk of the cancer growing in approx. 30-50% of women.	In 3-5 years, the risk of the cancer recurring in the breast or scar is 5%.
Follow-up	Regular check-ups to measure the tumour and check it has not started growing again.	Post-operative check-up with surgeon and mammograms.

Although overall survival rates between patients treated with PET and surgery was not found to be significantly different on meta-analysis of clinical trials (126), subsequent longer term follow-up of these trials and observational studies suggest that PET is associated with an inferior breast cancer specific survival, although treatment morbidity is better (127). Only patients who are unfit for surgery should therefore be denied surgery (92, 120).

1.3.4.4. Breast Cancer in Older Patients

Breast cancer mortality rates are strongly linked to age, with over 47% of UK deaths in women over 75 (128). These rates have continued to increase with a widening gap between the 'young old' and 'old old' age sub-populations. Some of the reasons for this include the following factors.

- **Breast screening programme cut-off**

In the U.K., the NHS Breast Screening Programme invites women between the age of 50 and 70 to routine appointments every three years. The rationale for this is related to efficacy, cost-effectiveness, and a lack of evidence to suggest there is value in screening in older women (this could be due to the fact that most clinical trials and research tends to exclude the oldest patients from studies). Most other western counties do not routinely offer breast screening to women over the age of 75, although the NHS is currently running a large RCT to extend screening to the age of 73, the AgeX Trial (129, 130). Although women over this age can request screening with no upper age cut-off, most are either unaware of this facility, forget to attend or have a perception that they are no longer at risk (131). Breast screening has the potential to diagnose cancer at an earlier stage, before onset of symptoms such as a lump or pain, at a point when treatment may be more effective. In comparison to the younger-old age group, older women may be at risk of a delayed diagnosis due to the lack of formal breast screening in the over 70 age group (131). There is also a correlation between increasing age and decreased mammography (132). In addition, women with dementia are even less likely to be offered regular screening and mammograms (133). As a result of all these factors, stage at presentation is generally higher in older women and higher still in older women with cognitive impairment. This will impact on both treatment needs and long terms survival outcomes.

- **Reduced awareness**

Research shows that older women are generally less breast aware than younger women (131) and check their breasts less often. Robb and colleagues (134) found that delayed diagnosis in older women was magnified in individuals with co-existent cognitive impairment.

- **Co-morbidities and age**

Treatment for older patients with breast cancer can be complicated by multiple-comorbidities, polypharmacy and frailty. Some studies have shown that older women with breast cancer are generally treated less aggressively than younger women (135) and PET is used more frequently in older populations with chronic comorbidities (136, 137). Comorbidity and age are also known to influence non-standard treatment of women (138) and impact on their survival after breast cancer (10, 139) with rates of adjuvant therapies lower amongst patients >80 with multiple comorbidities (140). Evidence-based SIOG guidelines recommend that surgery should not be denied to patients on the basis age alone, although older women continue to have a lower surgery rate than younger women (141).

- **Higher risks of adverse events**

While fit, older breast cancer patients should be considered for adjuvant therapies (142), there is evidence to suggest that due to the risk of adverse events (143, 144), surgery may be more suitable. In the Age Gap study, a significant number of older fitter women with high-risk tumours did not receive adjuvant chemotherapy (145). One explanation may be the perception that the benefits of adjuvant chemotherapy and radiotherapy are minor in some cases, such as treating ER+ HER2 negative breast tumours. A lack of robust data on local disease control in older frail patients indicates that new recommendations for management are needed, particularly as older women have been underrepresented in clinical trials due to their age (146). There is very limited data relating to chemotherapy use in older patients, in particular those over the age of 80 (86).

1.3.4.5. Breast cancer and people living with dementia

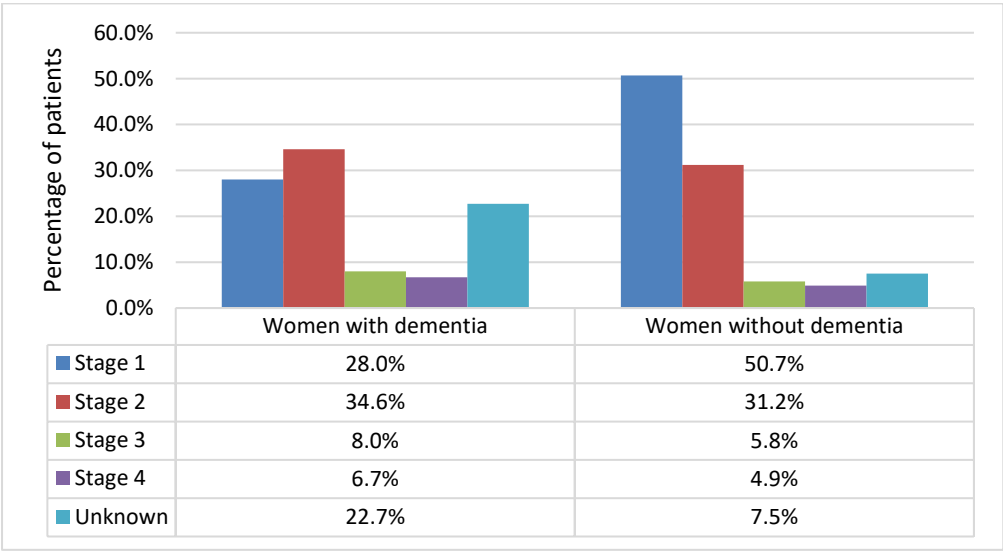
1.3.4.5.1. Screening

Breast screening and diagnostic interventions, such as ultrasound scans and mammograms, may be tolerated well by women with mild or even moderate dementia, however, in severe dementia, testing may be challenging for health care providers to perform. The first issue is obtaining consent to perform diagnostic tests

on people who have reduced capacity to consent to treatment themselves. The second issue is that undergoing such examinations can potentially cause emotional distress to people with dementia and their caregivers, particularly where the patient is frightened and unable to understand the reasons for the procedure. The decision to screen older people with dementia can therefore require a trade-off between benefit and harm for the patient (147). Some studies suggest that for these reasons it may be the case that in patients with dementia, mammograms pose more harm than benefit (133) and that the benefit of screening in this population is less than in those without dementia (148). There are also practical issues relating to gaining cooperation to undergo the mammogram, which requires the patient to stand still with their breast between the mammogram plates for many minutes. Where an abnormality is detected, the patient may also be required to cooperate with a biopsy which can be painful and potentially cause distress.

1.3.4.5.2. Diagnosis

People living with dementia are more likely to be diagnosed with breast cancer at a later stage than women without dementia. According to Raji and colleagues (148), 50% of patients without dementia were diagnosed with Stage 1 breast cancer, compared to 28% of patients with pre-existing dementia **(Figure 8).**



	Women with dementia	Women without dementia
Stage 1	28.0%	50.7%
Stage 2	34.6%	31.2%
Stage 3	8.0%	5.8%
Stage 4	6.7%	4.9%
Unknown	22.7%	7.5%

Figure 8: Breast cancer stage at diagnosis for patients with and without dementia

Source: Adapted from Raji et al (148).

Some explanations for higher stage presentation in women with dementia include a lack of symptom awareness (149) and reliance on either a caregiver or GP to continue physical examinations when screening programme invites end. There is also the pertinent issue that breast screening can result in high rates of over-diagnosis and over-treatment in approximately 25%, meaning that screening could diagnose a cancer which would not have threatened life if not diagnosed (150). The risk of over-diagnosis is higher in the elderly (151) and likely to be higher still in the elderly with dementia due to their generally reduced life expectancy.

1.3.4.5.3. Treatment

The type of breast cancer treatments offered will depend on a range of complex factors including disease stage, location, breast size and shape, and the patient's treatment tolerances and preferences. In the latter two respects, dementia will likely have a significant impact as some women may not be able to understand their treatment options fully, or express their preferences, although there has been very little research to address these differences (152). As mentioned previously, co-morbidities are much more likely to complicate the treatment of older people diagnosed with cancer, particularly those with multiple-morbidities (11). Around 70% of people with dementia have multiple-morbidities (43), and there is evidence to suggest that older people within this group, particularly those with AD, are even less likely to undergo surgery and receive adjuvant treatments (153). This can result in an inferior breast cancer specific prognosis for this population of women (10).

The practical implications of dementia in cancer care may mean that some treatment pathways will require complex discharge planning, pointedly where patients are unable to administer medications themselves (154). Systemic treatment such as chemotherapy and endocrine therapy will involve tablets being taken at regular intervals, and so a patient with dementia may require supervision to ensure adherence to the dosage and frequency of their treatment plan.

Many cancer treatments also have unpleasant side effects such as vomiting, joint pain and nausea; and so, patients will require substantial support mechanisms in place if

they live independently. Toxicity of treatment such as chemotherapy is also a key reason why this treatment is often used less in older patients, due to the high risk of long-term deterioration of cognitive function (155).

The experience and response to pain may also be different for people living with dementia, alongside the reduced ability to report serious side effects resulting from treatment (149). Most chemotherapy regimens are associated with immunosuppression, and patients are educated to spot the early signs of infection and seek early support. This self-management approach may be difficult for patients with dementia, exposing them to an increased risk of severe sepsis for example, unless there is close supervision. Similarly, some of the side effects associated with radiotherapy, such as nausea, skin reactions and risk of infection will also require close surveillance for serious adverse reactions.

Finally, there is the burden of polypharmacy, particularly where the patient already has a comprehensive treatment plan in place for managing the symptoms associated with dementia. As a result of a new diagnosis of cancer, the need for further appointments and check-ups may unsettle patients by removing them from their daily routine and familiar environment. Increased tiredness and fatigue from travelling to hospital for multiple sessions of treatment may also become burdensome for the patient and their caregiver (156). The combination of all these factors means that a tailored approach to treatment should be considered for patients with dementia and breast cancer.

1.4. Treatment Decision Making

Treatment decision-making involves using the information known about a particular disease or condition and weighing up the risks and benefits of the strategies that are available to treat the problem. The following section will explore breast cancer treatment decision-making, and the procedures for where a patient lacks capacity to make their own decisions (proxy or surrogate decision-making).

1.4.1. Breast Cancer Treatment Decision-Making

As mentioned at the beginning of this chapter, in the U.K., NICE guidelines (92) recommend specific treatments, alongside the scheduling and dosage, and modifications in scenarios where the treatment does not work as intended or adverse events/side effects occur. Treatment guidelines are based on clinical trial data, which test the safety and effectiveness of new drugs or medical devices. Such trials have a tendency to recruit younger and healthier volunteers, with the results often extrapolated to older populations. SIOG guidelines (120) state that treatment management decisions for older patients with breast cancer should take into account:

- Physiological age
- Life expectancy
- Risks versus absolute benefit
- Tolerance of treatment
- Barriers to treatment
- Patient preferences

Following a cancer diagnosis, treatment must take into account the stage, biotype and grade of the cancer, with the clinician providing the patient with enough information to help make an informed decision (92). The standard pathway for most newly diagnosed breast patients is a consultation to discuss the pathology results with a breast clinician and a breast nurse, who will explain the diagnosis and the treatment options available. The level and type of information offered to the patient will depend on their individual preference; for some women this might involve the use of decision aids such as leaflets, websites or decision-making grids such as BresDex (157).

When planning treatment, it is best practice to acknowledge that older adults are a diverse population with varied needs and preferences. Validated assessment tools can be used to determine if patients are suitable for particular types of treatments (158). The routine use of pre-operative assessments such as the CGA (outlined in **Section 1.1.2.1**) are available to assess older patients for cancer treatments (159) and guide them towards a particular intervention (160, 161). The use of the Instrumental

Activities of Daily Living (IADL) (162) and the Eastern Cooperative Oncology Group (ECOG) (163) assessments are also integral to the CGA, in that they consider the physical, mental and environmental factors that may impact on the patient's ability to tolerate treatment. The CGA can therefore be a useful guide for anticipating adverse events in older patients (20), however, in practice these sensitive, validated tools are rarely used and most women are not formally assessed in this way before decisions are made. The most widely used fitness tool is the ECOG performance status, although this is mainly used by medical oncologists rather than surgeons. This may be one reason why breast treatment for older women is highly variable across the U.K. (13, 127). A recent systematic review highlighted that the key challenges of using frailty assessments in breast cancer include slow uptake, lack of capacity to provide support for frailty assessments, lack of consistency in assessing older patients, few precise recommendations and the role of assessing women is not clearly defined in the cancer pathway (164).

From a medical perspective, treatment decisions will be aided by clinician knowledge, clinical guidelines, validated assessment tools and decision support tools. From a patient perspective, these discussions will be guided by their personal preferences, attitudes and beliefs. Shared decision-making approaches are considered best practice in the NHS, which involves HCPs and patients collaboratively reaching a decision together. For some patients, these discussions may also involve input from caregivers, clinicians, family and other health care professionals (165). Where a patient is unable to take an active role in the treatment decision, a proxy (or surrogate) decision-maker will be appointed to make help decisions on their behalf.

1.4.2. Proxy Decision Making

In England and Wales, informed decision-making is enshrined in the Mental Capacity Act (MCA) (71), which seeks to safeguard individuals who are unable to make their own treatment decisions. The Mental Capacity Code of practice is underpinned by the principle that capacity must be assumed unless it can be established that a person lacks capacity to make his or her own decisions (166). One of the well-established side effects of dementia is the reduced ability to make rational decisions (167); meaning

that at some point, another person may be appointed as the person's decision-maker. This is often called proxy or surrogate decision-making. A proxy decision maker is defined as someone who is authorized (either formally or informally) to make decisions on behalf of another individual (168). In some cases, caregivers assume the role of both a decision maker and service provider, and this will involve navigating which services and treatments are most appropriate for the patient (169).

1.4.2.1. Proxy Decision-Making Approaches

In medical ethics, there are a number of traditional approaches to making treatment decisions. Beauchamp and Childress (170) propose that medical decision-making should be approached on the basis of four general principles: autonomy, non-maleficence, beneficence and justice, although these principles are generally applied to patients who have the capacity to make informed decisions. In the context of decision making for a person with impaired capacity, Buchanan and Brock (171) state that three main models underpin the role of a proxy decision maker: **advance decisions, substituted judgment** and **best interests**. The Mental Capacity Act (71) does allow for all three models of decision-making, although the best interest framework is viewed as most dominant. These are described in more detail below.

1.4.2.1. Advance Decisions

Medical decision-making is predominantly based on the ethical principle of respect for autonomy. Autonomy is the capacity of an individual to use his or her own agency to make an informed decision free from coercion (170). A key principle of the MCA is to optimize self-determination by allowing patients the opportunity to make an autonomous decision (where and if they can). Research shows that 65% of older adults expressed a wish to discuss their prognosis with their doctor (172), suggesting that older adults are active in terms of their condition and treatment and it should not be assumed that they are simply passive in the decision-making process. For individuals with dementia, the capacity to be autonomous declines over time, meaning that at some point a proxy decision maker may assume these decision-making responsibilities. In instances where an individual has diminished capacity (such as mild

cognitive impairment), the patient may still be capable of making a rational decision, and this can be supported by advance care planning (ACP) (173).

The Mental Capacity Act (71) allows the legal right to appoint a lasting power of attorney or write an advance directive stating treatment preferences, should the person lack capacity in the future. An 'advance statement' describes any written statement or discussion where a person has expressed the type of care they wish to receive in the future and an 'advance directive' is a legally binding document that instructs the refusal of life-sustaining treatment (such as a do not resuscitate order) (166). The philosophical basis for ACP is that it extends the notion of patient autonomy into the future by allowing patients to actively participate in making decisions, while they still can. Advance care planning therefore empowers patients to state their care preferences in the event of losing capacity, and designate an individual as a health care proxy to make decisions on their behalf (174). One value of ACP is that it relieves some of the burden on caregivers (175), where an advance decision can help guide proxies towards a particular treatment that best represents the patient's wishes before losing capacity.

In situations where there are no advance directives to inform treatment decision making, a proxy would refer to the substituted judgment model.

1.4.2.2. Substituted Judgment

Substituted judgment is a decision-making framework that involves making a decision based on what the individual would want if they could decide for themselves (176). Making this judgment entails gathering information about a person's previously expressed preferences, values, attitudes and beliefs, and consider any advance decisions made prior to losing capacity (166). The fundamental underpinning of substituted judgment is that the individual's right to self-determination should be upheld, and if individuals with loss of capacity do not have an advance directive, substituted judgment is often used to make important decisions around care and treatment.

Lasting powers of Attorney (LPA), established in U.K. law under the MCA, allow patients to legally appoint an individual with the power to make decisions on their behalf in both substituted judgment and best interest models (177). In the U.K., a Health and Welfare LPA is commonly used to give or refuse consent to treatment and make decisions about care and living arrangements. Section 24-26 of the Mental Capacity Act (71) also allows for the decision to refuse treatment. Evidence suggests that older adults with dementia prefer that close family are involved in the decisions about their treatment and care (178), as they will have access to the patient's biographical narrative and allow them to make decisions that are consistent with the patient's preferences. Substituted judgment also allows proxies to 'frame the decision as the patient's own choice,' relieving some of the psychological burden entailed in making a choice for the patient themselves (179).

If there is limited information about the wishes and preferences of the patient, then the last option available in Buchanan and Brock's framework is the best interests model (171).

1.4.2.3. Best Interests

The best interests model differs from substituted judgment in that it involves the proxy decision maker basing a decision on an assessment of the individual's 'best interests' (166). The application of this approach rests on the principles of beneficence (positive benefit of treatment) and non-maleficence (avoiding unnecessary harm) (170) to promote the individual's best interests. In practice, this involves weighing up the risks and benefits of treatment available and any decision should not be motivated by surreptitious means. Section 4.6 of the MCA stipulates a statutory checklist of factors to consider when making a proxy decision, specifying that decisions should take into account the patient's past and present wishes, and the beliefs of the patient (71).

For any complicated decisions such as a procedure that may have both beneficial and harmful consequence for the patient (for example, surgical risks associated with general anaesthetic for an elderly frail individual), a best interests meeting is usually

held. This is a documented formal meeting that can be attending by anyone concerned with the patient's welfare, such as family, formal caregivers, close friends or other health care professionals. Independent Mental Capacity Advocates (IMCAs) may also be invited to such a meeting if there is conflict over the patient's care, or no family to make decisions based on their treatment (180).

There is some overlap between the best interest model and substituted judgment models where both involve taking into account the individual's preferences and wishes (181), however in the best interests framework, the decision should not only be guided by this (182).

1.5. Chapter Summary

This chapter has presented the background of the thesis which is concerned with decision-making for older women with breast cancer and dementia. An overview of the epidemiology and treatments for both conditions have been outlined, the challenges involved in screening and management for this population of patients, and the key principles of proxy decision-making.

In summary, older adults are a very heterogenous group: some are fit and living longer than ever before, whilst others live with very complex health needs and comorbidities. As the U.K.'s ageing population continues to grow, so will the number of older people who are living with comorbidities, such as dementia. This means that there will be complexities in the care pathway for people who go on to develop cancers, and thus require an increase in the level of support available. For caregivers, and family members who are involved in making decisions around care and treatment, a great deal of support and understanding of their needs is required. This is imperative where people are faced with making decisions in another individual's best interests.

The next chapter will outline the development of this PhD study, the structure of the thesis and how this research will attempt to bridge this gap (aims and objectives).

Chapter Two: PhD development

2.1. The Knowledge Gap

This thesis is an attempt to bridge the knowledge gap between how breast cancer treatment decisions are made for older women living with dementia, and the role of their caregivers in this process. To achieve this, the study explores the views and perspectives of caregivers who have been involved in making treatment decisions for older women with a new cancer diagnosis and who would otherwise not be able to make decisions for themselves. The motivations for undertaking this piece of research were to seek a greater understanding of the caregiver role in this context and determine the oncological outcomes for patients with breast cancer and dementia.

2.2. Research Questions

1. What is the impact of a cancer diagnosis on the treatment and outcomes for patients with dementia?
2. Which factors influence the treatment decision making process from the perspective of caregivers for patients with dementia and cancer?
3. What is the role of caregivers in making decisions for patients with a diagnosis of breast cancer and dementia?

2.3. Study Aims

1. To determine the oncological outcomes for older women with early breast cancer when also affected by cognitive impairment.
2. To determine the role of informal caregivers in making cancer treatment decisions for patients with cancer and dementia.
3. To determine the support needs and wishes of informal caregivers in the breast cancer care setting.

2.4. Study Objectives

1. Undertake a systematic review of the research literature relating to the role of caregivers in cancer decision making and the support of patients with dementia and cancer.
2. Analyse data from a prospective observational multi-centre cohort study of older women (>70) with early breast cancer (Bridging the Age Gap trial) to determine the baseline characteristics, cancer characteristics, cancer treatment and survival outcomes of women with breast cancer and cognitive impairment.
3. Design and apply a bespoke quantitative questionnaire to a sub-group of caregivers for patients with dementia and breast cancer, recruited to the Bridging the Age Gap trial.
4. Undertake qualitative interviews with caregivers for older patients with dementia to explore the experience of decision-making and caring for a relative with dementia and breast cancer.
5. A mixed methods synthesis of quantitative and qualitative findings to gain an in-depth understanding of the challenges facing caregivers and patients with dementia and breast cancer.

2.5. Study Components

This thesis presents a mixed method study with both qualitative and quantitative components:

- Systematic review **(Chapter Five)**
- Statistical analysis of treatment and survival outcomes of cohort study data **(Chapter Six)**
- Quantitative questionnaires of caregivers for patients with dementia and breast cancer **(Chapter Seven)**
- Qualitative semi-structured interviews of patients with dementia and breast cancer **(Chapter Eight)**
- Mixed method triangulation **(Chapter Nine)**

The study schema **(Figure 9)** is displayed at the beginning of each chapter to guide the reader through each stage of the project.

Figure 9: Schema of study components

2.6. Thesis Structure

- **Chapter One: Introduction**

Chapter One outlines the epidemiology, diagnosis and staging of dementia and breast cancer. An overview of the treatments available for both conditions is discussed. The final section discusses treatment decision making in the context of patients with dementia and the principles that underpin proxy decision making.

- **Chapter Two: PhD Development**

Chapter Two justifies the knowledge gap, research aims, objectives and study components. The project team and researcher role are summarised in this section and the structure of the thesis is outlined.

- **Chapter Three: Methodology**

Chapter Three details the philosophical underpinnings of the study and the methodological approach. This section will give an overview of paradigms, epistemology and ontology, and justify the reasons for adopting a pragmatic approach.

- **Chapter Four: Methods**

Chapter Four outlines the study design and research methods used. Data collection, sampling and analysis techniques used in the systematic review, quantitative (cohort analysis, questionnaire), qualitative (interviews) and mixed method (triangulation synthesis) components of the study are presented in this section.

- **Chapter Five: Systematic Review**

Chapter Five contains the systematic review article which was published in Psycho-oncology, 2019*; 'How are caregivers involved in treatment decision making for older people with dementia and a new diagnosis of cancer?'* This publication considered studies for inclusion that recruited formal or informal caregivers for older people with dementia and cancer. The article establishes the knowledge gap in the wider literature, and future research recommendations.

- **Chapter Six: Treatment and Survival Analysis**

Chapter Six contains an analysis of cohort study data; patient treatment and survival outcomes for women with cognitive impairment recruited to the Bridging the Age Gap trial. The analysis examined the tumour characteristics, treatment, survival and mortality outcomes of women with dementia versus women with normal cognition recruited to the trial.

- **Chapter Seven: Quantitative Questionnaire**

Chapter Seven details the recruitment process, questionnaire development, critical appraisal and analysis of the quantitative questionnaire results. Limitations are discussed.

- **Chapter Eight: Qualitative Interviews**

Chapter Eight presents the recruitment process, framework analysis, and findings of the qualitative semi-structured interviews, undertaken with caregivers who responded to the study questionnaire. Limitations are discussed.

- **Chapter Nine: Mixed Method Synthesis**

Chapter Nine integrates the four study components - systematic review, cohort data, quantitative and qualitative findings - as a triangulated mixed method synthesis. This chapter will address the overarching thesis research questions.

- **Chapter Ten: Discussion**

Chapter Ten presents a discussion of the study findings. The reflexive account of the research process and study limitations are detailed. The dissemination and communication of findings is outlined.

- **Chapter Eleven: Conclusions**

Chapter Eleven presents the final conclusions, implications for clinical practice, and recommendations for future research.

2.7. Project Team and Roles

This research study formed part of the wider NIHR funded programme ***'Bridging the Age Gap in Breast Cancer: Improving outcomes for older women'*** which opened to recruitment in 2012. This PhD project was developed from an initial idea to explore the treatment and outcomes for patients with breast cancer and dementia. The project was then developed with input from the wider Bridging the Age Gap steering group. Five study components had additional input from co-authors involved in the Bridging the Age Gap programme (roles and specific input is detailed at the beginning of each chapter).

- **Systematic Review:** Anne Shrestha (PhD student/breast surgeon), Maria Burton (PhD supervisor), Lynda Wyld (PhD supervisor/breast surgeon), Karen Collins[†] (PhD supervisor).
- **Age Gap Analysis:** Michael Bradburn (Senior Statistician), Lynda Wyld (PhD supervisor/breast surgeon).
- **Questionnaire Component:** Karen Collins (PhD Supervisor), Lynda Wyld (PhD supervisor/breast surgeon), Yorkshire and Humber Consumer Research Panel (PPI group).
- **Interview Component:** Anne Shrestha (PhD student/breast surgeon), Maria Burton (PhD supervisor), Lynda Wyld (PhD supervisor/breast surgeon), Yorkshire and Humber Consumer Research Panel (PPI group).
- **Mixed Method Synthesis:** Maria Burton (PhD supervisor), Lynda Wyld (PhD supervisor/breast surgeon).

2.8. Chapter Summary

This chapter has outlined the knowledge gap, the research question, aims and objectives, the study components and thesis structure. The next chapter presents the methodological approach of this study, and the philosophical underpinnings of mixed method research.

[†] Prof Karen Collins retired from role as PhD supervisor in 2017. Supervisor role assumed by Dr Maria Burton.

Chapter Three: Methodology

3.1. Introduction

This chapter presents the methodological approach and philosophical underpinnings of this thesis. The qualitative and quantitative methodologies that were considered for this project are detailed, and the development of mixed method research.

3.2. Study Design Overview

This study used a pragmatic mixed method design. A systematic review of the literature on proxy decision-making for people living with dementia and cancer was undertaken and the findings from the review informed the development of the research question, aims and objectives. A quantitative questionnaire and qualitative interview topic guide were used to explore the caregiver experience of making breast cancer treatment decisions. Patient data from the Bridging the Age Gap trial was analysed to assess the impact of cognitive impairment on U.K. practice and survival outcomes for patients with breast cancer. Finally, the findings from the systematic

review, cohort data analysis, questionnaire and interviews were integrated as a mixed method analysis to answer the study research questions, aims and objectives.

3.3. Methodological Approach

Methodologies constitute the wide range of procedures and strategies that can be used to explore a particular topic or research question. Before embarking on a piece of research, Crotty (183) highlights four key decision-making elements to consider when developing a new study:

- Epistemology
- Theoretical Lens
- Methodological Approach
- Data Collection Methods

Crotty (183) suggests that each element informs the other, as do King and Horrocks (184), who take the view that all four components are interconnected and should not be viewed separately. A simplistic overview of each component in the context of the design and methods used in this study is shown in **Figure 10**.

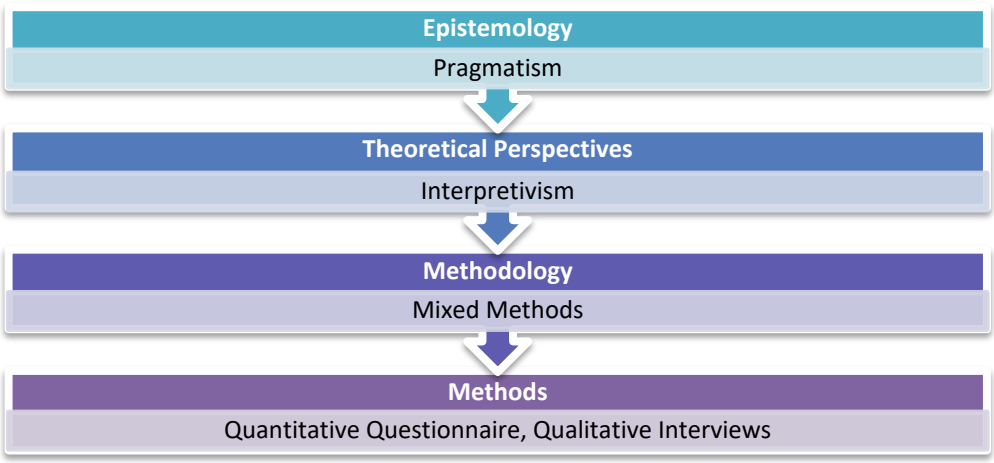


Figure 10: Four elements of a research study.

Source: Adapted from Crotty (183)

The following sections will present a detailed overview of Crotty's suggested research elements and explain how each step informed the development of this study.

3.3.1. Epistemology

Before discussing the epistemological stance, it is important to define what is meant by 'paradigms.' The term *paradigm* was first coined by Thomas Kuhn (185) to describe the philosophical assumptions that frame the researcher's worldview. Outlining the stance of the researcher at the outset is important, as Kuhn argues that these beliefs have a huge influence on the way in which a piece of research is carried out. According to Guba (186) research paradigms are characterized according to ontology (view of reality), epistemology (the relationship to what is being researched), and methodology (the research approach).

Epistemology, in this context, is therefore concerned with where the researcher sits within a paradigm and their 'view of reality.' A summary of the main three worldviews (positivism, pragmatism, and constructionism) situated within Crotty's (183) four principles of research is summarised in Table 6.

Table 6: Positivist, pragmatist and constructivist paradigms

	Paradigms		
	Positivism	**Pragmatism**	**Constructivist/ Interpretive**
Epistemology	Objectivity. Observing reality and truths	Objective and subjective. "what works"	Subjectivity. Knowledge generated through interaction.
Theoretical Perspective	Positivism and post-positivism. Empiricism.	Pragmatism. Relativism. Realism.	Interpretivism Phenomenology Symbolic interactionism
Methodology	Experiments, RCTs, Surveys, Grounded Theory	Mixed Methods. Action Research.	Ethnography, Grounded Theory
Method	Quantitative, Statistical Analysis, Questionnaires	Combination of Qualitative and Quantitative Methods	Qualitative: Interviews, Case Studies, Observation, Narratives

Source: Adapted from Crotty (183) and Creswell (187)

The next section gives an overview of positivism, constructivism and pragmatism, and states their underlying epistemologies.

3.3.1.1. Positivism

Classical positivism emerged from the work of Augustus Comte and is grounded in an ideological stance concerned with objectivism. Objectivists believe in one single reality (or truth), that can be observed and measured empirically. Comte's positivism dominated up until the 1950s era of post-positivism. Post-positivism sought to reconcile some of the methodological flaws of positivism concerning the view of reality and the positioning of the researcher (188). Quantitative research is traditionally aligned with the positivist/post-positivist school of thought as it advocates the use of scientific methods of inquiry to systematically measure the cause and effect of relationships, with a focus on reliability and validity. Positivists also argue that the role of the researcher is independent to the phenomena being observed and advocate the use of deductive reasoning to test theory.

3.3.1.2. Constructionism

In contrast, constructivists (and other approaches such as interpretivism), are more concerned with observing and interpreting human behaviour from a subjective perspective; believing in multiple realities which are dynamic and negotiated. Social reality, in this context, is constructed by individuals, and not merely external to them (189). The constructivist view is that the researcher plays an active role within the research itself, advocating inductive reasoning to generate theory. Qualitative research is therefore more typically aligned with this philosophical stance, through interviews, participant observation and thematic analysis.

3.3.1.3. Pragmatism

Occupying the "middle ground" between post-positivism and constructivism is the pragmatic paradigm. Pragmatists subscribe to the belief of using a 'what works' approach, rather than being bound by one single view point (188). Reality from this standpoint is not fixed, and continuously renegotiated. For many pragmatists, this worldview is more concerned with using the method that best fits the research question and addressing 'real life' practice, rather than being overly concerned with methodological pureness (190). The pragmatic school of thought allows the mixing of

data collection and is more commonly associated with mixed methods – the combination of quantitative and qualitative methods.

3.3.2. Qualitative, Quantitative and Mixed Methods Approaches

Quantitative and qualitative research methods propose two fundamentally distinct approaches to collecting data. Deciding which approach to use will be dependent on the aims and objectives of the study and a consideration of its appropriateness in the context of what, or who, is being researched. The following section gives an overview of quantitative, qualitative and mixed methods research.

3.3.2.1. Quantitative Research

Quantitative methods are principally associated with positivism and objectivist approaches, as described previously. By design, quantitative methods are generally more concerned with hypothesis testing and the use of statistical analysis. One example could be the use of standardized surveys with closed questions to generate numerical data. Other methods include randomized control trials and systematic observations. An overview of the quantitative data collection tools considered for this study, and their advantages and disadvantages are shown in **Table 7**.

Table 7: Overview of quantitative data collection tools

Data Collection Tool	Description	Advantages	Disadvantages	Data collected
Closed Questionnaire	Paper based set of fixed choice questions that participants can complete either individually or with the researcher.	Easy to administer and gather information quickly. Cost-effective.	Responder biases. Closed questions limit the answers that participants give.	Primary, Quantitative Data
Postal Survey	Paper based set of fixed choice questions sent via post to participants.	Cost-effective. Ease of collecting information across large geographical distances.	Responses could go missing upon return. The researcher is not present to aid completion.	Quantitative

The justification for using a quantitative data collection approach to address the aims and objectives of this study:

- Collecting questionnaire data is a cost-effective method for gathering information on the role of caregivers in making treatment decisions and their support needs.
- Quantitative approaches can deal with large samples, which would be ideal if there were an unprecedented number of caregiver responses to the study questionnaire.

The weakness of using a quantitative data collection approach in this study:

- Collecting quantitative data through a questionnaire can sometimes create an unnatural environment, meaning that the responses from caregivers may not necessarily reflect what happens in the real world.
- Some research designs (such as pre-set closed questions in a survey) can place a limitation on the answers that respondents are able to give to a particular question. The responses may therefore not accurately reflect the respondents' thoughts and feelings.
- A closed questionnaire can be a disadvantage in terms of capturing less detail and lacking context to participant responses.

3.3.2.2. Qualitative Research

Qualitative research is exploratory by nature and involves observing phenomena to collect non-numerical data. Analysing qualitative data involves searching for meanings, concepts and themes. Interviews are commonly used in qualitative research to explore the underlying reasons behind a particular phenomenon or opinion. Other methods of data collection may include focus groups, case studies and participant observation.

An overview of the qualitative data collections tools considered for this study are presented in **Table 8**.

Table 8: Overview of qualitative data collection tools

Data Collection Tool	Description	Advantages	Disadvantages	Data Type
Focus Group	Asking a group of participants with similar characteristics a set of questions	Can capture a large volume of data from participants at the same time. More cost-effective than individual interviews.	Participants may be influenced by each other's answers. Some voices might be more dominant than others.	Primary. Qualitative Data
Semi-structured Interview	Asking an individual a set of questions led by a topic guide but can explore answers in more depth.	Telephone interviewing can be cost-effective. Answers may be more reliable compared to questionnaire.	Can be time-consuming if interviewing a large sample of individuals.	Primary. Qualitative and Quantitative Data.

The justification for using a qualitative data collection approach to address the aims and objectives of this study:

- Collecting qualitative data is an ideal method for exploring the support needs of caregivers, and their experience of caring for a relative with dementia and breast cancer.
- Caregiver interviews would be undertaken in real-time and allow for more researcher flexibility (i.e., this would allow for probing on responses and exploring caregiver responses in-depth).
- Qualitative data would be useful for dealing with smaller samples, with a focus on collecting rich in-depth data. This would be ideal for a study such as this, which explored an under-researched area.

The weaknesses of using a qualitative data collection approach in this study:

- Qualitative data collection and analysis of interviews can be more time consuming than collecting questionnaire data due to the depth of detail. Undertaking a large number of caregiver interviews would be resource intensive, as this study is led by one PhD researcher.

- Qualitative interview data cannot be generalised to the wider population, although this is not the intention of this study, which seeks to explore the caregiver experience rather than quantify it.

A comparison of both quantitative and qualitative methodologies is shown in **Table 9.**

Table 9: Quantitative and Qualitative Analysis overview

	Quantitative	Qualitative
Paradigm	Post-positivist	Constructivist
Stance	Objective	Interpretivist
Design	Experimental Design RCTs, Questionnaires, Surveys	Ethnography, Case studies, Narrative research, Phenomenological research
Data Collection Tools	Pre-determined instruments often validated. Close-ended questions.	Observation, interviews. Open-ended questions.
Analytical Techniques	Numerical, statistical analysis	Thematic Analysis, textual and image analysis
Sampling Procedures	Larger samples, randomization	Smaller samples, purposive sampling
Focus	Narrow-angle lens	Wide-angle lens
Outcomes	Projectable over population base	Generalized and directional

Taking into account the characteristics of each approach, the use of both quantitative and qualitative methods to explore the research question was chosen primarily for the reason that two methods of data collection would give context to both sets of findings. Another reason was that using one method in isolation, such as a questionnaire, would mean that unanswered questions remain unknown. Following up a quantitative questionnaire with a qualitative interview would create the potential to explore ambiguous answers, resolve missing data, and probe for deeper meanings behind caregiver responses. The following section gives an overview of the mixed methods approaches and designs that were considered for this study.

3.3.2.2. Mixed Methods Approaches

Teddlie and Tashakkori (191) define mixed methods as the *'third methodological movement,'* bridging the ideological gap between qualitative and quantitative approaches. Prior to this, researchers would traditionally take one side in the metaphorical 'paradigm wars' (191). Pragmatism emerged as a way of bridging the ideological divide and led to the adoption of a 'mixed method' approach that incorporated both quantitative and qualitative methods of data collection and analysis.

The established body of work in this field has been led by key authors such as Campbell and Fiske (192), Tashakkori and Teddlie (188), and Plano Clark and Creswell (193). The definition of *mixed methods* continues to evolve, with key authors taking different perspectives and viewpoints. It has been termed interchangeably as multi-method, mixed method and triangulation of methods by different authors, however the interpretation of 'mixed methods' for this study is closely aligned to the viewpoint of Tashakkori and Creswell, who define the method as:

> *"Research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of inquiry"*
>
> **Tashakkori and Creswell (194) p4.**

The benefit of using a mixed method approach is that it allows for both qualitative and quantitative data to be collected and integrated in a variety of ways **(Figure 11).**

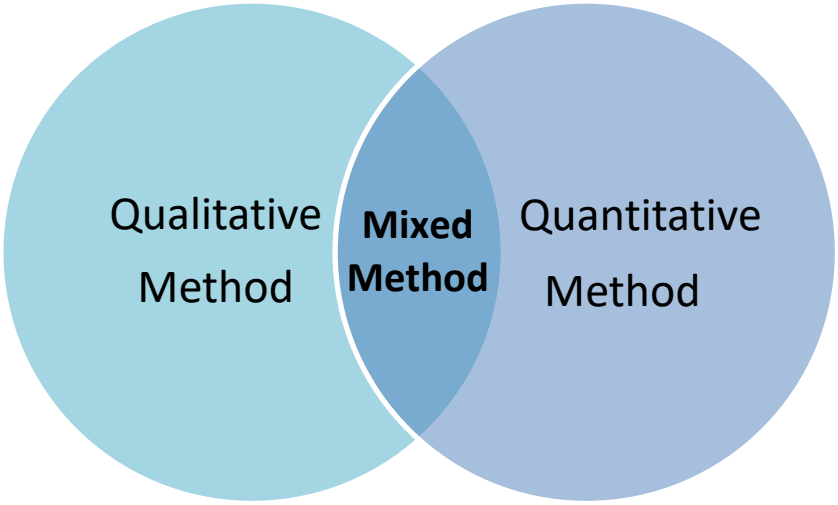


Figure 11: Simple Venn diagram of mixed methods research

The justification for using a mixed method approach to meet the aims and objectives of this study:

- The integration of data through two different components (i.e., quantitative questionnaire and qualitative interview) would capture the wider context behind treatment decision-making and meet the aims of the research question.
- The collection of both data types would overcome the limitations involved in using one method alone; thus, offsetting the weaknesses associated with using one method in isolation. This would give the data greater completeness and depth of understanding of the decision-making experience for caregivers.

The challenges associated with using a mixed method approach in this study were:

- Quantitative and qualitative questions may measure different constructs. This may be problematic when the findings from both sets of data are integrated in the analysis and triangulation stages.
- The argument that some paradigm purists believe that qualitative and quantitative approaches should not be mixed and are therefore 'doomed to failure due to the inherent differences in the philosophies underlying them' (188).

A number of mixed method designs had the potential to answer the study research questions. An overview is given in the next section.

3.4. Mixed Method Designs

To date, over 40 mixed method approaches have been developed (188). Creswell and Plano Clark (190) summarise these as four approaches; triangulation, embedded, explanatory and exploratory **(Table 10).**

Table 10: Mixed Method (MM) designs

	Triangulation Design	Embedded Design	Explanatory Design	Exploratory Design
Definition	A one-phase concurrent design. Collecting concurrent separate data using different methods to address the research question. Data is merged during the interpretation stage	Can be a one-phase or two-phase approach. One method of data collection has more priority than the other (i.e., one method is supplemental)	Two-phase design. QUANT data is collected and analysed in the first phase, QUAL data collected and analysed in the second phase.	Two-phase design. QUAL data is collected and analysed in the first phase, QUANT data collected and analysed in the second phase.
Design variants	Convergence model. Data Transformation model. Multilevel model.	Correlational model. Experimental model.	Participant selection model. Follow-up explanations model.	Taxonomy development model. Instrumental development model.
Strengths	Ability to compare and contrast findings. Ability to validate findings. Efficient for collecting data during one phase at the same time.	Useful where the researcher has limited resources for collecting data – priority can be given to one method over the other.	Useful where QUAL data is able to explain or expand on QUANT results. Straight-forward for one researcher to conduct both phases in sequence.	Straight-forward for one researcher to conduct both phases in sequence. Can apply design to multi-phase and single-phase studies.

Challenges	Reconciling findings that converge can be difficult. May require the re-examination of data or further data collection if results cannot agree.	Integration of findings (where each research method answers a different research question) can be difficult.	Can be issues around sampling (anticipating the number of participants to select in the second phase)	Can be issues around sampling (anticipating the number of participants to select in the second phase)

Source: Adapted from Creswell and Plano Clark (190)

For this study, a two-phase sequential strategy (an explanatory or exploratory design) was chosen, as this would allow for the collection of data in two separate phases. A sequential design was chosen over a concurrent design for the following reasons:

- By collecting data at two different time points, the results from the first stage could be built on directly to fill in missing gaps, explain ambiguous responses or collect further details
- Taking a phased approach would be less burdensome on caregivers, particularly where potentially emotional topics are explored
- To maximise participation by allowing caregivers to take part in either/or both strands of the research study

The next section will describe the mixing strategies chosen to collect, analyse and interpret mixed method data in the study.

3.4.1. Sequential mixed method designs

There are two sequential designs that can be used in a mixed method study: exploratory or explanatory **(Figure 12).**

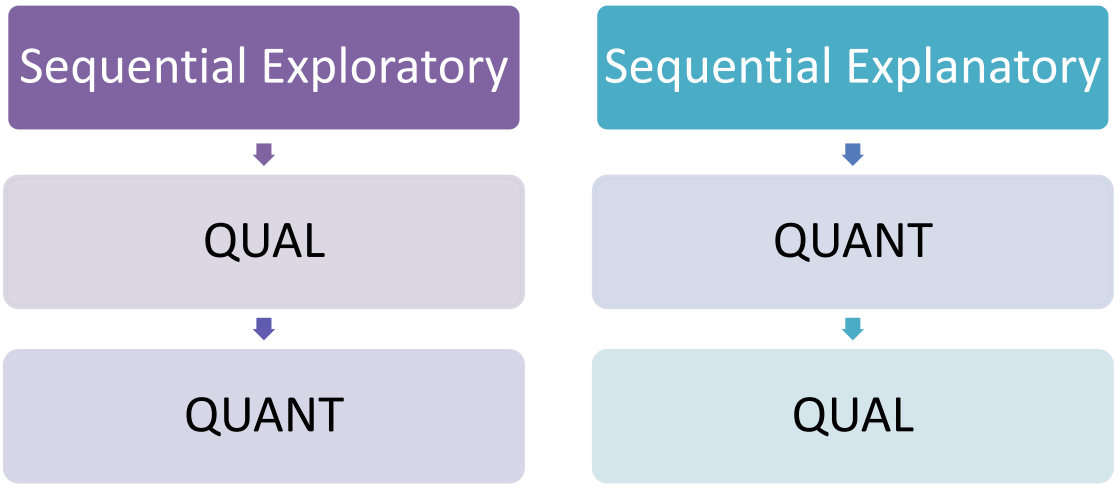


Figure 12: Sequential Types of Mixed Method research

In an exploratory sequential study, qualitative data collection is collected and analysed first. These findings are then used to develop the quantitative strand of the study, such as developing a survey which is then used to collect and analyse quantitative data. The advantage of this design is that the qualitative phase can help to design new data collection tools (such as a questionnaire) where one is not available.

When using an explanatory sequential design, it is the reverse; quantitative data is collected and analysed first, before using a qualitative approach to identify aspects of the quantitative data to explore in-depth. The advantage of this design is that it allows the qualitative phase to be based on the learnings from the quantitative results. In both sequential designs, the qualitative and quantitative data is then interpreted as mixed method analysis.

The advantage of using a sequential explanatory design to address the aims and objectives of this study:

- Using a questionnaire would verify that participants (caregivers) had been involved in making a proxy treatment decision by completing the questionnaire before taking part in an interview.

- The questionnaire would ask caregivers to indicate the treatment selected for each patient. This would allow an amendment of the interview topic guide to tailor questions which were appropriate and specific to the treatment pathway.
- Undertaking the qualitative phase later in the study would allow for probing questionnaire responses which were unclear or contradictory.

3.5. Chapter Summary

This chapter has given an overview of the philosophical underpinnings of the study, which adopted a sequential explanatory mixed method stance to answer the research question. The strengths and weaknesses of quantitative and qualitative data have been presented, and the justification for using a mixed method design.

The next chapter presents the data collection and methods used to undertake a systematic review; statistical analysis of cohort study data; and the mixed method study (questionnaires, interviews and triangulation synthesis).

Chapter Four: Methods

4.1. Introduction

This chapter presents the methods used to meet the aims and objectives of this study. The procedures used for collecting and analysing each stage of data are described, and the development of data collection tools used **(Figure 13).** The methods for the following components are presented:

1. Systematic review using thematic analysis
2. Mixed method study
    a. Statistical analysis of cohort patient data, using univariate analysis and propensity score matching
    b. Quantitative questionnaire data collection, using descriptive statistical analysis
    c. Semi-structured qualitative interview data collection, using the Framework Approach
    d. Mixed method synthesis and interpretation using a triangulation matrix

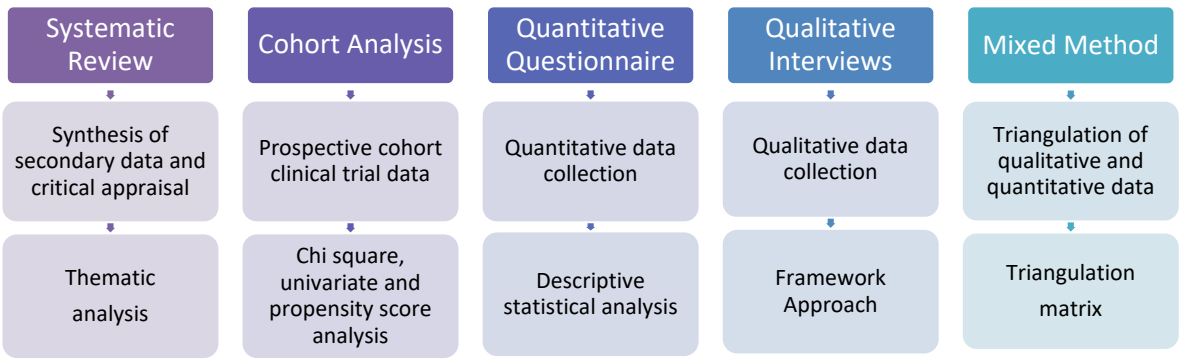


Figure 13: Overview of methods used for study components

4.2. Systematic Review Methods

The systematic review was undertaken in accordance with the Cochrane Handbook for Systematic Reviews (195) which is a methodological guide for practice. Systematic reviews typically begin with a research question, which is then framed by a PICO framework (population, intervention, comparator and outcome). The PICO framework can be adapted depending on the method of the systematic review; for example, a qualitative or mixed method systematic review may use a PCO. The key planning stages are outlined in **Figure 14**.

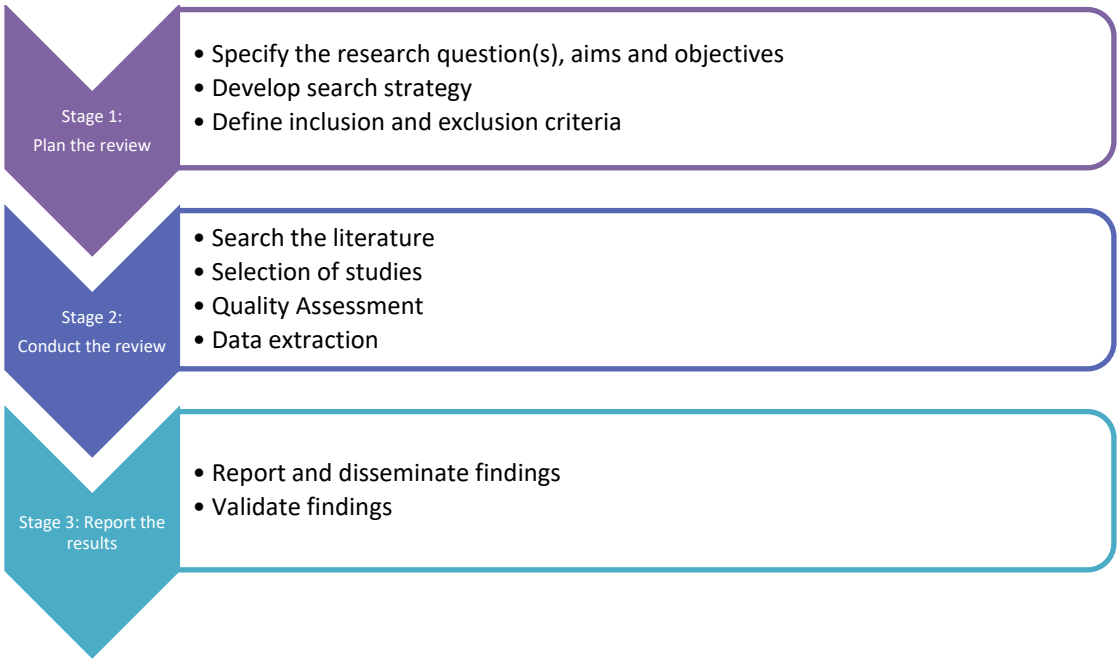


Figure 14: The stages of a systematic review

The next stage is to define the inclusion and exclusion criteria for the review. This can include restricting to a particular study type (e.g., RCT, case study), methodology (e.g., quantitative, qualitative) or population (e.g., adults, adolescents). Limits can also be introduced, such as language and date of publication. After defining the inclusion criteria, a search strategy is developed, which outlines the databases used, which will each have their own search terms to use. Medical Subject Headings (MeSH) terms can be used with some databases to develop a search strategy.

After searching databases, the reviewers (ideally two researchers working independently) will then screen the titles, abstracts and full texts of studies against the eligibility criteria. Reasons for exclusion at each stage are recorded. Data are extracted from the full text studies using a pro forma to record information such as the study title, year, participants, aims and results. A quality assessment is then undertaken to assess the papers for any bias. Again, this should be undertaken ideally by two independent reviewers. Validated tools for assessing bias include the mixed methods appraisal tool (MMAT) (196) and the Cochrane Risk of Bias tool (197), although there are a number of quality tools depending on the type of included studies (qualitative, RCTs, quantitative, etc).

The next stage is to synthesize the data to group the types of studies. It is at this point that analysis is performed. For quantitative studies, meta-analysis is a common way to analyse data, but is not always possible for small numbers of studies and also may be limited if there is significant heterogeneity in the trial design and outcomes recorded. For qualitative studies, thematic analysis can be used to search for themes within the data. Lastly, the review should report its conduct, and this is usually done using PRISMA guidelines (198).

The systematic review is presented in **Chapter Five**.

4.3. Quantitative Methods

4.3.1. Prospective cohort study analysis

A cohort study is a non-experimental approach that involves observing a group of individuals with shared characteristics over a defined period of time, examining the relationship between exposures and outcomes (199). Unlike an RCT, patients in an observational trial are non-randomized, which can lead to confounding bias and selection bias. This can have implications for the direct comparison of groups, as their outcomes may be explained by variables that have been unaccounted for. There are some options to control for confounding, such as stratification, linear regression models and propensity score matching. A prospective cohort study design is considered the gold standard of observational studies. Some examples of studies that have used a prospective design to examine breast cancer outcomes include Hurria and colleagues (155), Lavelle and colleagues (135) and the Bridging the Age Gap trial (200)

The Bridging the Age Gap in Breast Cancer trial was an NIHR funded 7 year programme, which recruited from 2012-2019 in England and Wales (201). The programme used a prospective cohort design to collect detailed information on fitness, tumour characteristics, treatment and survival in women (>70) years. One aim of this PhD study was to determine the oncological outcomes of older women with breast cancer and dementia. To assess the differences between two groups of participants taken from the cohort study (older women with/without cognitive impairment), statistical analysis was used to perform a treatment and survival analysis. The statistical methods are outlined in the next section.

4.3.1.2. Statistical techniques for analysing cohort data

- **Cross-tabulations (chi-square)**

Chi-square (χ^2) can be used to cross-tabulate non-parametric data to test for differences between groups of patients. Comparison tests look for statistical significance between groups by calculating p-values. For most analysis, a 95% confidence interval is taken, and cut-off for significance is an alpha of 0.05. Therefore, if a p-value is less than 0.05, we would reject the null hypothesis. If a p-value is over

0.05, the result would be not statistically significant, meaning that we cannot be sure if there is a significant difference between two groups.

- **Logistical regression**

Kaplan-Meier (202) is a non-parametric method for estimating survival probability between time points for different groups. A Log-rank test can be used to test if there is a difference between the survival times in two groups. A logistical regression model, such as the Cox Proportional hazards model can be fitted to produce a Hazard Ratio (HR), and to investigate the effect of multiple covariates on an outcome.

- **Propensity score matching**

Propensity score matching (203) is a quasi-experimental method for reducing selection bias in non-experimental, longitudinal studies. A propensity score is the probability of a subject with certain characteristics being treated. The approach adjusts for variations between treatment and control groups by distributing observed baseline covariates. This balances the groups, making them more comparable in respect to observed confounders. This then allows direct comparison of outcomes between groups in the propensity matched sample. The procedure for propensity scoring follows a number of steps **(Table 11).**

Table 11: Propensity score matching procedure

Steps		Example
Data Preparation	Clean data. Assign cases from the data sample into groups.	Treatment and comparison groups
	Define endpoint (outcome of interest)	Mortality rates, side effects.
Selection of covariates	Identify potential confounders. Calculate effect size for each covariate.	Demographics, co-morbidities, socio-economic characteristics
Propensity score estimation	Estimate propensity score by fitting a regression model. These values become the propensity scores.	Logistical regression, classification and regression tree.
Matching algorithms	Using the estimated scores, individuals with a similar probability are matched to produce a comparison group.	Nearest-neighbour matching (1-1 or 2-1 matching), calliper width matching

Evaluation of matching quality	Matching quality is assessed to check if the confounders are balanced.	Tests for standardized bias, Kernel density plots.
Outcome analysis	Perform analysis based on chosen endpoints. Report matched and unmatched results.	Matching, weighting or subclassification

1. Data preparation

Subjects are allocated groups (such as treatment and control). At this stage, the outcome of interest is also defined.

2. Selection of covariates

To ensure group comparability, confounding variables are identified. Rubin and Thomas (204) propose selecting covariates based on theoretical subject-knowledge rather than simply relying on statistically significant predictors. If a covariate lacks reliability this may lead to instability in the model (205).

3. Propensity score estimation

Propensity scores create a balance between the two groups of subjects. There are two common methods for obtaining a propensity score; logistical regression (used for binary outcomes), and classification and regression tree analysis (non-parametric option) (206).

4. Matching algorithms

After estimating scores, the propensity method is selected. This may include stratification or matching to produce sets of subjects who share similar scores. Some techniques include nearest-neighbour matching (1-1 or 2-1 matching) and calliper width matching. Statistical software such as SAS, R (MatchIt) or STATA (PSmatch2) can be used.

5. Evaluation of matching quality

Matching quality is assessed to ensure that the covariates between the two groups are balanced (203). Balance analysis includes standardised mean difference, and density plots to compare the distribution of covariates in the model. Statistical software such as STATA is often used (207).

6. Outcome analysis

Outcome analysis is performed using the matched data. This can be achieved by running a regression model using the matched pairs, or by estimating the effect between sub-class categories (subclassification). Again, statistical software such as STATA and SPSS are used.

The analysis of patient cohort data is presented in **Chapter Six**.

4.3.2. Quantitative Questionnaire

Questionnaires are a widely used research tool for collecting primary data. Before embarking on a questionnaire study, Fallowfield (208) advises that the researcher should reflect on four key considerations:

1. Does a suitable questionnaire already exist?
2. Who will complete the questionnaire?
3. What response format will be used?
4. Are questions brief, relevant, and unambiguous?

Taking into account these initial considerations in relation to this study:

While Fallowfield notes that a 'well-validated, standardised measure' is the ideal, an in-depth literature search found no such questionnaires that existed. The closest was the Adult Carer Quality of Life Questionnaire (AC-QoL), however the focus of the questions were not specific enough to the research topic and would not meet the aims of the study.

Caregivers would be completing the questionnaire; specifically, those who had been involved in the breast cancer treatment decision for a patient recruited to the Bridging the Age Gap trial. The minimum age threshold for patients in the trial was 70 years, therefore it could be assumed that the age of most caregivers would either be 40+ (adult children or adult spouses), assuming an average literacy level.

The response format of the questionnaire was a postal survey, meaning that the questionnaire would be completed by the respondent at home without assistance from the researcher. At the time of applying for ethics approval, approximately 9% (n=109) of patients recruited to the Bridging the Age Gap study had a dementia diagnosis. The small sample size meant that complex analysis would not be possible. Influenced by this, the questionnaire would use a mixture of simple questions that could be answered by the respondent to give insight into their role and experiences. The questions would be brief and relevant to only the topic of making proxy decisions; relevant by way of being developed and informed by the literature review. A scoping

exercise was used to identify any potential ambiguities in the questions and provide a glossary and contact details for the researcher to give further explanation.

The following sections will outline the characteristics of the study sample, the questionnaire development and recruitment strategy for the quantitative component of this mixed method study.

4.3.2.1. Quantitative Sampling Techniques

Sampling refers to a group of units or individuals taken from a larger population. To meet the aims of the study, the sample included individuals who had been involved in making treatment decisions for patients with breast cancer and dementia. Within the Bridging the Age Gap trial was a sub-group of older women who joined the study by proxy consent, given either by a caregiver or relative who had been present at either the breast cancer diagnosis or treatment decision consultation.

The following process for identifying participants was proposed:

1. To stratify the Bridging the Age Gap population into two groups: Normal cognition (women consenting themselves to the study) and cognitively impaired (women assented to the study by an advocate).
2. Identify individuals with a formal diagnosis of dementia (dementia subgroup) within the cognitively impaired group.
3. Contact all caregivers within the dementia subgroup who had assented the patient to the study.

The key reason for taking this approach was that the caregivers for trial participants within the dementia subgroup would be representative of an individual involved in making a cancer treatment decision for an older person with dementia. This would meet the aim of the study, which was to determine the caregiver's role in making treatment decisions. Secondly, this approach aligned with the ethos of this study, which was not to make generalizations, but to explore the experiences of this group of caregivers.

4.3.2.1.1. Probability Sampling

In quantitative research, the aim is often to generalise findings to the wider population, such as hypothesis testing. This means that it is important that the study sample is representative of the population, in order to achieve external validity. The most widely used method in quantitative studies is probability sampling. Four common techniques and their strengths and weaknesses are illustrated in **Table 12.**

Table 12: Probability sampling techniques

	Simple random sample	Systematic sample	Stratified sample	Cluster sample
Sampling Type	Units or participants are randomly selected from the sample.	Assigning numbers to each unit within the population, using a formula to select.	Stratify population into subgroups, then randomly sample from each subgroup.	Dividing the population into clusters. Then randomly select clusters.
Tools	Random number generators.	Assigning numbers.	Random or systematic sampling of subgroups.	Random selection of subgroups or systematic sampling.
Strengths	All units within the sample have an equal chance of selection, which reduces risk of bias.	The sample is evenly spread over the population.	Representative of different characteristics within the sample. Reduces human bias potential.	Deals with large populations. Clusters may not be representative.
Challenges	Sample selection bias may occur. Requires a full list of all members in the study population.	Risk of introducing bias if there is a periodicity in the sample (this may compromise representativeness)	Issue of overlapping, where subjects fall into more than one subgroup.	Risk of sampling error or biased sampling.

After revisiting the aims and objectives of the study, a probability sampling approach was deemed unfeasible for the following reasons:

- Simple random selection from the Bridging the Age Gap population may result in the selection of participants who do not meet the inclusion criteria (i.e., women with normal cognition)

- The dementia subgroup within the trial was small (<10% of the Bridging the Age Gap population), therefore systematic, stratified and cluster sampling could drastically reduce the number of participants even further.
- Access to caregivers for the cognitively impaired subgroup was determined by ethical constraints and approval being granted at each centre which recruited the patient and caregiver to the Bridging the Age Gap trial.

Non-probability sampling techniques for questionnaires are presented in **Table 13**. These approaches can be used where probability sampling strategies such as random selection are not feasible. By their very nature, these non-probability approaches are considered subjective as they do not involve random selection. This means that the interpretations made from such findings cannot be generalized to the wider population.

Table 13: Non-probability sampling for Questionnaires

	Convenience Sample	Voluntary Response Sample	Purposive Sample	Snowball Sample
Sampling frame	Individuals or units who are readily available and accessible to the researcher	Individuals volunteer to participate (rather than being directly contacted by the researcher).	The researcher selects the sample which meets the purposes of the research	Individuals recruit new participants
Strengths	Ease and inexpensive.	Ease of access (the researcher does not need to search extensively for participants).	Useful for multi-phase studies. Flexibility for targeting individuals with shared characteristics.	Useful for accessing hard-to-reach hidden populations and targeting specific groups.
Weaknesses	Sample may not be representative of the population. Results cannot be generalised.	Self-selection bias in the characteristics of the sample. Sample may therefore not be representative of the population.	Unit selection can mean the sample is not representative. Difficult to generalise.	Difficult to identify sampling errors. Difficult to generalise to the wider population (may not be representative)

According to Andres (209) the ideal method of sampling for small scale studies is the approach that *best fits*. This ethos aligns with the pragmatic stance of this mixed

method study, which adopts a *what works best* approach. In mixed method studies, a multi-stage purposeful approach can be used where identification of a population is complex (210). For these reasons, the study purposively sampled the dementia subgroup from the Bridging the Age Gap trial, by identifying patients who were assented to the study by a caregiver.

The advantages of using a purposive approach to meet the aims of this study were:

- To maximise the sampling frame
- To ensure that only caregivers meeting the criteria were contacted and were representative of the sample, increasing external validity
- To minimise unnecessarily sending invites to ineligible participants, which may cause confusion or distress

The challenges associated with using a purposive approach in this study were:

- That purposive sampling would introduce an inherent bias
- That the results cannot be generalized, beyond the sample (limiting the data analysis to descriptive statistics)

A detailed overview of non-probability sampling in relation to qualitative research is detailed in **Section 4.4.3.** and validity concerns are explored later in this chapter.

4.3.2.1.2. Sample Size Calculation

At the time of designing this study there were 45 breast units actively recruiting to the trial (later increasing to 56 units), with 37 sites having recruited a patient by proxy with a formal diagnosis of dementia. After inviting all centres to participate, 13 centres agreed to take part, with a total of 147 participants in the consultee participation arm (prior to data cleaning).

The inclusion and exclusion criteria for the study is outlined in the Study Protocol **(Appendix 1),** with an abridged version given here.

4.3.2.1.2.1. Inclusion Criteria

1) Adult caregivers aged 18 years and over, and capable of giving informed consent.
2) An individual involved in making treatment decisions for a patient with the following characteristics:
    a. Female, >70 years of age at time of cancer diagnosis
    b. Primary operable (TNM categories: T1, T2, T3, N0, N1, M0) invasive breast cancer.
    c. Formal diagnosis of cognitive impairment (ICD-10 categories: F00.0-F00.9, F01.0-F01.9, F02.0-F02.8, F03) or an MMSE score indicating severe cognitive impairment.
    d. Incapable of giving informed consent to their breast cancer treatment

Potential barriers to recruitment identified

1. Access to caregivers would be dependent on individual ethics and Research and Design (R&D) permission being granted at each unit.
2. It was highlighted at a steering group meeting that some trial participants may have been miscategorised as having dementia through misunderstanding of the 'data collection' consent level within the Bridging the Age Gap trial. A verification procedure would be followed by the researcher to confirm presence of dementia diagnosis before inviting the patient's caregiver to take part in this study.
3. The ethics committee stipulated that caregivers could not be contacted where the patient they cared for had passed away (this check would be dependent on the site having current follow-up information on patient mortality status). A mortality check would be undertaken by the researcher and recruiting site to exclude these patients and their caregiver from the study sample.

4.3.3. Questionnaire development

Questionnaires and surveys are commonly used to capture responses from the wider population (211, 212). Validated questionnaires are widely used with patients in health-related research, although bespoke surveys can also be created if one does not

already exist. There are a number of key considerations to consider when developing a bespoke questionnaire, as it is important to ensure the accuracy and consistency of the measures being used (validity, reliability and risk of bias).

4.3.3.1. Criteria for validity in quantitative research

- **Validity and reliability**

Validity is a necessary component of quantitative research; it concerns the ability of the questionnaire to measure what it claims to (193). Quantitative reliability refers to ability of the questionnaire to consistently measure what it purports to measure. The Test-retest approach can be used to assess reliability by administering the questionnaire twice to each respondent and then comparing the responses from each time point. In this study it would not be feasibly possible due to ethics committee restrictions on contacting caregivers more than once (unless they agreed to take part in the interview), and for the reason that some questionnaires could be returned anonymously from respondents.

Content validity and how this was addressed in the context of data collection for this study is described in **Table 14**.

Table 14: Validity considerations in questionnaires

Validity type	Face validity	Construct validity	Concurrent validity
Definition	Refers to the extent to which the questionnaire appears on face value to measure what it claims to.	Refers to the extent to which the questionnaire measures theoretical constructs.	Refers to the extent to which the questionnaire relates to existing similar measures
How this will be addressed in the study	No specific statistical tests can measure this. The study will have input from a PPI group, expert opinion from Age Gap study and breast surgeons.	The questionnaire is not measuring any theoretical constructs; therefore, this will not be addressed.	The questionnaire is bespoke and cannot be compared against any other measures as they do not exist.

- **Responder bias**

Responder bias refers to the conditions that can influence the way in which respondents complete a questionnaire. Consideration of responder bias and how these concerns would be addressed in the design of the study questionnaire is described in **Table 15.**

Table 15: Responder bias considerations in questionnaires

Bias type	Recall bias	Response style bias	Question order
Definition	Refers to respondents giving honest, accurate responses to the questionnaire (i.e., acquiescence and dissent bias)	Refers to having an equal number of responses from the study sample.	Refers to the way in which the sequential order of questions may lead respondents to give biased responses.
How this will be addressed in the study	Each question will be phrased in an unbiased neutral way to imply to the respondent that there is no 'right' answer.	Each questionnaire pack will be sent with a personalized cover letter explaining the purpose of the research and giving further details to contact the researcher with any concerns.	The questionnaire will use a diverse mix of response formats (i.e., scales and binary) to make completion engaging. The questions will be grouped around similar topics and follow the breast cancer journey.

- **Generation of topics and questions**

The wider literature was searched to identify any pre-existing validated tools that could be used to explore this specific area of decision-making, however none existed. A bespoke questionnaire was designed, based around a framework which was informed by the systematic review and feedback from clinicians in the field of breast cancer. Six topics were established to address the research aims and give insight to the experience of caregivers when making proxy treatment decisions **(Table 16).**

Table 16: Questionnaire framework

Topic	Description
Demographics	Collect caregiver details on age, gender, ethnicity, where they lived and occupation. Setting the scene for the questionnaire by asking some simple questions about demographics, before building up to more in-depth questions later.
Caregiver relationship	Collect details on the relationship of the caregiver to the participant. This would cover how long the participant had been caring for the person with dementia, if they lived together, and the number of hours spent caring per week. This section would also ask if the caregiver had LPA for the person they cared for and if any advance decisions were made prior to the decision.
Information needs	Capture details on the information received prior and during the time that the treatment decision was made. To explore any awareness of breast cancer prior to diagnosis, which treatments were available, and caregiver satisfaction with the information received from the hospital
Making the decision	Recall of the treatment decision process. Capturing information on access to support and information, and the factors that were most important when making the decision.
Type of decision	To collect information on the decision-making styles used by caregivers: an advance decision, substituted judgment or best interest decision.
After making the decision	To ask caregivers to reflect back on the experience of making the treatment decision and report their level of satisfaction for the decision they made.
Final thoughts	A free text box to encourage caregivers to give their final thoughts on making treatment decisions and highlighting any information that may not have been covered in the questionnaire. An open question would allow respondents to voice any comments about the research or otherwise highlight any particular points to follow-up in the interview. This may potentially generate new questions.

An additional section at the end of the questionnaire asked the caregiver if they would be interested in taking part in future research, including an interview, and if they would like to receive the results of the study.

4.3.3.2. Questionnaire Psychometrics

Each section of the questionnaire contained questions related to the research aims and objectives. Designing the questionnaire involved developing appropriate response scales for each question. The format of scales depended on the context of

the question being asked, and this had some advantages and disadvantages **(Table 17)**.

Table 17: Response Scales

Response scale	Dichotomous Scale Questions	Rating Scales	Semantic Differential Scales
Description	Two-point scale with opposing options	Rating scales, most commonly 1-10, 1-7 or 1-5 (Likert scale)	Multi-point scales with opposite adjectives on either end.
Example	"yes or no" "true or false"	"strongly agree (5), agree (4), neutral (3), disagree (2), strongly disagree (1)"	"very unsatisfied, unsatisfied, neutral, satisfied, very satisfied"
Advantages	Prevents the respondent from giving a neutral answer	Universal method of data collection. Ease of analysis.	Useful for gaining insight into attitudes, opinions and measuring satisfaction.
Disadvantages	Too many questions of this type may lead to responder fatigue and less nuanced responses	Can generate neutrality by having a "middle category"	Can get neutrality from respondents, and it may be difficult to establish ambiguous responses.

Closed-ended questions were mainly considered, as the data these generate would be easier to collect and analyse. The disadvantage of this, however, is that it limits the range of responses; in particular, responses could not be directly clarified unless the participant agreed to take part in an interview. For this reason, an "other" box was used for some questions, which allowed caregivers to elaborate on their responses. Examples of the response scales used in each section of the questionnaire are shown in **Table 18**.

Table 18: Examples of response scales used in the questionnaire

Questionnaire Section	Example question	Response scale	Open or closed question
Demographics	"What is your gender"	Dichotomous scale	Closed-ended
Caregiver relationship	"How many hours a week do you spend caring for this person?"	Frequency scale	Closed-ended
Information needs	"Were you satisfied with the information you received at the hospital?"	Likert scale, 1-5	Closed-ended
Making the decision	"Did the consultant recommend a particular type of treatment?"	Multiple choice	Closed-ended
Proxy decision making styles	"Which type of proxy decision matches the type of decision you made?"	Multiple choice	Closed-ended
After making the decision	"I felt happy with the decision I made"	Rating scale Likert 1-5 response	Closed
Final thoughts	"Do you have any thoughts on proxy decision making that has not been covered in this questionnaire?"	Free text response	Open-ended

- **Usability and effectiveness**

To increase usability, the length of the questionnaire was kept short to avoid respondents skim-reading the questions, as this would reduce the likelihood of caregivers misinterpreting questions or responder fatigue. Questions were grouped together under themed topics to help the respondent to contextualise similar questions. The sequence of questions was ordered in a structure that reflected the chronological events of the patient's cancer journey. The aim of this was to help the responder with retrospective recall. The questionnaire also contained a glossary of definitions on the back page and instructions on how to complete the questionnaire

on the front page. Details for the researcher were included for the respondent to make contact for further clarification or to ask questions. A personalised cover letter detailing the aims of the research study was attached. The final version of the study questionnaire is included in **Appendix 2.**

4.3.3.3. Field Testing and Feedback

University Research Ethics Committee (UREC) approval was obtained to run a focus group with caregivers to test the face validity of the questionnaire. The focus group was recruited though the Sheffield Dementia Involvement Group, which had membership of people living with dementia and caregivers. The group however fell through due to some of the participants having family members pass away and being unable to arrange care for the person they cared for, while attending the focus group. Over the next month, attempts were made to rearrange the group however this was unsuccessful, and a new date could not be arranged.

A PPI group, who had been involved in a breast cancer study and had previously advised on proxy consent procedures, was approached; the Yorkshire and Humber Consumer Research Panel (213). The group membership included people with lived experiences of breast cancer. The study was presented at the PPI quarterly meeting, with input involving initial feedback on the questionnaire development and reviewed a first draft.

An overview of comments and feedback on the study design and materials is shown in **Table 19**.

Table 19: Study design comments and feedback

	Study documents	Questionnaire
Ethics Committee	Revise participant information sheet to clearly explain details of how potential disclosures would be handled during the course of the study.	Further consideration to how the results of the questionnaire will be fed back to interested participants.
Supervisor and expert opinion from Bridging the Age Gap steering group	Inclusion of a personalised cover sheet with university header. Colour printing to increase quality.	A member of the steering group put forward PPI support to review the questionnaire – Yorkshire and Humber Consumer Research Panel. Glossary of definitions – some respondents may not understand what we mean by 'advance decision'
PPI Group	No comments on the study documents.	Found the questionnaire clear, well-structured and easy to follow. 15 pages at first seemed long but this had left space for questions, which were clear and relevant. The question "Did you enjoy completing the questionnaire?" is not relevant and seems a little inappropriate.

The following action was taken to address comments and feedback on the study documents and questionnaire

- The participant information sheet made clear the procedure for handling disclosures
- The cover letter included University of Sheffield headers and space to personalise towards the respondent
- A section was included in the questionnaire asking the respondent to indicate if they would like to receive the results of the study
- A glossary was included in the back of the questionnaire

- The question “Did you enjoy completing the questionnaire?” was omitted from the revised questionnaire.

4.3.4. Questionnaire Recruitment Strategy

The full recruitment strategy is detailed in the Study Protocol **(Appendix 1)** however an overview is given here. An initial count of eligible patients was taken prior to submitting the IRAS application, and then checked again following ethics approval of the study. Each recruiting centre with eligible participants was contacted initially with an email outlining the project, the study protocol and ethics approval letter. Some sites were approached face-to-face at monitor visits by the lead researcher. Expression of interest from centres was then followed-up with a phone call to discuss set-up of the study and further explanation of how participants would be identified.

Prior to set-up, centres were instructed to undertake a data quality check to confirm that all patients who had been consented by a consultee had a recorded diagnosis of dementia. Following local R&D procedures, sites were set-up as Participant Identification Centres (PIC)s, which meant that the involvement of local research staff would be minimal. The researcher provided local research staff with a finalised list of eligible individuals to receive an invitation pack. The pack comprised of a cover letter, patient information sheet, consent form, study questionnaire, and freepost envelope. Completed questionnaires and consent forms were returned directly to the researcher. Informed consent was obtained by postal consent and countersigned by the researcher on the date received.

4.3.5. Questionnaire Analysis

Each returned questionnaire was entered into a password protected Excel spreadsheet to organise the responses and undertake any data cleaning. The dataset was then imported into SPSS once recruitment had ended and analysed using descriptive statistics. A comparison of descriptive and univariate analysis is shown in **Table 20**.

Table 20: Descriptive and Univariate Analysis

	Descriptive	Univariate
Summary	Data that describes or summarises patterns in data.	Data that makes generalizations about the populations (where samples are taken from).
Measures	Measures of central tendency (such as median and mean) and spread (standard deviation).	Estimating parameters, variance analysis and testing hypotheses.
Outputs	Tables, graphs, charts and statistical commentary.	Significance tests, Chi square, P values.
Advantages	Useful for smaller data sets. Presents raw data in a meaningful way. Simple interpretations of data.	Useful for larger data sets. Can make inferences about the wider population and generalizations
Disadvantages	Cannot make generalizations beyond the data.	Time consuming. Requires higher level of researcher skill.

By virtue of the sampling approach and questionnaire design, descriptive analysis was used to produce summaries across the data. This method was chosen primarily for the reason that the study aims were not attempting to make generalizations to the wider population. The study sample was small and descriptive statistical analysis would be more useful for handling small datasets. By virtue of the study design, a quality inferential analysis would not be suited where data was collected using a non-probability sample approach.

4.3.6. Quality Appraisal

The Centre for Evidence Based Management CEBMA (214) Critical Appraisal Checklist was used to assess the questionnaire as it was designed with a focus on cross-sectional research. The checklist summary of items in the appraisal framework is shown in **Table 21**.

Table 21: CEBMA Critical Appraisal Checklist for Questionnaires

	Appraisal Question
1.	Did the study address clearly focused question/issue?
2.	Is the research method (study design) appropriate for answering the research question?
3.	Is the method of selection of the subjects clearly described?
4.	Could the way the sample was obtained introduce selection bias?
5.	Was the sample of subjects representative with regard to the population to which the findings will be referred?
6.	Was the sample size based on pre-study considerations of statistical power?
7.	Was a satisfactory response rate achieved?
8.	Are the measurements (questionnaires) likely to be valid and reliable?
9.	Was statistical significance assessed?
10.	Are confidence intervals given for the main results?
11.	Could there be confounding factors that haven't been accounted for?
12.	Can the results be applied in your organization?

Source: CEBMA (214)

The analysis and findings of the questionnaire component of the study is presented in **Chapter Seven**.

4.4. Qualitative Interviews

Qualitative interviewing is a frequently used strategy for exploring subjective experiences in-depth. The two common types of interviews are face-to-face and telephone, and these can both be conducted in a structured or semi-structured way. The next section will explore the interview modes that were considered for this study and the development of the topic guide.

4.4.1. Face-to-face and Telephone Interviews

Interviews are considered to be the primary method used in qualitative research (215, 216). The face-to-face interview is often held as the gold standard in qualitative research, although telephone interviews have been increasingly used where sensitive topics are explored (217). The decision to use either method is dependent on the purpose and feasibility of the study (such as time constraints, location), the information being collected and how appropriate either method is within the context of the research study (218). The advantages and disadvantages of face-to-face and telephone interview are shown in **Table 22.**

Table 22: Face-to-face and telephone interview types

		Face-to-face Interviews	Telephone Interviews
Advantages	***Interviewer Context***	Ability to capture field notes on non-verbal cues (facial expressions and body language). Ability to sense distress within the participant while discussing sensitive topics.	Reduce the financial + time costs incurred by travel and room hire. Ability to interview hard-to-reach respondents or widely geographically distributed, in shorter space of time. Ease of notetaking without disrupting the interview. The respondent may be less influenced by the characteristics of the interviewer (e.g., gender, age)
	Respondent Context	Allows participants who are hard of hearing to lip read the interviewer.	Respondents may feel more anonymous in a telephone interview and comfortable to discuss sensitive topics.

		Respondents may feel more able to open-up and empowered being able to see the researcher; advantages of human interaction versus a voice on a phone	May feel less formal and more casual. Allows participants with disabilities and mobility restrictions to participate with no requirement to travel.
Disadvantages	***Interviewer Context***	Safety concerns (e.g., if the interview were to be conducted in a non-public space) Financial and time costs of travel, room hire, refreshments.	May have a higher drop-out rate. The interviewer would be unable to comfort the respondent if they were to become distressed or upset in the same way they could in a face-to-face interview.
	Respondent Context	Respondents may not feel their anonymity is protected if meeting the interviewer face-to-face	Technological issues (e.g., phone line quality, recording the call). Some populations might prefer face-to-face interaction.

Both face-to-face and telephone modes of interviewing were utilized for the following reasons.

- Having both options increased flexibility over where and when to schedule the interview. This maximised participation by allowing caregivers to take part in a way that was most comfortable for them. This reduced the pressure to take part in a face-to-face interview if a telephone interview would be more convenient (or vice versa).
- Some caregivers lived with the person they provided care for, and so may have been be less able to take part in a face-to-face interview if they could not arrange temporary care cover. Some caregivers may also work during the week, meaning that a telephone interview may be more desirable.
- Some questions in the topic guide covered sensitive topics, which caregivers may find easier to discuss over the telephone. Creating more social distance may improve responses and result in respondents feeling more comfortable in terms of disclosing their thoughts and feelings.
- Telephone interviews would be cost-effective for the researcher and allow more interviews to take place during a short space of time.

- Funding was available for room hire, refreshments and reimbursement of travel for both the interviewer and respondent where face-to-face interviews were preferred.

The aim of this flexible strategy was to maximise the reach of participants who might be seldom heard in research and enable all eligible caregivers to take part in a way that was most convenient for them.

4.4.2. Qualitative Interview Approaches

The main approaches to qualitative interviewing are structured, semi-structured unstructured interviewing. Structured interviews are guided by a pre-defined set of questions that are asked in the same standardized order to each participant, with no deviation. Unstructured interviews are conversational by nature and involves pursuing lines of questioning as they come up in the interview. Meeting both approaches in the middle is the semi-structured approach, which involves using a topic guide or framework of questions. This allows for the interview to deviate the discussion from the guide to maximise the information gained. The advantages and disadvantages of semi-structured and structured interviews are summarised in **Table 23**.

Table 23: Structured and semi-structured interview approaches

	Structured Interviews	Semi-structured Interviews	Unstructured Interviews
Procedure	Questions specified ahead of the interview. Structured, closed-ended questions. Can generate quantitative data.	Follows a topic guide but can pursue new lines of questions as they develop. Allows for open-ended responses. Generates qualitative data.	Questions are not pre-planned. Unstructured open-ended questions in any order. Generates detailed qualitative data.
Advantages	Asking the same set of questions increases reliability and generalizability of findings. Consistency across interviews. Minimises researcher bias. Useful approach for studying large samples.	Flexibility to pursue and probe beyond initial responses. Depth and validity.	High validity, useful for exploring sensitive topics. Flexible line of questioning and clarification of responses.

Disadvantages	Limits validity as questions chosen in advance. Limited scope for probing and flexibility.	Lack of standardisation. Risk of interviewer bias. Can be time consuming to analyse.	Lack of comparability. Risk of interviewer bias. Time consuming to analyse. May lack reliability.

A semi-structured interview approach was chosen as it would allow for probing on caregiver responses and maximise the ability to gain more in-depth detail. This strategy would also allow re-direction of the topic or line of questioning in scenarios where the caregiver became emotional or upset when discussing sensitive topics. Semi-structured interviewing would also allow an exploration of the questionnaire responses in more depth and adapt the interview questions to reflect the respondent's experience. This would avoid repetition if questions were answered out of sequence and create a natural conversational tone between the researcher and the caregiver.

4.4.3. Qualitative Sampling Technique

4.4.3.1. Sampling Frame

It is widely accepted that smaller sample sizes are the norm in qualitative research, with less emphasis on frequencies. The sampling frame for the qualitative interviews included the caregivers who responded to the questionnaire. In the returned questionnaire, respondents were able to express their interest in participating in a follow-up interview.

To maximise the representativeness of caregivers in the study, the following process for selecting interviewees was undertaken

1. Each questionnaire asked all respondents to indicate their interest in a follow-up interview, regardless of age, gender and ethnicity
2. There were no restrictions on geographical distances, as the researcher had the ability to travel extensively or conduct interviews by telephone
3. According to Mason (219) the guiding principle of qualitative research should be data saturation (the point at which no new themes are observed in the data). This aligned with the view of ethics committee members, who advised

against attempting to interview beyond data saturation. The study therefore aimed to avoid recruiting beyond saturation of themes.

4. After data cleaning, quality checks and R&D approval, all questionnaire respondents were deemed eligible to participate, although the literature review revealed that previous studies included very small numbers in this hard-to-reach group. It was acknowledged that the study may not achieve a high number of responses.

4.4.3.2. Non-probability Sampling

While quantitative research is often more concerned with generalising findings to the wider population, the aim of qualitative studies is often exploratory and less concerned with making statistical inferences. The main method of sampling in qualitative research is non-probability sampling. Non-probability sampling techniques are often used in qualitative studies where the primary concern is exploratory (220). This means that units or individuals are selected based on non-random criteria. The four main techniques and their strengths and weaknesses are illustrated in **Table 24**.

Table 24: Qualitative Sampling Techniques

	Convenience Sample	Voluntary Response Sample	Purposive Sample	Snowball Sample
Sampling frame	Individuals or units who are readily available and accessible to the researcher	Individuals volunteer to participate (rather than being directly contacted by the researcher).	The researcher selects the sample which meets the purposes of the research	Individuals to recruit other participants
Strengths	Ease and inexpensive.	Ease of access (the researcher does not need to search extensively for participants).	Useful for multi-phase studies. Flexibility for targeting individuals with shared characteristics.	Useful for accessing hard-to-reach hidden populations and targeting specific groups.
Weaknesses	Sample may not be representative of the population. Results cannot be generalised.	Self-selection bias in the characteristics of the sample. Sample may therefore not be representative of the population.	Participant selection can mean the sample is not representative. Difficult to generalise.	Difficult to generalise to the wider population (may not be representative)

A voluntary response sampling approach was chosen for the main reason that this would allow caregivers to directly choose to participate in the interview after completing the questionnaire. This approach meant there was easier access to caregivers who had already been contacted to complete the questionnaire. Finally, this approach would comply with ethics committee restriction of only contacting caregivers who chose to respond to the information pack. Some potential biases associated with this approach included volunteer bias (overrepresentation of some typologies of respondent over others) and selective non-response (under-representation of some respondent types).

4.4.3.3. Eligibility

The eligibility criteria for the qualitative interview stage were the same as detailed in **Section 4.3.2.1.2.1.** with the addition of two criteria.

1. Respondent must have completed the questionnaire prior to the interview
2. Respondent must be willing to participate in either a face-to-face or telephone interview

4.4.3.4. Recruitment

Questionnaire respondents who had specified their interest in participating in an interview were contacted directly by the researcher. Before making contact, the researcher interrogated the Bridging the Age Gap trial database for recent information about the circumstances of the individual that each caregiver provided cared for. If the individual cared for was still mid follow-up on the trial, and there was evidence that the person had been seen in the last two months, the recruiting centre was contacted to undertake a mortality check. If a study withdrawal or death form had been completed, the caregiver was withdrawn from the study.

4.4.4. Developing the Interview Guide

Topic guides (or interview schedules) are used to guide discussion in structured and semi-structured qualitative interviews. Topic guides are constructed by the researcher based on their interpretation of the key points for investigation. Prior to developing the guide, a list of initial topics was informed by the systematic review findings

(Chapter Five). The wider literature was explored to find similar studies and theoretical approaches to semi-structured interviewing.

The structure of the topic guide was informed by Kvale (215)'s interview typologies work to construct a list of questions **(Table 25).** This approach involved using a range of question types such as probing (to extend the respondent's answers) and specifying questions, to gain more detail in the interview.

Table 25: Interview Topics

Type of Interview Question	Example
Introducing question	"Can you tell me about how you first came to be involved in the decision making for another person?"
Follow-up questions	"Had you been involved in any treatment decisions for another person before?"
Probing questions	"Could you give me some examples of decision-making aids or resources you considered while making the decision?"
Specifying questions	"How did you feel throughout the decision-making process?'
Direct questions	"Do you think that you made the right decision?"
Indirect questions	"How do you think your [relative/spouse] would have made that decision? Do you believe your [relative/spouse] would have made the same choice if they could decide for themselves?"
Structuring questions	"I would now like to introduce another topic…"
Interpreting questions	"Can you explain what you meant back when we discussed how you felt throughout the decision-making process"

Source: Table created using 'types of interview questions' from Kvale (215)

Prior to the interview, the questionnaire responses were reviewed, and the topic guide was adapted accordingly. This bespoke approach personalised the interview towards the caregiver and ensured that only relevant questions were asked. The intention of this was to create a more conversational feel to the interview, rather than a 'researcher and participant' dynamic.

4.4.5. Pilot and Feedback

Feedback from the ethics committee, PhD supervisors and PPI group on the qualitative component of the study (topic guide and interview procedure) is presented in **Table 26**.

Table 26: Feedback on topic guide and conduct of interviews

	Study Documents	Interview Procedure	Action taken
Ethics Committee	Confirm that a lone working policy will be adopted to ensure the safety of applicants Agree a procedure to manage disclosures and explain this procedure in the information materials Confirm protocol to manage withdrawal of participants due to the individual in their care dying in the interval between contacts Revise PIS and consent form to provide further information on interview participation expectations (location, timing and duration)	Cautioned against interviewing beyond data saturation – advised this would be onerous and inappropriate to take individuals through an interview if this was not required Submit a topic guide for ethical approval, to provide an overview of potential issues to be discussed	Lone worker and procedure for handling disclosures added to the PIS and protocol Quality check agreed for mortality status of patients Revised study documents to give details of the timing and location of interviews Topic guide submitted to ethics committee via Substantial Amendment Agreed to interview up until the point of data saturation
PhD supervisors, PPI group and Bridging the Age Gap steering group	Undertake a scoping exercise of the wider literature to pull out the key issues around caregiving for patients with dementia-caregiving To structure the topic guide around the breast cancer narrative/journey, sets the scene for the respondent.	To confirm procedure for lone working and face-to-face interviews – provide details of location and contact number to team administrator when travelling to interviews.	A systematic review of the wider literature was carried out A lone worker policy adopted

4.4.6. Interview Conduct

Prior to each interview, the researcher sent a reminder 24 hours before by email or telephone. Before beginning the interview, Kvale (215) advises the researcher to reiterate the purpose of the interview and ask if there are any questions. The researcher therefore ensured that the participant had read and understood the information sheet before taking consent and spent 5-10 minutes establishing rapport with some warm-up questions to put the interviewee at ease.

4.4.7. Interview Analysis

Qualitative interviews can be analysed using a range of techniques. The two common approaches for analysing interviews are content analysis (221) and thematic analysis (222). A comparison of these approaches is shown in **Table 27.**

Table 27: Qualitative analysis techniques

	Content analysis (221)	Thematic analysis (222)
Aims	Examining content	Interpretive approach
Philosophical grounding	Deductive Quantitative	Realist, constructionist stance Qualitative
Analysis	Immersion in the data. Open coding, generating categories. Report generates conceptual models and mapping.	Familiarising with the data. Generating initial codes, searching and review of themes. Reporting analysis and linking back to the research question, aims and objectives

4.4.7.1. Thematic Analysis

Thematic analysis is a widely used method for analysing qualitative data, and in recent years it has become increasingly recognised as a method in its own right. Braun and Clarke (222) describe thematic analysis as:

> *"A method for identifying, analysing and reporting patterns (themes) within data. It minimally organises and describes your data set in (rich) detail.*
>
> **Braun and Clarke (222) p79.**

Thematic analysis can be used to explore a wide range of inter-disciplinary research questions and phenomena, such as the cultural norms, social processes or factors that lay beneath the surface. This approach can also be used to analyse different sources of data including focus groups, interviews, case studies and systematic reviews. Thematic analysis also works well with analysing both small and large datasets and can be used in combination with multiple methods.

The two approaches to undertaking thematic analysis are deductive or inductive. Both are distinct in their approach and the way in which they can be used to look for themes within the data, however the commonality between them is that both are concerned with identifying the themes that highlight the patterned meanings within data. Themes are defined within these approaches in the following ways:

1. The first approach is to conceptualise themes as *buried treasure*, which pre-exist the data, and are discovered by the researcher within the data
2. The second approach considers themes as being *actively constructed* by the researcher, rather than being discovered

A summary of these approaches is displayed in **Table 28**.

Table 28: Inductive and deductive thematic analysis approaches

Deductive Approach	Inductive Approach
Theory driven approach	Data driven approach (e.g., Grounded Theory) where theory is built from the data.
Associated with quantitative methods	Associated with qualitative methods
Highly structured approach	Iterative and flexible structure
The position of the researcher is independent to the research process. Often guided by a coding frame (with pre-defined set of themes) which are then applied to the data	The position of the researcher as a *storyteller* who is actively engaged in the research process and the interpretation of themes

There is also a third *in-between* approach that adopts principles from both inductive and deductive schools of thought; bringing with it some pragmatic advantages. One example is the Framework Approach (223), which is explored in the next section.

4.4.7.2. The Framework Approach

The Framework Approach is a variant of content analysis, and was developed in the 1980s by researchers Ritchie and Spencer at the National Centre for Social Research (224). In recent years it has been used widely in the field of health research, particularly studies that have undertaken in-depth analysis of patient experiences and observations. A key strength of the approach is that it is multidisciplinary and not typically aligned with one epistemological position, complimenting the pragmatic stance and exploratory aims of this mixed method study.

The Framework Approach seeks to uncover similarities and variances within a dataset by searching for themes. The approach can also be useful for analysing data sources such as focus groups and interviews. A description of each step of the Framework Approach is presented in **Table 29.**

Table 29: The 5 Steps of the Framework Approach

	Step	Description
1	Familiarisation	Listening to recordings, transcribing and reading through the data. Taking analytical notes. Actively reading, with the researcher reflecting on their own understandings of the data.
2	Identifying a thematic framework	Using the notes and observations from the familiarization stage, a framework is devised around the significant points found within the data. For inductive research, this can involve open coding.
3	Indexing	Application of the framework to data, to identify corresponding themes.
4	Charting	Arranging the indexed themes into a matrix to summarize the data extracts.
5	Mapping and interpretation	An analysis across the dataset of any concepts and phenomena, and the identification of final themes.

Source: Adapted from Ritchie and Spencer (223)

4.4.7.3. Criteria for qualitative rigour

While quantitative approaches are concerned with the concept of validity and reliability, qualitative research aligns itself with the notion of rigour and trustworthiness. Lincoln and Guba (225) conceptualise this as four criteria for

achieving rigour in qualitative research; credibility, dependability, confirmability and transferability. These criteria and how they will be addressed within the study are presented in **Table 30.**

Table 30: Framework for achieving rigour in qualitative research

	Credibility	Dependability	Confirmability	Transferability
Definition	Refers to the confidence in the truth of the findings.	Refers to the findings being consistent and replicable.	Refers to clearly demonstrating how the interpretations of the data were reached.	Refers to the generalisability findings in other contexts.
How this will be addressed in the study	Peer debriefing with PhD supervisors and PPI group Detailing the research procedure in the PIS, protocol and consent procedures Providing packs to each PIC unit to ensure recruitment is consistent across all sites Ethical peer review from REC	Recording all changes to study documents through ethical amendments Recording the steps taken to analyse data to allow replication	Keeping a reflexive record of the data collection process Discussing the interpretation of findings with PhD supervisors. Triangulating the data to achieve confirmability and credibility of findings	The study will not seek to make generalisations. Iterative analysis of the data, providing rich descriptions of findings.

Source: Adapted from Lincoln and Guba (225) and Tobin and Begley (226)

4.4.7.4. Qualitative data organization

The qualitative interview data was managed in NVivo software (Version 12). NVivo is widely used for indexing and categorizing interview data; and the software has high compatibility with the Framework Approach. This software was chosen as it would allow a second researcher to collaboratively work on the data set. The researcher had

skills in the use of NVivo which led to a preference for use over other qualitative software such as ATLAS and MAXQDA, which were also considered.

4.4.8. Quality Appraisal

To appraise the qualitative interviews, Spencer and colleagues' (227) *Framework for Assessing Research Evidence* was adopted. This framework was chosen as it was designed with a focus specifically on qualitative research, such as interviews. The appraisal framework is shown in **Table 31**. The application of the quality appraisal will be discussed later in the qualitative chapter.

Table 31: Quality appraisal framework adopted

	Appraisal Question
Findings	How credible are the findings?
	How has knowledge/understanding been extended by the research?
	How well does the evaluation address its original aims and purposes?
	Scope for drawing wider inference – how well is this explained?
	How clear is the basis of evaluative appraisal?
Design	How defensible is the research design?
Sample	How well defended is the sample design/target selection of cases/ documents?
	Sample composition/case inclusion – how well is the eventual coverage described?
Data Collection	How well was the data collection carried out?
Analysis	How well has the approach to, and formulation of, the analysis been conveyed?
	Contexts of data sources – how well are they retained and portrayed?
Reporting	How clear are the links between the data, interpretation and conclusions – i.e., how well can the route to any conclusions be seen?
	How clear and coherent is the reporting?
Reflexivity & Neutrality	How clear are the assumptions/theoretical perspectives/values that have shaped the form and output of the evaluation?
Ethics	What evidence is there of attention to ethical issues?
Auditability	How adequately has the research process been documented?

The analysis and findings of the qualitative component of the study is presented in **Chapter Eight**.

4.5. Mixed Method Triangulation

4.5.1. Sequential Explanatory Design

The study used a sequential explanatory approach to collect data in two consecutive phases **(Figure 15).** Phase 1 of the study adopted a quantitative approach by collecting data using a structured questionnaire. An explanatory design was chosen as this pragmatically allowed both strands of qualitative and quantitative methods to inform one another. Phase 2 carried out in-depth semi-structured interviews with a sample of the questionnaire respondents.

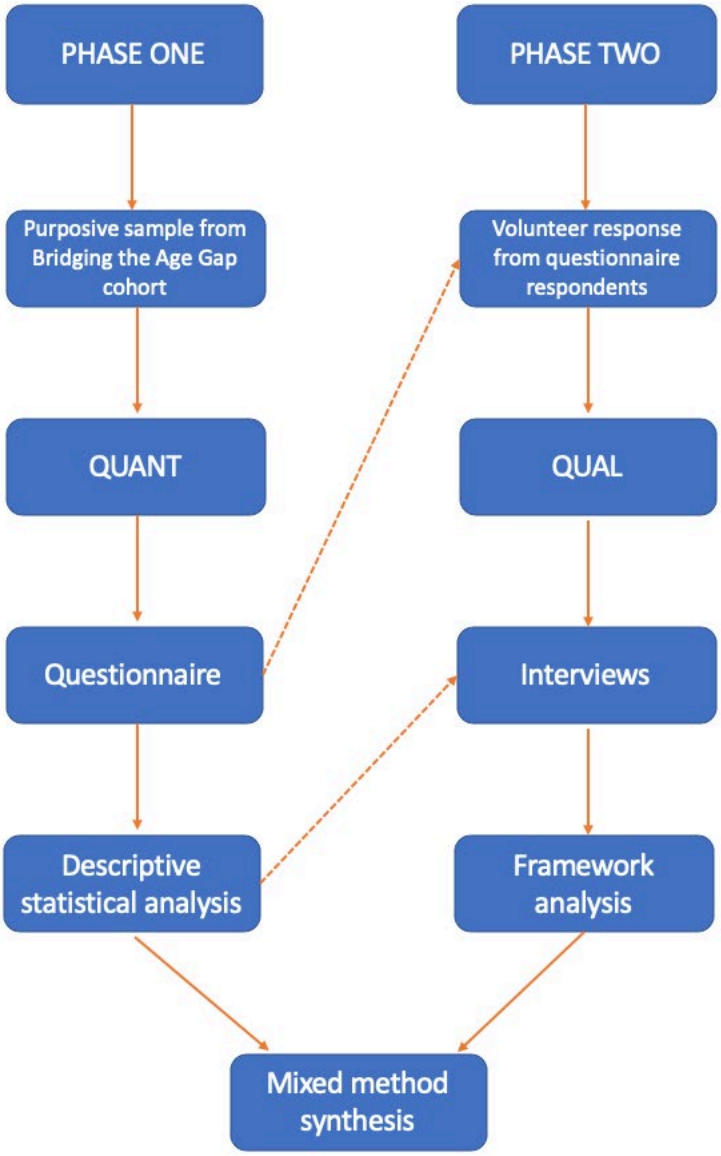


Figure 15: Sequential Explanatory Mixed Method Design

4.5.2. Mixed Method Analysis

The four components synthesized in this study are the systematic review, quantitative (patient cohort data, questionnaire) and qualitative (interview) findings. Farmer and colleagues (228) and O'Cathain and colleagues (229) describe the techniques for integrating mixed method data, making reference to how triangulation can be used to improve the validity (and trustworthiness) of results by achieving a more complete overview of the subject explored.

4.5.2.1. Triangulation Protocol Method

The triangulation protocol approach was adopted to bring together each strand of data collection. This was based on the six step approach developed by Farmer and colleagues (228), outlined in **Table 32**.

Table 32: The 6 steps of a Triangulation Protocol

	Step	Description
1	Sorting	Organise data into categories that aim to address the research question
2	Convergence Coding	Classify themes across the data using a *coding scheme*
3	Convergence Assessment	Review findings
4	Completeness Comparison	Comparison of data sets
5	Researcher Comparison	Compare findings with research team
6	Feedback	Feedback findings to research team, participants or PPI group

Source: Adapted from Farmer et al **(228)**

A triangulation protocol was chosen primarily for the reason that it would allow validation of data across the four data sets (systematic review, cohort data, questionnaire and interview findings). This approach was used to identify areas of agreement and dissonance across the data collected.

4.5.3. Quality Appraisal

To assess the quality of this research study, the Good Reporting of A Mixed Method Study (GRAMMS) **(Table 33)** developed by O'Cathain, Murphy and Nicholl (230) was

used. This framework was chosen as it is widely used to assess the quality of mixed method studies and encourages good quality reporting of mixed method research in publications. The application of the GRAMMS appraisal will be discussed in the reflexive account **(Chapter Ten, Discussion)**.

Table 33: Quality appraisal for mixed method studies

	Appraisal Question	How/where this is addressed
1.	Describe the justification for using a MM approach to the research question	The justification for MM approach and design is discussed in **Chapter three (3.4).**
2.	Describe the design in terms of the purpose priority and sequence of methods	The mixed method design and sequence of methods is discussed in **Chapter four (4.5).**
3.	Describe each method in terms of sampling, data collection and analysis	Sampling, data collection and analysis is discussed in **Chapter four**. The individual methods used for each study component are described in each chapter.
4.	Describe where integration has occurred, how it occurred and who has participated in it	Integration is described in **Chapter four (4.5)**.
5.	Describe any limitations of one method associated with the presence of the other method	The limitations for each study component are described in each chapter.
6.	Describe any insights gained from mixing or integrating methods	The insights gained from mixing and integrating methods are described in **Chapter ten** (discussion and reflexive account)

Source: O'Cathain, Murphy and Nichol (230) p.97

4.6. Ethics and Study set-up

The study protocol in **Appendix 1** details the full recruitment, ethics and study set-up procedures. An overview is given here.

4.6.1. Ethical Considerations

- **Research involving vulnerable people**

The content and line of questioning involved the recollection of sensitive issues that could potentially cause upset and distress to individuals taking part in the study. Caregivers may be vulnerable to psychological and emotional distress, in different degrees, at different points in their lives. The following steps were taken to mitigate any foreseeable risk to caregivers during their participation in the study.

1. A PPI group was approached to give lay audience feedback on the content of the questionnaire, study documents and interview guide
2. The researcher complied with legal requirements set out by the ethics committee, specifically with regards to withdrawals of any caregivers for patients who had passed away
3. The researcher avoided the use of any biased language during the interviews.
4. A mutually agreed location was chosen for each interview, where both the researcher and the participant felt most at ease
5. Where an interviewee became visibly upset or uncomfortable with any questions asked, the conversation was placed on hold and resumed after a break

- **Confidentiality**

Sites that agreed to participate posted the information packs directly to the caregivers, asking for permission to access their details and take part in the study. Questionnaires could be returned anonymously, and some participants remained anonymous unless they wished to participate in an interview. The researcher then contacted only those who had provided their details to take part in an interview.

- **Informed consent**

Interest was expressed by responding to the invitation pack, completion of the consent form and the questionnaire. No further attempts were made to contact caregivers who did not respond to the invite letter or refused consent after considering the study. Individuals were reminded that they were free to withdraw from the study at any time without giving a reason.

- **Ethics and governance**

This research was undertaken in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (231). Permission to conduct this study was granted by the Research Ethics Committee (REC) and Health Research Authority (HRA) in July 2016 **(Ethics approval letter, Appendix 3).** The study sought site-specific research and development (R&D) approval from each individual NHS Trust using the Integrated Research Application System (IRAS) form. The study was also accepted for inclusion on the NIHR CRN portfolio and recruitment figures were reported for this study.

- **Safeguarding policies**

The researcher completed Good Clinical Practice (GCP) training. The researcher adhered to The University of Sheffield lone worker policy when undertaking interviews, and the ethical principles outlined in the Declaration of Helsinki (2008) and The University of Sheffield Research Ethics Policy.

- **Data protection**

All data items collected as part of this study were handled in accordance with the Data Protection Act, 1998. Any information pertaining to the identity of study participants was kept confidential. Study documents such as consent forms and recruitment logs were securely stored in a locked cabinet.

4.7. Chapter Summary

This chapter has detailed the data collection and analysis approaches that were used in this study. The procedures for sampling, recruitment, ethical considerations and data protection policies adhered to throughout the course of this study have also been outlined. The next chapter presents the systematic review component of this study,

which explored the topic of treatment decision making for older people with dementia and cancer.

Chapter Five: Systematic Review

5.1. Introduction

This chapter presents the systematic review which was undertaken during the development stages of this research study. The aim of the review was to explore the role of caregivers involved in making cancer treatment decisions for people living with dementia. The methods, search strategy and analysis are presented in this section, followed by the results and recommendations for future research on this topic.

5.2. Systematic Review

The aim of the systematic review was to meet the following study objective:

- Undertake a systematic review of the research literature relating to the role of caregivers in cancer decision making and the support of patients with dementia and cancer.

The systematic review was published in ***Psycho-oncology***, June 2019.

Martin C, Shrestha A, Burton, M, Collins K, and Wyld L. 'How are caregivers involved in treatment decision making for older people with dementia and a new diagnosis of cancer?' *Psycho-Oncology*. 2019. doi: 10.1002/pon.5070.

The role of the lead researcher (CM) involved developing the search strategy; screening of papers; analysis of data; data quality assessment and writing up the manuscript. Anne Shrestha (AS) was involved in the data quality assessment stage of the review. Lynda Wyld (LW) and AS supported the selection of final studies included in the review. The PhD supervisors LW and Maria Burton (MB) provided oversight in drafting the manuscript.

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5.2.1. Abstract

Objective: To explore how caregivers are involved in making treatment decisions for older people living with dementia and a new diagnosis of cancer.

Method: A systematic review of PubMed, CINAHL, PsycINFO, Web of Science and Scopus databases were conducted. Studies recruiting formal or informal caregivers for older people with dementia and a diagnosis were considered for inclusion.

Results: Of 1761 articles screened, 36 full texts were assessed for eligibility and 6 were included in the review. This review has identified that health care professionals (HCPs) are often unaware of the co-existence or severity of dementia in cancer patients, and therefore fail to properly address care needs as a result. While caregivers are relied on to help make decisions, they have unmet information needs and feel excluded from decision-making.

Conclusion: Treatment decision-making in the context of older adults with dementia and a new diagnosis of cancer needs further research. This will help HCPs to understand their needs and improve the experience of decision-making for both caregivers and the people that they care for.

5.2.2. Background

Over the past 25 years there has been a substantial growth in the older adult population who now represent the fastest group demographic in the U.K. (232). Older adults are now living much longer with advanced stages of age-related co-morbidities, such as cognitive impairment, and have an increased vulnerability to age-related disease and cancers. Dementia is a disease characterised by a progressive set of conditions that include loss of judgement, reasoning ability and memory; all of which will impair capacity to make informed decisions (233). The scope of dementia impacts so much more than just memory; it can impair language, perception, and the ability to undertake daily tasks without additional care and assistance. Together, these changes over time can place a profound burden on family and caregivers, especially in the later stages of dementia, which will increase the need for care services, psycho-social support and assistance with treatment decision-making (40).

Caregivers can be either formally or informally appointed to help make decisions on behalf of a person who lacks capacity (168). Under current U.K. law, caregivers must have LPA for health and welfare in order to make treatment related decisions on behalf of another person. The role of the caregiver in this scenario is to elicit the preferences of the person living with dementia and navigate which treatments are in their best interests (179). In the literature, this is often referred to as proxy or surrogate decision-making.

As the ageing process varies, some older adults may be considered fitter than others and able to withstand different levels of treatment. Treatments for a new cancer diagnosis should therefore be tailored and take into account any existing co-morbidities and treatment regimens (40). For people living with dementia, the process of diagnosis may differ significantly to those without cognitive impairment; screening opportunities may be limited, and undergoing diagnostic investigations may present a burden to the person living with dementia and their caregiver (147). People with dementia may also lack the capacity to understand the treatments available to them, and information may need to be adapted or presented in a manner adapted to their cognitive capacity. Caregiver involvement may therefore be needed to interpret the

patient's wishes and help guide the consultant towards a treatment plan that takes into account the wishes of the patient and is in their best interests.

As a result of these issues, caregivers may be presented with difficult decisions where they are asked to assist in the decision-making process within a range of legal frameworks. This may mean that caregivers need to use their own judgment to establish which types of treatments the patient might choose for him or herself if they had the capacity to do so. In cases where it is not possible to determine which treatments the patient might decide for himself or herself, the principle of best interests should be used. This principle is underpinned by the Mental Capacity Act (71).

Little is currently known about how caregivers are involved in making cancer treatment decisions for the older, cognitively impaired population. Previous reviews have struggled to identify many studies that have directly explored the experiences of people with dementia and their caregivers in this context (234). A recent review by Hopkinson and colleagues, which sought to explore the experiences of people living with cancer and dementia, found that people with dementia were more likely to have a delayed diagnosis and receive fewer treatments compared with cancer patients who did not have dementia (235).

The aim of this review was to address the gap in knowledge by exploring how caregivers are involved in making cancer treatment decisions for older people with dementia who receive a new diagnosis of cancer.

5.2.3. Methods

5.2.3.1. Search question

How are caregivers involved in making treatment decisions for older people with dementia and a new diagnosis of cancer?

5.2.3.2. Search strategy

A comprehensive search of the literature was conducted in accordance with PRISMA guidelines (198) between June and September 2018, and revised again in January 2019. The following databases were searched: CINAHL, PubMed (via MEDLINE),

PsycINFO, Scopus and Web of Science. Hand-searching reference lists and the grey literature also obtained references. The search was limited to the English language. Given the nature of the research question, an adapted "PCO" framework (236) was used for this review. A broad range of key search terms were used based around the topics of "proxy decision making," "caregivers," "dementia," and "cancer." A combination of free text searches and MeSH terms were used to identify articles. An example of the search strategy for PubMed (via MEDLINE) is shown in the **Appendix 4.**

5.2.3.3. Eligibility criteria

The search aimed to identify qualitative, quantitative or mixed method studies that recruited caregivers (both informal and formal) for people living with dementia. Studies were included if they made reference to cancer treatment decision-making for older people living with dementia. This included studies that observed treatment discussions in consultations and caregiver perspectives on hypothetical treatment scenarios. Reviews, letters, case studies, editorials, and conference abstracts were excluded. Studies were limited to those that focused on older adults (>60), as this age is widely accepted as a lower cut-off for chronological older age (237).

5.2.3.4. Quality appraisal

Two reviewers (CM and AS) discussed and selected the articles included in this review. The rationale for including studies with either a mixed method, qualitative or quantitative design was that this would allow a broad understanding of the research topic. Search results were imported to Endnote for screening and full text retrieval. Studies were selected for this review using a two-step process; articles were first screened by title and abstract to determine relevance to the review. The PRISMA search strategy (198) was used to filter articles and remove any duplicates. Full text articles were then retrieved to assess relevance against the inclusion criteria and then independently reviewed.

The Mixed Method Appraisal Tool (MMAT) (196, 238) quality checklist was used to appraise each study. The MMAT criteria includes two screening questions, and 19

items to appraise five types of study (qualitative, quantitative randomized controlled trials, quantitative non-randomised, quantitative descriptive, and mixed methods). Quality assessment scores were calculated for each study using the MMAT score; ranging from one criterion met (25%) to all criteria met (100%). No study was excluded on the basis of quality assessment as the authors chose to include studies that represented the small amount of literature exploring decision-making for people with dementia and cancer. However, for qualitative studies, the question *"(1.4). Is appropriate consideration given to how findings relate to researchers' influence, e.g., through their interactions with participants?"* was unclear or not always addressed.

5.2.3.5. Analysis

Thematic analysis was undertaken in accordance with the Framework Approach (224, 239). This process involved coding the key findings across studies, and then developing themes, which were then summarized within a framework matrix. Reviewing the matrix generated the final themes. The analysis was guided by an interpretivist approach.

5.3. Results

The search strategy produced a total of 1935 results **(Figure 16)**. Of these, 174 duplicates were removed, and 1725 were excluded, as they did not meet the inclusion criteria. The remaining 36 articles were retrieved for full text review and six of these were deemed suitable for inclusion. The term 'caregiver' has been used throughout this review to represent carers and informal caregivers. Health care provider (HCP) has been used as a comprehensive term for the treating clinician, consultant or oncology staff.

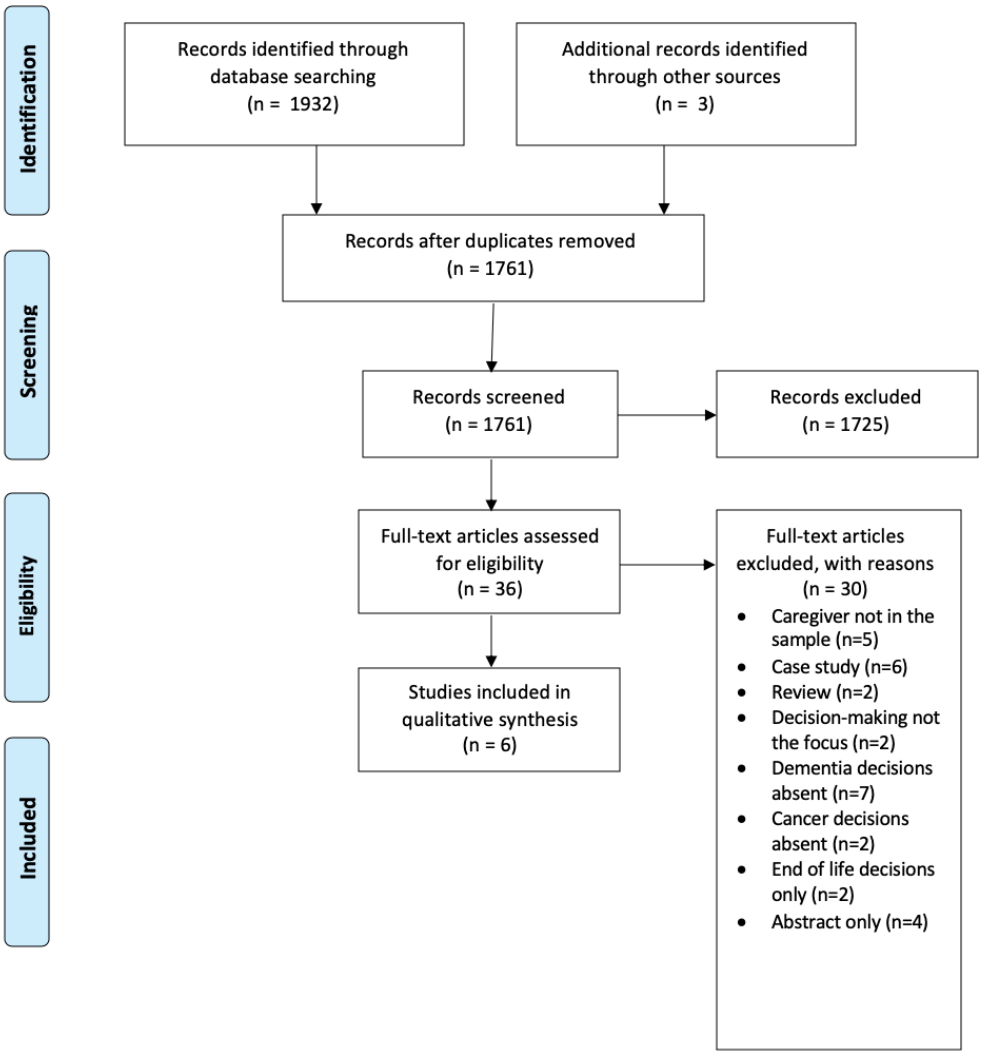


Figure 16: PRISMA flow chart

5.3.1. Study characteristics

Of the six studies included **(Table 34)**, five were conducted in the U.K and one in the USA. One study used a quantitative cross sectional design (240) and five studies used a qualitative design (156, 241-244). Two studies explored treatment decision-making in the context of hypothetical treatment scenarios (240, 241), three studies observed prospective treatment decision-making in clinical scenarios (242-244) and one study interviewed patients and caregivers who were reflecting retrospectively on the cancer diagnosis and treatment decision-making process (156).

Table 34: Studies included in the review

Author(s) and year of publication	Study population and setting	Objective(s)	Design	Method	Summary of themes	MMAT score
Smyth, 2009 (241)	Family caregivers (n=23) of women with dementia. Recruited from Alzheimer's Disease Research Centre Registry, USA.	To explore breast screening and treatment decision-making in older women with dementia.	Qualitative.	Semi-structured telephone interviews. Thematic Analysis.	(1) Perceived importance of regular screening mammograms. (2) Perceived appropriateness of breast cancer treatment options.	75%
Harrison Dening et al, 2016 (240)	Dyads of family caregivers and people with dementia (n=60). Recruited from memory clinics in UK.	To explore choices and preferences of caregivers and people with dementia.	Quantitative Cross-sectional study.	Semi-structured interviews. Descriptive statistics.	(1) Treatment choices and caregiver agreement in prediction. (2) Uncertainty. (3) Caregiver burden, distress, and quality of relationship.	75%
Courtier et al, 2016 (242)	Caregivers and people with dementia. 33 consultations observed. 10 consultations recorded, 16 interviews (n=6 patient-caregiver dyads; n=1 lone patient; n=5 staff). Medical record review (n=338). Recruited from 4 outpatient clinics in 1 UK cancer centre.	To observe the management of patients with dementia, memory loss and cancer. Explore the needs and preferences of outpatient cancer services,	Qualitative Case Study Design.	Retrospective case note review; observation; interviews; recorded consultations. Framework Analysis.	(1). Memory and the cancer consultation. (2) Staff attitudes. (3) Management Approach. (4) Caregiver role.	75%

McWilliams et al, 2018 (156)	Informal caregivers (n=9); people with dementia-cancer (n=10), and oncology HCPs (n=12). Recruited from a regional NW England Cancer Centre, UK.	To explore the information needs and experiences of caregivers, patients with dementia-cancer and oncology HCPs.	Qualitative. Cross Sectional Design.	Semi-structured face-to-face interviews. Thematic analysis.	(1) Leading up to the cancer consultation. (2) Communicating clinically relevant information. (3) Adjustments to cancer care. (4) After cancer treatment finishes.	100%
Witham et al, 2018 (244)	Informal family caregivers (n=7). Recruited from a psycho-oncology unit at a regional cancer centre, UK.	To explore the experiences of caregivers of relatives with cancer and dementia.	Qualitative. Narrative Approach.	Semi-structured face-to-face interviews using interview guide. Analytical Framework.	(1) Communication with Health Care Professionals: Maintaining caregiver identity. (2) Decision making and maintaining personhood. (3) Negotiating cancer care.	100%
McWilliams et al, 2018 (243)	Family caregivers (n=9); people with dementia-cancer (n=10). Recruited from a regional NW England Cancer Centre, UK.	To explore the decision-making and treatment options for people with dementia-cancer, and their family caregivers.	Qualitative. Exploratory.	Semi-structured face-to-face interviews. Thematic approach.	(1) Reaching a diagnosis of cancer. (2) Adjusting to the cancer diagnosis when living with dementia. (3) Weighing up the cancer treatment options. (4) Undergoing cancer treatment.	100%

All six studies used semi-structured interviews (face-to-face or telephone) with informal/familial caregivers to collect primary data. Five qualitative studies used a framework, thematic or narrative analysis (156, 241-244) and one study used descriptive statistics (240). Two studies observed or interviewed HCPs in addition to caregivers (242, 243) and four studies also included the views of people living with dementia (156, 240, 242, 243).

Four studies specified a clinical diagnosis of dementia for the patient being cared for in their inclusion criteria (156, 240, 243, 244), and one study included caregivers for patients with a memory problem, as judged by the HCP and patient (242). Five studies recruited participants from either cancer clinics (156, 242-244) or memory clinics (240), and one study recruited caregivers from a dementia registry (241).

Three studies reported their sampling method as purposive (156, 243, 244), while others were unclear (240-242). The sample sizes of interviewees reported in the qualitative studies ranged from 6 to 60 patient-caregiver dyads (156, 240, 242), and 7 to 23 caregivers interviewed individually (241, 243, 244). Two studies interviewed patients with dementia individually in their case sample (156, 243).

Thematic analysis using established theorists such as Wolcott's framework, and Braun and Clarke's thematic analysis were used in three qualitative studies (156, 242, 243) and Riessman's narrative approach was used in one study (244). One study measured responses using caregiver specific questionnaires, such as the Quality of Carer Patient Relationship questionnaire (QCPR) (240).

5.3.2. Findings

Due to the study design of selected papers, a meta-analysis was not possible. Data have been categorized into three themes that interplay with the caregivers' experience of making proxy treatment decisions.

1. HCP dementia awareness and knowledge in the clinical consultation
2. Treatment decision-making discussions, information and communication needs
3. The caregiver role and the caregiver-patient relationship.

5.3.2.1. HCP dementia awareness and knowledge in the clinical consultation

Following screening and diagnosis, the initial cancer consultation was often the first point in the cancer treatment pathway where HCPs met with patients and their caregivers to discuss treatment options. Four studies explored the experiences of caregivers and HCPs in the cancer setting through observation of consultations (242) and semi-structured interviews (242-244). Caregivers in one study reflected back on

the consultation where the person living with dementia received their cancer diagnosis (156).

Having access to detailed patient information, such as past medical history, comorbidities and cognition level enabled HCP's to plan sufficient time for discussion in the consultation (243). McWilliams and colleagues noted that cognition status was not always known to the HCP in advance of the consultation (243), and dementia was also infrequently documented in the patient's referral information or medical records in the study led by Courtier and colleagues (242). In both studies, the identification of memory problems was often reliant on caregiver disclosures (242, 243). As a result of this unawareness, one caregiver described a scenario where the HCP failed to acknowledge the patient's distress when undergoing a clinical investigation, alongside failing to fully explain what the procedure entailed and what was expected (156).

In most studies, the caregiver accompanied the patient to the consultation where treatment options were discussed. In the study led by Witham and colleagues, one caregiver described a series of scenarios that led to missed appointments where the patient attended their appointment unassisted; this was due to unclear signage in the clinic and an absence of staff to guide the patient once in the hospital (244). The cognitively impaired patient also had a coexisting hearing problem and was unable to hear their name being called. Another caregiver in this study highlighted the logistics of transporting people with dementia who live on their own in the community to their appointments. A scenario was recalled where the patient's erratic sleep pattern was incompatible with the arranged transport pick-up time. This meant that without prompts, the patient would miss their transport to the appointment (244).

In the context of consultation discussions, caregivers felt that some decisions had been made by HCP's prior to the initial consultation (243) and relayed feeling excluded from decisions (244). Caregivers in McWilliams and colleagues' study highlighted the uncertainties around taking consent from people with dementia to undergo clinical investigations and the level of responsibility expected from caregivers (156).

Caregivers also highlighted the need for additional appointments, where treatment plans could be discussed further, independently from the patient (244).

Caregivers in the study led by Courtier and colleagues noted that the cancer consultation had a tendency to focus primarily on cancer treatments, rather than cognition-related problems (242). This subsequently led to memory problems remaining undiscovered. In two studies, it was noted that patients would often underplay memory problems (242) and dispute their inability to cope with treatment as a result of their impairment (244). Cancer diagnostic investigations were often delayed due to the combination of limited HCP awareness of memory problems and a failure to detect the signs associated with dementia (243). The lack of timely organisation of support for people with memory problems was therefore an issue (242, 243).

Two studies highlighted that dementia awareness training for cancer clinicians was needed (242, 243). The reasons for this included a lack of awareness of the impact that dementia may have on cancer screening (243) and the potential for interaction between the patients' dementia symptoms and cancer treatment (242). Being unaware of the patients' ability to give informed consent may result in HCPs taking the refusal of treatment at 'face value,' as noted by a caregiver in the study by Witham et al (244). Witham and colleagues describe one situation where a patient failed to complete their radiotherapy treatment due to refusing to attend appointments. This scenario was a result of the HCP failing to acknowledge that the person with dementia lacked the capacity to make informed decisions. In examples where HCPs were made aware of cognition problems in the patient, there was an uncertainty on how to best support them (242).

In Smyth's (241) study of breast screening and treatment preferences, caregiver decisions were found to be influenced by HCPs in regard to continued breast imaging; with a tendency to continue screening based on the clinician's recommendations. Witham and colleagues (244) also noted the dominance of the HCP's knowledge in the

consultation, through a scenario where a caregiver relayed feeling that their judgment of the patient's progress and response to treatment was challenged.

The need to involve dementia-specific support at the outset was emphasised by caregivers, with one study highlighting the example of a designated dementia nurse and biographical tool which was used in clinic to enhance support for patients with dementia (242). Two studies highlighted the need for HCP familiarity and how this was accomplished by using a designated HCP to coordinate care (243, 244). This avoided the need for repetitive recall of the patients' medical history and unnecessary frustration and anxiety for the patient (244). McWilliams and colleagues reported a positive scenario where the caregiver found it helpful when the HCP repeated information to her husband and paid attention to the pacing of the consultation. This led to a positive experience for both the caregiver and the person with dementia (156).

5.3.2.2. Treatment decision-making discussions, information and communication needs

Weighing up the pros and cons of treatment options for a person living with dementia may not only involve the caregiver; the HCP and patients themselves may also be involved in making these decisions. Five studies reported on the direct influence of having a dementia diagnosis on cancer treatment discussions (156, 241-244).

For people with dementia or memory issues, extra time may be needed to communicate information about their cancer diagnosis and treatment options. One study highlighted a scenario where the caregiver relayed their mother's lack of diagnosis awareness due to her dementia, and relayed a scenario of conveying the diagnosis to the patient using a 'creative strategy' and metaphors (156). Caregivers in Witham and colleagues' study also described the need for 'complex communication strategies' (244). Examples of this in other studies included taking more time to discuss options (156), 'slowing down' information delivery and using a change in language to communicate complex treatment information (243).

In situations where patients lacked capacity, the caregiver gathered treatment information and negotiated on behalf of the patient (242, 244), acting *'as a reliable messenger'* or '*relayer of information'* between the HCP and the patient (156, 243). In another study, one caregiver reflected on their role in assisting the HCP during cancer investigations; describing a scenario where they would stay in the room to reassure the patient, and break down complicated instructions from the HCP (156).

In respect to treatment decisions, caregivers in Smyth's study expressed the view that side effects would have an influence on the pursuit of any hypothetical cancer treatments, with some only willing to opt for active treatments when the side effects were less severe (241). It was noted in another study, however, that comprehensive treatment information on the risks and side-effects were not always fully explained to caregivers, and often misunderstood (243). In respect to the level of information received, some caregivers reported receiving enough verbal information, such as leaflets, but others described feeling they had to seek information for themselves post-consultation (156).

Smyth's study of current practices in breast cancer treatment found that dementia severity had an impact on the decision-making of caregivers towards screening and hypothetical treatment scenarios (241). For caregivers of women with severe dementia, only comfort care was suggested, whilst in women with mild-moderate dementia, caregivers were more likely to choose typically 'aggressive' treatments. It was also noted that caregiver treatment decisions, while hypothetical, did not always take into consideration the patient's co-morbidities and life expectancy (241).

Courtier and colleagues highlighted that people with dementia are likely to receive less treatment than patients without dementia (242). Reasons for this include the implications of dementia on life expectancy and the inability to tolerate treatments with complex regimens and severe side effects (242). McWilliams and colleagues also noted that the combination of cognition and communication impairments had a direct influence on treatment options, particularly the potential for side effects (243) and

the impact on quality of life for the person living with dementia was noted in another study (156).

The impact of dementia on treatment was not always considered by HCPs, and there was little regard for how treatment pathways could be adapted to meet the patient's needs (244). In this context, Witham and associates posit that the adaption of treatment regimens is needed for this population (244). When discussing treatment options with the HCP, caregivers reported unmet information needs; whereby information was not always communicated in an appropriate format, nor adapted in a way that was specific to patients with a cancer-dementia diagnosis (243).

5.3.2.3. The role of the caregiver and the caregiver-patient relationship

The caregiver plays an important role in cancer treatment decision-making, mainly by facilitating discussion around the treatment and care preferences of people who lack capacity. All six studies recruited caregivers (156, 240-244).

In the study led by McWilliams and colleagues, caregivers played a role in both uncovering symptoms and seeking help for the person with dementia, describing these as 'detective stories' (156). In other studies, family and informal caregivers were described as the key to a successful consultation (242, 243) and best placed to represent the voice of the patient; particularly in scenarios where the caregiver knew the patient well (242). This point was also echoed in McWilliams and colleagues' study, whereby the researcher reflected on the significance of the 'longitudinal and biographical' knowledge of the caregiver in research interviews (156). In some cases however, Witham and colleagues (244) noted that patients were prone to downplaying the importance of the caregiver role and that this in turn meant that advocating on behalf of the patient could be challenging for their relatives.

Caregivers are often relied upon to ensure that patients adhere safely to treatment and monitor any untoward side-effects (242). New treatment regimens, additional appointments and assistive home care needs may increase the demand on caregivers themselves, such as radiotherapy treatment, which may require repeated trips to

hospital (156). These additional burdens on the caregiver were not always considered during treatment discussions (243), and HCPs were not always found to enquire about the needs of the caregiver (242). As a result, some caregivers reported feeling excluded from the patient's cancer journey (244). Caregivers in the same study felt that their role was often marginalized by the HCP; describing a scenario where their knowledge and judgment of the person with dementia was questioned by the HCP (244).

It is posited that the caregiver-patient relationship itself may have a direct impact on the outcome of treatment decisions. Courtier and colleagues (242) noted that in scenarios where the caregiver did not know the patient personally, *'memory loss acted as a barrier to a successful consultation'*. The HCP reliance on informal and family caregivers was also highlighted by McWilliams and colleagues (243), who reported difficulties where patients with dementia had attended clinic with a caregiver who had limited knowledge and no relationship to the patient.

People living with dementia often rely on caregivers to make decisions on their behalf. In Courtier's paper, HCPs were happy to conduct consultations with the caregiver taking the lead decision-making role, however this could sometimes have the unintended effect of disguising memory difficulties experienced by the person with dementia, unless it was disclosed, or made known to the clinician (242). However, Harrison Dening and colleagues (240) reported that the dependency on caregivers to interpret patient decisions might be misplaced. In their study of hypothetical treatment scenarios, caregivers and patients did not always agree consistently on future treatment scenarios. Where asked about advanced cancer treatment scenarios, patients with dementia had a preference for antibiotic treatment (47%) over CPR (30%) and tube feeding (37%). Within dyads there was a low level of agreement (240).

5.4. Discussion

The key findings from this review highlight the lack of dementia specific support at the start of the cancer journey. People with dementia require additional support and time

for discussion when planning treatment and attending appointments. While caregivers are often relied upon for their biographical knowledge of the patient, their support and information needs are not always considered by HCPs. These findings highlight a missed opportunity for allowing caregivers a more active role in consultations and treatment decision-making for people with dementia and cancer.

The main aim of this review was to explore how caregivers are involved in making treatment decisions for older people living dementia who receive a new diagnosis of cancer. This aim, however, was only partially achieved. One reason for this was the limited scope of studies that have focused specifically on caregiving for this sub-population. The intention was to review studies that explored treatment decision-making in the context of early-stage cancer, with a focus on life-sustaining treatment, rather than end of life treatment decision-making. However, very few studies could be found in the initial scoping stages of the review.

Although the search strategy focused on studies that recruited caregivers, one theme emerging from this review is the notion that discussions around memory and the behavioural and psychological symptoms (BPSD) of dementia are absent from the cancer consultation. It is therefore unclear if these symptoms are taken into account when discussing the suitability of different treatments. The studies included in this review have highlighted some of the barriers to navigating health care appointments and treatment discussions. These issues are consistent with the wider literature, which highlights the complexities involved in HCP encounters for people with dementia (74).

While some of the studies included in this review have explored the impact of dementia on treatment decision-making, there has been insufficient focus on how caregivers make treatment decisions, the type of information that caregivers would prefer to receive, and how advance decisions are used in the decision-making discussions. Only one study made reference to the theme of maintaining the 'pre-dementia' preferences of people with dementia in respect to breast screening,

however these preferences were not upheld as the severity of dementia increased (241).

A significant finding from the literature was the lack of knowledge and dementia awareness amongst health care professionals. There may be other complex issues influencing the treatment decision that have not been fully addressed. This may include the age, frailty, mobility and independence of the person with dementia.

5.4.1. Limitations

The small number of studies in this review highlights the need for further research into the cancer treatment decision-making experiences of older people with dementia and their caregivers. One explanation for the lack of studies in this area may be that this population is difficult to access and obtain consent to participate in research studies. The settings for the included studies were cancer clinics (156, 242-244), dementia registries (241) and memory clinics (240), which are key settings for recruiting patients with dementia and their caregivers. Despite this, recruitment was still challenging. Two studies reflected on the challenges in identifying participants, the consent process and small number of eligible participants (240, 242). Courtier and colleagues (242) reflected on how their study sample was smaller than expected, hinting at underlying inequalities in access to cancer services for patients with a dementia diagnosis.

Of the studies included in this review, the level of cognitive impairment (mild/moderate/severe) and functioning of patients was not always clear, except in the two studies, which reported dementia subtypes (156, 244). It is therefore not possible to make generalizations regarding all older patients with dementia. It is not possible to make any assumptions about the experiences of caregivers for people with mild dementia versus severe dementia, and more research is needed to translate findings to a range of cancer populations (242).

5.4.2. Clinical implications

The involvement of people living with dementia in research requires a high level of ethical scrutiny. In addition, there are strict safeguarding policies in place for any research involving participants with limited cognitive capacity. The small numbers of participants included in these papers hint at the complexities involved in recruitment and the additional support that caregivers and patients in this population may need to participate in research.

Low recruitment may also be linked to the sensitive nature of making decisions for another person, at what is undoubtedly a highly emotive time in their cancer journey. Receiving a cancer diagnosis can be psychologically stressful for both people with dementia and their caregivers. Therefore, deciding on the right time to approach caregivers may affect their willingness to take part in research. For this reason, many researchers may be cautious about causing distress, and caregivers may gate-keep access to people with dementia (245).

The themes identified in this review are consistent with the background context of dementia-cancer research. This review has identified a clear need to increase specialist dementia support for both the patient and caregivers from the initial consultation and throughout the cancer care pathway. Ensuring that HCPs have appropriate training and can identify memory, behavioural and cognition problems will mean that any advice or treatment recommended is tailored appropriately to the patient. More specific information tailored towards caregivers and people living with dementia is also needed in order to optimize treatment decision-making.

5.5. Conclusion

Cancer treatment decision-making for older people with dementia remains a complex issue. With an ever-increasing aged population, this research raises concerns about the management of people with cancer who lack mental capacity and the support needs of those who are directly involved in making difficult choices on behalf of the people they care for. Further exploration of caregiver experiences in this context is needed.

5.6. Chapter Summary

This chapter has presented the systematic review which explored the role of caregivers in cancer decision-making and supporting patients with dementia and cancer. The review highlights the complexities involved in decision-making and the small amount of literature that has specifically explored this topic.

The next chapter will present a sub-analysis of patient treatment and survival data, taken from a prospective trial of breast cancer patients (with and without dementia)

Chapter Six: Analysis of breast cancer treatment outcomes

6.1. Introduction

The following chapter presents an analysis of treatment and survival outcomes of older women with cognitive impairment and primary breast cancer, compared with non-cognitively impaired older women. The aim of the analysis was to determine the oncological outcomes for older women with early breast cancer when also affected by cognitive impairment. The analysis was performed using patient data collected by the Bridging the Age Gap in Breast Cancer trial.

6.2. Analysis of treatment and survival outcomes for older women (>70) with breast cancer and cognitive impairment

The aim of undertaking the analysis was to meet the following study objective:

- Analyse data from a prospective observational multi-centre cohort study of older women (>70) with early breast cancer (Bridging the Age Gap trial) to

determine the baseline characteristics, cancer characteristics, cancer treatment and survival outcomes of women with breast cancer and cognitive impairment.

This analysis was published in ***Journal of Geriatric Oncology,*** December 2020.

Martin C, Shrestha A, Morgan J, Bradburn M, Herbert E, Burton M, Todd A, Walters S, Ward S, Holmes G, Reed MWR, Collins K, Robinson T, Ring A, Cheung KL, Audisio R, Gath J, Revell D, Green T, Lifford K, Edwards A, Chater T, Pemberton K, and Wyld L. 'Treatment outcomes for older women (>70) with breast cancer and dementia: Results from a prospective, multicentre cohort study.' *Journal of Geriatric Oncology*, 2020. doi: 10.1016/j.jgo.2020.12.006

The role of the lead researcher (CM) in undertaking this analysis included the initial concept; adjudicating cognition categories to the dementia cohort from baseline data and participation level; descriptive and chi-squared analysis of treatment allocation; selection of variables used in the propensity matching model; Kaplan Meier curves and Cox regression plots and writing the manuscript. Anne Shrestha (AS) had a role in the selection of variables used in the propensity matching model. Lynda Wyld (LW) had a role in the development of the initial concept and drafting the manuscript. Michael Bradburn (MB), Esther Herbert (EH), and LW provided guidance on undertaking the statistical analysis. MB performed the matching approach used in the propensity scoring model, quality control, and had oversight in drafting the manuscript.

6.3. Abstract

Background: Dementia and breast cancer are both common conditions linked to ageing. The presence of dementia co-existing with a diagnosis of breast cancer may render management more challenging and have a substantial impact on oncological outcomes. The aim of this analysis was to examine the treatment and outcomes of older women with a co-existing diagnosis of cognitive impairment and primary breast cancer.

Methods: Data was taken from a prospective, multicentre UK cohort study of women aged 70 years or over with primary operable breast cancer. Patients with and without cognitive impairment were compared to assess the differences in treatment decision and survival outcomes. Comparative statistical analysis was performed using Chi squared. Survival was calculated using Kaplan Meier method and Cox regression to compare the two cognition sub-groups (cognitively impaired and normal cognition).

Results: In total, 3416 women were recruited between February 2013 and June 2018. Of these, a diagnosis of dementia or cognitive impairment was identified in 478 (14%) patients, of whom 70% were subcategorised as mild, 12% moderate and 17% severely impaired. For women with normal cognition the rate of surgery was 85%, compared to women with mild (74%) moderate (61%) and severe impairment (40%) (p=0.001). Although patients with cognitive impairment had shorter overall survival (HR: 2.10, 95% CI: 1.77-2.50, p<0.001), there were no statistically significant differences in breast cancer specific survival.

Conclusion: Cognitive impairment appears to play a significant part in deciding how to treat older women with breast cancer. Standard treatment may be over-treatment for some women with severe impairment and careful consideration must be given to a more tailored approach in these women.

6.4. Background

The UK population is living longer than ever before, posing substantial societal and health challenges. Many diseases and co-morbidities are linked to ageing; the majority of cancers are more common in older age groups and often present in patients with age-related comorbidities, including dementia. With increasing age, the possibility of having a co-existing cancer and a diagnosis of dementia increases (35) and is associated with decreased cancer specific and overall survival (11, 246).

It is estimated that 7-10% of breast cancer patients have a co-existent diagnosis of cognitive impairment or dementia (148). Compared to non-cognitively impaired patients, this group has a six-fold higher risk of all-cause mortality within two years of diagnosis, which emphasises the importance of minimising treatment morbidity in this group (247). Patients with dementia often present with later stage disease (153),

which contributes to inferior breast cancer specific survival for these women (10, 148). Overall survival is also reduced in patients with dementia and cancer, as cognitive impairment increases the risk of all-cause mortality (248), in particular pneumonia (249). In a previous analysis of UK registry data, patients with breast cancer and dementia had inferior overall and breast cancer specific survival if surgery was omitted (250). Dementia was also an independent risk factor for non-guideline concordant care (14, 148).

People living with dementia may present complex challenges from legal, ethical and practical perspectives; particularly in cases where the patient does not have capacity to give informed consent to treatment and has not put in place an advance care plan. Dementia itself is a complex disease with multiple aetiologies and symptoms including memory loss, lack of cognitive capacity, confusion, mood alterations and anxiety. The impact of cancer treatments will vary according to the severity of dementia and the ability to monitor side effects. Surgery under general anaesthetic in the over 70s may cause prolonged post-operative cognitive dysfunction (251), acute post-operative delirium (252) and long-term cognitive decline, especially following major surgical resections, further compromising cognitive function (253). The precise aetiology of this is not clear (254). Cognitive impairment may also complicate the delivery of adjuvant treatments, including chemotherapy. For example, it is vital that patients receiving chemotherapy proactively report side-effects, including fever, which may signal life-threatening sepsis. Furthermore, patients undergoing chemotherapy may experience a degree of cognitive dysfunction, such as chemo-brain, which might exacerbate existing cognition problems in a person living with dementia (255, 256).

In some cases, reduced life expectancy may reduce the risk of breast cancer mortality, especially with indolent cancers, and some low grade, oestrogen receptor positive (ER+) breast cancers. Primary endocrine therapy (PET), where surgery is omitted in women with ER+ breast cancer, may be selected in these situations, trading reduced therapeutic benefit (reduced breast cancer specific survival and a higher rate of local disease progression) against reduced surgical morbidity (257).

The decision-making process to select treatments for older patients is complex and wide variation exists in their use (12, 141), leading to some patients being under- or over-treated; patients being treated with palliative or supportive intent, or potentially curative treatments, respectively. These latter treatments can, in some cases, reduce patients' quality-of-life, cause acute confusion, pain and distress, and have little impact on life expectancy, which is significantly reduced in the presence of severe dementia.

The treatment decision making process for patients with dementia is therefore challenging and should include consideration of the cancer prognosis, the physical health of the patient, the degree of dementia, and the wishes of the patient and their caregivers. It is important that the patient is involved if they have the capacity to express their preferences, or have previously expressed them via an advanced directive, or even verbally. Similarly, the voices of family and caregivers may give guidance on the patient's ability to tolerate treatments and their likely preferences.

The aim of this analysis was to examine a large prospective UK cohort of older women with primary breast cancer, with or without co-existing cognitive impairment or dementia, and evaluate their treatment patterns and survival outcomes.

6.5. Methods

6.5.1. Ethics and governance

Ethics and research governance approval was obtained for the Bridging the Age Gap in Breast Cancer trial (IRAS 115550, REC reference: 12/LO/1808). All patients (or their proxy, if cognitively impaired) gave written informed consent before participating in the trial. The ethics approval was granted by a Mental Health Act Compliant REC to permit the recruitment of patients with a diagnosis of dementia.

6.5.1.1. Recruitment of women with cognitive impairment

The study complied with Section 33 of the MCA (71), which applies to all research in England and Wales. The following approach was adopted:

- Recruiting centres assume the responsibility to assess the capacity of individual to give informed consent. This process involves establishing if the patient is able to:
    - Understand the information about the study and what taking part involves
    - Retain the information about the study
    - Be able to weigh up the study information
    - Be able to communicate their decision to take part or decline the study
- If it is established that the patient does not have capacity, a personal consultee (a family member or friend; a person acting under LPA; a court appointed deputy) should be identified to act on their behalf.
- If a personal consultee is not available, the patient will be excluded from the study.
- If the patient loses capacity during the research project, the recruiting site will follow the MCA guidelines to identify a consultee.

A personal consultee was defined as someone who knew the patient in a personal capacity and was able to advise on the person's wishes and feelings in relation to taking part in the trial.

6.5.2. Recruitment and eligibility criteria

The study recruited a total of 3416 participants across 56 centres in England and Wales between February 2013 and June 2018. Follow-up to the study ended in December 2018 to ensure that all patients had a minimum of 6 months follow up data.

Participants were recruited after a new diagnosis of primary operable breast cancer had been made. Eligibility criteria: women over age 70 at the time of diagnosis, primary unilateral or bilateral operable invasive breast cancer (TNM: T1-3, N0-1, M0). Exclusion criteria: metastatic disease, previous invasive breast cancer within 5 years. There were no limits for language, ethnicity or cognitive function. The study recruited women both with and without cognitive impairment. Cognition status was identified in the following ways:

1) **Proxy consent** (the patient was deemed to lack capacity, and was assented to the study by a consultee)
2) **Self-consenting patients** (the patient was judged as having capacity to consent themselves to research)
    a. Cognition status was indicated by completion of the Charlson Co-Morbidity Score (22) which has a field for dementia (yes/no)
    b. Cognition status indicated by participant completion of the Mini Mental State Examination (MMSE) (258), which categorized cognition as normal (27-30), mild CI (21-26), moderate CI (11-20), and severe CI (0-10) (MMSE used under license).

The study recruited both women with and without cognitive impairment (CI) to two levels of participation: Self-Consenting and Proxy Consent **(Figure 17).** Both participation levels involved either patient or caregiver completion of validated health questionnaires, alongside research nurse completed forms which captured patient demographics, treatment, and tumour characteristics.

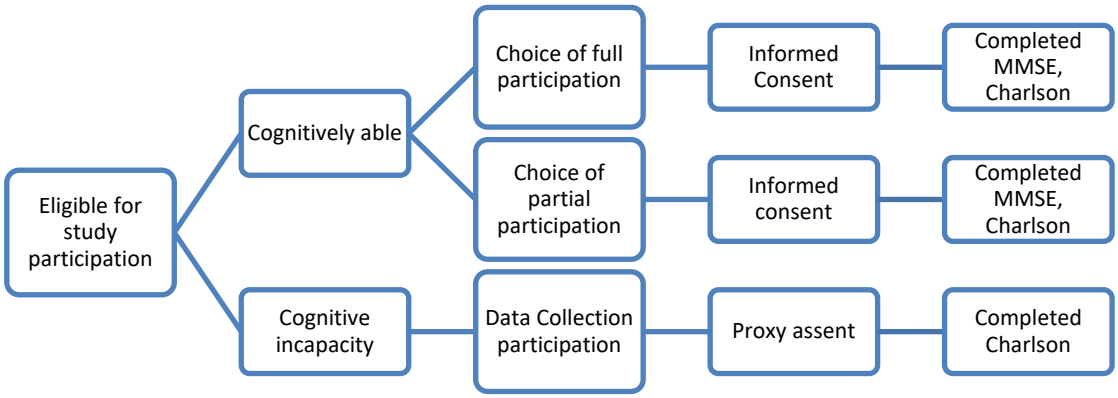


Figure 17: Participation level and cognition assessment tools completed

To identify individuals with cognitive impairment, participants who were assented to the study by a consultee were categorised as having severe impairment, as proxy

consent was an indicator for the patient being unable to give informed consent to participate in the trial. Of the patients who consented to the study themselves, and therefore were assumed to have the capacity to participate in research, 395 women had either a diagnosis of dementia recorded on the Charlson Index form (22) form, which was categorized as “mild,” or completed an MMSE form, scoring participants as having mild, moderate or severe impairment according to standard scoring protocols (normal (27-30), mild CI (21-26), moderate CI (11-20), and severe CI (0-10)) (258). The MMSE score always took precedence over Charlson Index categorization if available. A review of current medications was also performed. Participants who were able to give informed consent to join the study and had no indication of impairment according to the Charlson or MMSE scores were assumed to have normal cognition.

6.5.3. Study Data Collection

Baseline

Patient data items were collected at the baseline appointment visit, defined as the timeframe after the cancer diagnosis and before treatment was commenced. Patient demographics and co-morbidity data were collected using a Modified Charlson Co-Morbidity (CCI) score; for the purposes of these analyses, age and presence of dementia were omitted from the standard CCI calculation. Functional status was determined by the validated Activities of Daily Living (IADL) score (259), Instrumental Activities of Daily Living (IADL) (162), and the Eastern Cooperative Oncology Group performance status (ECOG-PS) (163) scores. Nutritional status was assessed using the Abridged Patient Generated Subjective Global Assessment (aPG-SGA) (260-262). Scoring of each tool followed standard published criteria. Primary breast tumour characteristics collected included grade, biological subtype and tumour stage (clinical, imaging and pathological stage used the TNM system, Version 8 (263)). Pathological axillary stage was not collected for patients who did not have surgery, but clinical assessment and pre-operative ultrasound and biopsy of nodal disease were recorded.

Follow-up measures

All patients were directly followed up at 6 weeks, 6, 12, 18 and 24 months to collect data on the treatment they received, adverse events and survival. Cause of death was assessed by death certification and classed as either breast cancer specific or other cause. Mortality and survival outcomes were obtained directly from participating breast cancer units for up to 24 months, and from the UK cancer registry (following specific patient or caregiver consent), for up to median follow-up of 52 months.

6.5.4. Analysis

Statistical analyses were performed in IBM SPSS (Version 26.0) and Stata (Version 16.1). Each patient or tumour characteristic was summarised in relation to cognitive category. Discrete characteristics were summarised by numbers and percentages, with statistical significance assessed by Chi-squared test. Continuous characteristics were summarised as the median and range, and statistical significance assessed by a non-parametric Kruskal Wallis test.

Overall survival and breast cancer specific survival were both compared between patients with CI (of any severity) and without impairment using propensity score matching. Two matching approaches were used. In the first analysis, patients with cognitive impairment were matched with up to three non-impaired patients that had the same category of Nottingham Prognostic Index (NPI; risk categories ≤3.4, >3.4 to ≤5.4, >5.4), oestrogen receptivity (ER) and treatment (surgery and ER+, surgery and ER-, PET and ER+), and age to within a calliper width of 1 year (approximately 1/6th of a standard deviation) (264). The second approach matched on NPI category, ER category and treatment and also a more detailed propensity score including functionality (ADL, IADL, and ECOG), nutrition (aPG-SGA) and co-morbidity (CCI score excluding dementia and age) to a calliper of 0.015 propensity score units (approximately 0.2 standard deviation) with up to two matches allowed. Residual balance and overlap were assessed by Kernel density smoothers separately for each variable in the propensity model. The comparisons were quantified by Kaplan-Meier

curves and Cox regression, presented for unadjusted and the matched analyses; matching was accounted for by use of a shared frailty term (265).

6.6. Results

6.6.1. Patient characteristics

A total of 3416 women were included in the analysis (summarised in Figure 18). Of these, 2938 (86%) were considered to have normal cognition and 478 (14%) had some level of cognitive impairment, identified by MMSE score completion or a previous diagnosis of dementia by a clinician.

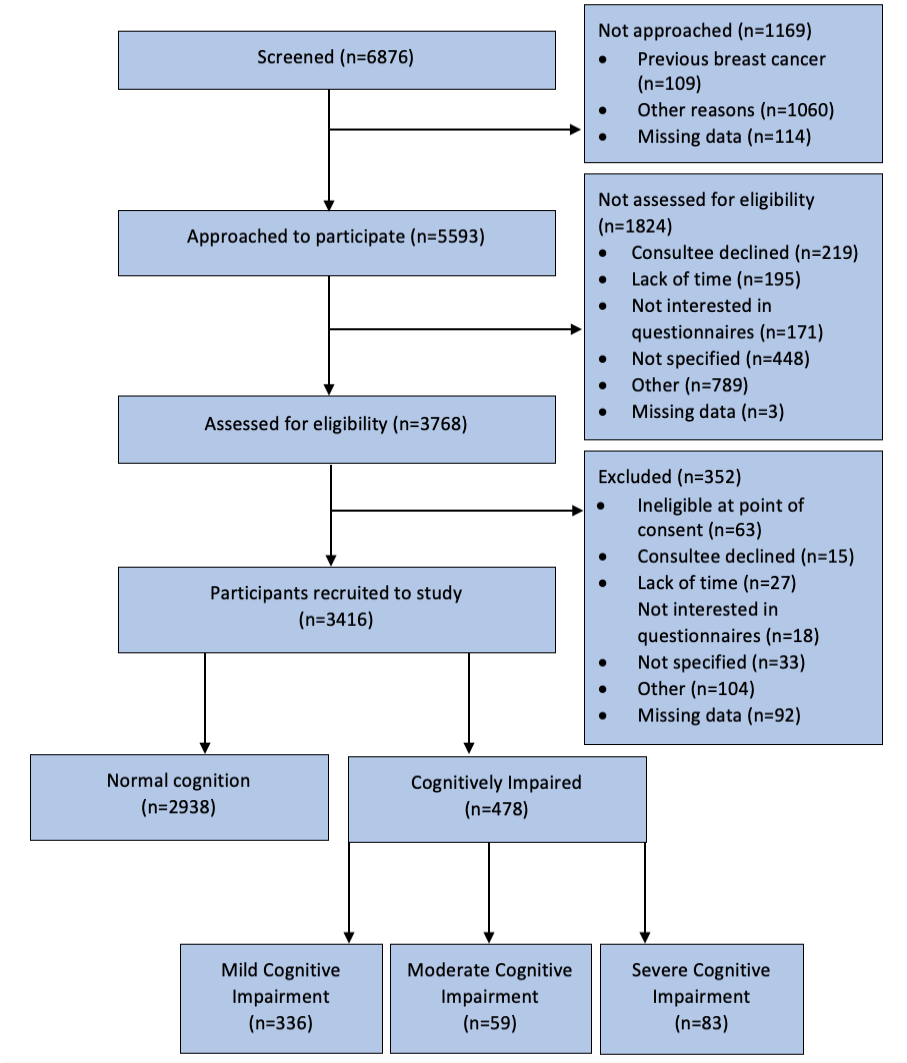


Figure 18: Patient flow diagram

The median age of women with normal cognition was 76 years (range 69-102; five women attended shortly before their 70th birthday and were retained in the study), while women with mild, moderate and severe cognitive impairment had a median age of 79, 80 and 83 respectively. The ADL, IADL and CCI scores are summarised in **Table 35.**

Table 35: Baseline demographics and characteristics of study participants by cognitive impairment level

	Cognition Category				
	Normal Function (N=2938)	**Mild Impairment (N=336)**	**Moderate Impairment (N=59)**	**Severe Impairment (N=83)**	**P value**
Age Median (range)	76 (69-102)	79 (70-96)	80 (70-99)	83 (70-97)	<0.001
ADL* Median (range)	100 (5-100)	100 (30-100)	100 (30-100)	70 (20-100)	<0.001
IADL Score Median (range)**	8 (0-8)	8 (0-8)	7 (0-8)	2 (0-8)	<0.001
CCI Score* Median (range)**	1 (0-13)	1 (0-7)	1 (0-8)	2 (0-7)	<0.001

***ADL interpretation: Ordinal rating scale assessing the ability to perform ten tasks independently. Scoring criteria: 0-20 = "total" dependency; 21-60 = "severe" dependency; 61-90 = "moderate" dependency; 91-99 = "slight" dependency.**
****IADL interpretation: Scale rating independent living skill and functional ability. Scoring range for females: 0 (low function, dependent) to 8 (high function, independent).**
*****CCI: Predicts 10-year survival in patients with multi-comorbidities. 17 items, maximum score of 37 points. Age and presence of dementia were omitted from the standard CCI calculation.**

6.6.2. Tumour characteristics

Tumour characteristics were similar between groups, with no statistically significant difference found in terms of nodal status, grade, ER and HER2 status. There was difference in the size of tumour at presentation; women with moderate or severe cognitive impairment were more likely to have larger tumours than women with normal cognition (p<0.001) **(Table 36).**

Table 36: Tumour characteristics of study participants by cognitive impairment level

	Cognition Category					
Tumour characteristics	**Normal function**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Total**	**P value**
						0.239
Unilateral	2871 (97.7%)	326 (97.0%)	59 (100%)	79 (95.2%)	3335 (97.6%)	
Bilateral	67 (2.3%)	10 (3.0%)	0 (0%)	4 (4.8%)	81 (2.4%)	
Tumour Size						
T1	1745 (59.4%)	205 (61.0%)	29 (49.2%)	34 (41.0%)	2013 (58.9%)	<0.001
T2	1110 (37.8%)	122 (36.3%)	24 (40.7%)	48 (57.8%)	1304 (38.2%)	
T3	71 (2.4%)	8 (2.4%)	6 (10.2%)	0 (0%)	85 (2.5%)	
Unknown	12 (0.4%)	1 (0.3%)	0 (0%)	1 (1.2%)	14 (0.4%)	
Number of positive nodes						
None	2468 (84.0%)	284 (84.5%)	46 (78.0%)	68 (81.9%)	2866 (83.9%)	0.538
1-3	380 (12.9%)	44 (13.1%)	6 (10.2%)	9 (10.8%)	439 (12.9%)	
4 +	23 (0.8%)	1 (0.3%)	1 (1.7%)	2 (2.4%)	27 (0.8%)	
Unknown	67 (2.3%)	7 (2.1%)	6 (10.2%)	4 (4.8%)	84 (2.5%)	
Provisional grade						
1	455 (15.5%)	48 (14.3%)	5 (8.5%)	15 (18.1%)	523 (15.3%)	0.259
2	1760 (59.9%)	212 (63.1%)	33 (55.9%)	52 (62.7%)	2057 (60.2%)	
3	587 (20.0%)	62 (18.5%)	18 (30.5%)	13 (15.7%)	680 (19.9%)	
Unknown	136 (4.6%)	14 (4.2%)	3 (5.1%)	3 (3.6%)	156 (4.6%)	

NPI						
<=3.4	1290 (43.9%)	139 (41.4%)	17 (28.8%)	32 (38.6%)	1478 (43.3%)	0.189
>3.4 to <=5.4	1297 (44.1%)	159 (47.3%)	28 (47.5%)	38 (45.8%)	1522 (44.6%)	
>5.4	121 (4.1%)	11 (3.3%)	5 (8.5%)	5 (6.0%)	142 (4.2%)	
Unknown	230 (7.8%)	27 (8.0%)	9 (15.3%)	8 (9.6%)	274 (8.0%)	
ER						
Negative	343 (11.7%)	40 (11.9%)	7 (11.86%)	8 (9.6%)	398 (11.7%)	0.951
Positive	2561 (87.2%)	292 (86.9%)	52 (88.14%)	74 (89.2%)	2979 (87.2%)	
Unknown	34 (1.2%)	4 (1.2%)	0 (0%)	1 (1.2%)	39 (1.1%)	
HER2						
Negative	1992 (67.80%)	207 (61.61%)	45 (76.27%)	60 (72.29%)	2304 (67.45%)	0.389
Inconclusive	83 (2.83%)	12 (3.57%)	1 (1.69%)	1 (1.20%)	97 (2.84%)	
Positive	283 (9.63%)	37 (11.01%)	5 (8.47%)	4 (4.82%)	329 (9.63%)	
Unknown	580 (19.74%)	80 (23.81%)	8 (13.56%)	18 (21.69%)	686 (20.08%)	

6.6.3. Primary treatment (PET versus Surgery)

Treatment data were available for 3315 patients, of whom 2811 (82.3%) underwent surgery (+/- adjuvant treatment) and 504 (14.8%) were treated with PET **(Table 37).**

Table 37: Primary treatment for all patients and tumour types

	Cognition Category					
Primary treatment	**Normal function**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Total**	**P value**
Surgery (+/- adjuvant therapy)	2494 (84.9%)	248 (73.8%)	36 (61.0%)	33 (39.8%)	2811 (82.3%)	<0.001
PET	365 (12.4%)	75 (22.3%)	21 (35.6%)	43 (51.8%)	504 (14.8%)	
No treatment/ Unknown	79 (2.7%)	13 (3.9%)	2 (3.4%)	7 (8.4%)	101 (3.0%)	
Totals	2938	336	59	83	3416	

Breast cancer surgery was significantly higher in women with normal cognition compared to cognitively impaired patients; 84.9% of women with normal cognition underwent surgery compared to women with mild (73.8%), moderate (61.0%) and severe (39.8%) impairment (p=0.001).

A total of 2735 surgeries could be categorized according to cognition status with 56 cases of missing data, which could not be analysed. Of these, rates of wide local excision and mastectomy were comparable across all groups **(Table 38).** There was a trend for women with cognitive impairment to undergo mastectomy compared to breast conserving treatment, however this difference did not reach statistical significance (P<0.186). For women with normal function, the rate of wide local excision (57.4%) was higher than those undergoing mastectomy (36.5%), whereas for women with severe impairment, rates were almost equal (16/33, 48.5%). This may be accounted for by the slightly larger primary tumour size seen in cognitively impaired participants.

Table 38: Breakdown of surgical treatment type for all patients undergoing surgery

	Cognition Category				
Type of surgery	**Normal function**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Total**
Wide local excision	1432 (57.4%)	132 (53.2%)	18 (50.0%)	16 (48.5%)	1598 (56.8%)
Therapeutic mammoplasty	46 (1.8%)	3 (1.2%)	1 (2.8%)	1 (3.0%)	51 (1.8%)
Mastectomy	911 (36.5%)	110 (44.4%)	13 (36.1%)	15 (45.4%)	1049 (37.3%)
Mastectomy and reconstruction	34 (1.4%)	1 (0.4%)	2 (5.6%)	0 (0%)	37 (1.3%)
Other	19 (0.8%)	0 (0%)	1 (2.8%)	0 (0%)	20 (0.7%)
Missing	52 (2.1%)	2 (0.8%)	1 (2.8%)	1 (3.3%)	56 (2.0%)
Totals	2494	248	36	33	2811

Cognitive impairment was associated with an increasing rate of PET in the 2979 women with ER+ cancers. Only 362/2561 (14.1%) women with normal cognition were treated with PET compared to 75/292 (25.7%) of women with mild, 20/52 (38.5%) moderate and 43/74 (58.1%) with severe impairment (p<0.001, Table 39)

Table 39: Primary treatment for patients with ER+ tumour types

	Cognition Category					
Treatment classification	**Normal function**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Total**	**P value**
Surgery (+/- adjuvant)	2139 (83.5%)	208 (71.2%)	30 (57.7%)	25 (33.8%)	2402 (80.6%)	<0.001
PET	362 (14.1%)	75 (25.7%)	20 (38.5%)	43 (58.1%)	500 (16.8%)	
No treatment/ unknown	60 (2.3%)	9 (3.1%)	2 (3.8%)	6 (8.1%)	77 (2.6%)	
Totals	2561	292	52	74	2979	

6.6.4. Adjuvant therapies

Use of adjuvant chemotherapy following surgery was more similar between the groups. Among the 1520 women with high recurrence risk cancer, chemotherapy was given to 342/1346 (25.4%) women with normal cognition compared to 28/139 (20.0%) with mild impairment, 4/18 (22.2%) with moderate impairment and 2/17 (11.8%) with severe impairment (p=0.321, Table 40).

Table 40: Adjuvant treatment for ER+ patients with high-risk tumours

	Cognition Category					
Adjuvant Therapy	**Normal function**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Totals**	**P value**
Chemotherapy in women with high recurrence risk cancer*	342/1346 (25.4%)	28/139 (20.0%)	4/18 (22.2%)	2/17 (11.8%)	376/1520 (24.7%)	0.321
Radiotherapy in women following BCS or high-risk histology post mastectomy**	727/1161 (62.6%)	66/110 (60.0%)	9/15 (60%)	4/13 (30.8%)	806/1299 (62.0%)	0.123
Trastuzumab in women with HER2 positive disease***	126/289 (43.6%)	10/34 (29.4%)	1/4 (25.0%)	2/5 (40.0%)	139/332 (41.9%)	0.392

***Among participants for whom chemotherapy should be considered on the basis of having any of the following: (i) HER2+; ii) ER-; iii) ER+ and histological grade 3; iv) presence of one or more positive lymph nodes or v) oncotype DX recurrence score of 30 or above.**
****Among participants for whom radiotherapy should be considered on the basis of having any of the following after mastectomy: i) tumour of >5cm or T4, ii) presence of four or more positive lymph nodes, iii) tumour resection margins positive, iv) histological grade 3 AND any nodal disease, v) nodal disease (1-3 nodes) if other risk factors such as adverse tumour biology (triple negative phenotype or HER-2 positive), or all women following breast conserving surgery**
*****Among participants for whom Trastuzumab should be considered on the basis of a HER-2+ tumour greater than 0.5 cm.**

The use of radiotherapy and trastuzumab were slightly higher amongst patients with normal cognitive function, though not significantly so. Similarly, analysis of the use of trastuzumab was limited by very small numbers of patients with HER2 positive disease in patients with cognitive impairment. Use of radiotherapy (if indicated by breast conservation surgery or high-risk histology after mastectomy) also appeared higher in

the normal cognition group, although numbers did not reach statistical significance (P<0.123). There were 727/1161 (62.6%) with normal cognition having radiotherapy compared to 4/13 (30.8%) in those with severe cognitive impairment.

6.6.5. Adverse events and systemic complications

Data on adverse events related to surgery and other treatments were recorded during study follow-up according to standard Common Terminology Criteria for Adverse Events (CTCAE) (266). There were seven systemic complications in patients with cognitive impairment compared to 50 in women with normal cognition. There was no clear association between systemic complications following surgery and cognitive capacity (numbers were too small for univariate analysis) **(Table 41).**

Table 41: Systemic complications frequencies

	Systemic Complications				
Adverse events	**Normal function**	**Mild Impairment**	**Moderate Impairment**	**Severe Impairment**	**Total**
Arrhythmia	11	1	0	0	12
Stroke	2	0	0	0	2
Allergic Reactions	2	1	0	0	3
Somnolence	29	3	0	0	32
Infarction	2	1	1	0	4
DVT	3	0	0	0	3
Atelectasis	1	0	0	0	1
Totals	50	6	1	0	57

6.6.6. Survival Analysis

6.6.6.1. Overall Survival

Overall survival data was available for 97.8% (3342/3416) of patients **(Table 42)**. Chi-squared analysis demonstrated that patients with cognitive impairment had reduced overall survival compared to women with normal cognition (p<0.001).

Table 42: Overall Survival for normal versus dementia sample

		Normal cognition	Dementia (mild/moderate/severe)	P value
Overall survival	**Data available**	**(N= 2871)**	**(N = 471)**	
	Alive	2331 (81.2%)	303 (64.3%)	
	Died	540 (18.8%)	168 (35.7%)	<0.001

0 cells (0.0%) have expected count less than 5. The minimum expected count is 99.78.

Figure 19 shows univariate analysis of survival by cognition level (dementia versus normal cognition). The Kaplan Meier curves demonstrate that patients with dementia had reduced overall survival compared to those without impairment. The hazard ratio indicates that women with dementia have less survival time until death, and that there is a statistically significant difference between survival for the two groups (HR: 2.101, 95% CI 1.76 to 2.49, p<0.001).

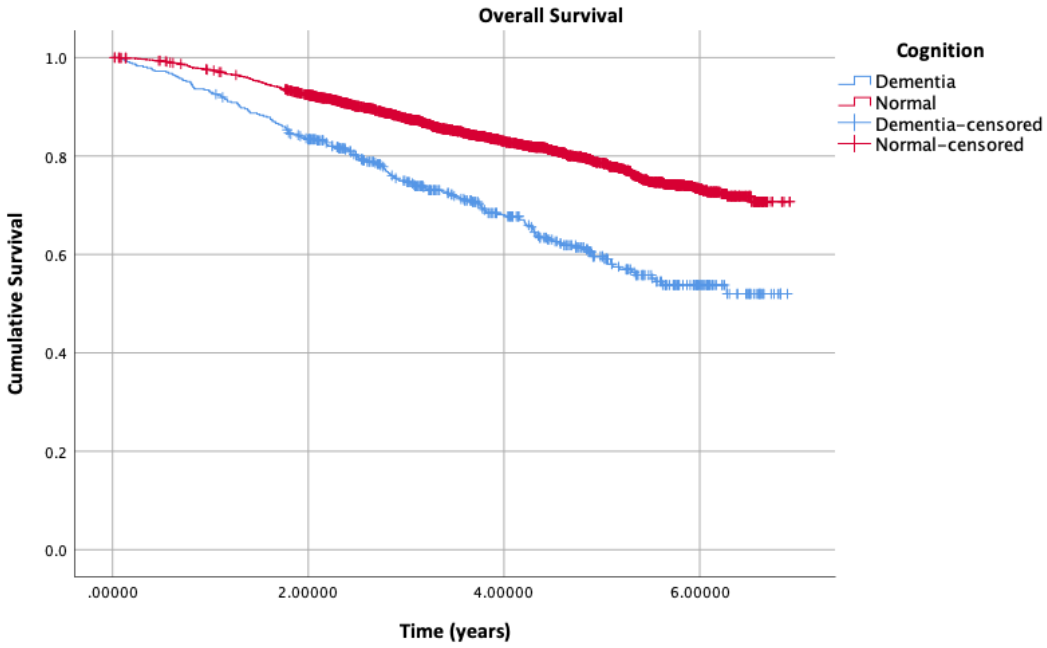


Figure 19: Kaplan Meier curve for overall survival of patients with and without dementia in the study cohort

In the propensity score matched analysis; age, functionality, treatment and NPI were modelled to determine if overall survival was due to cognition or functionality **(summarised in Table 43, Figures 20-22)**

Table 43: Overall survival in cox regression propensity model

Comparison	Hazard Ratio (95% CI)	P value
Unmatched	2.101 (1.767, 2.499)	<0.001
Matched for age, treatment, NPI	1.386 (1.092, 1.760)	0.008
Matched for age, treatment, NPI, functionality	1.220 (0.936, 1.592)	0.142

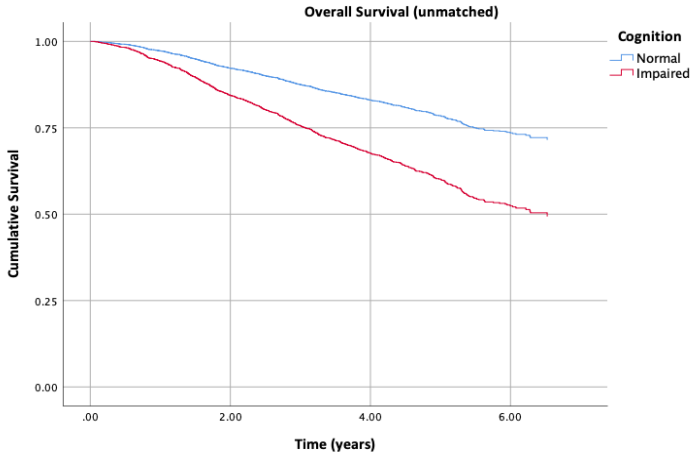


Figure 20: Kaplan Meier curve for overall survival: unmatched analysis of normal versus dementia cohort

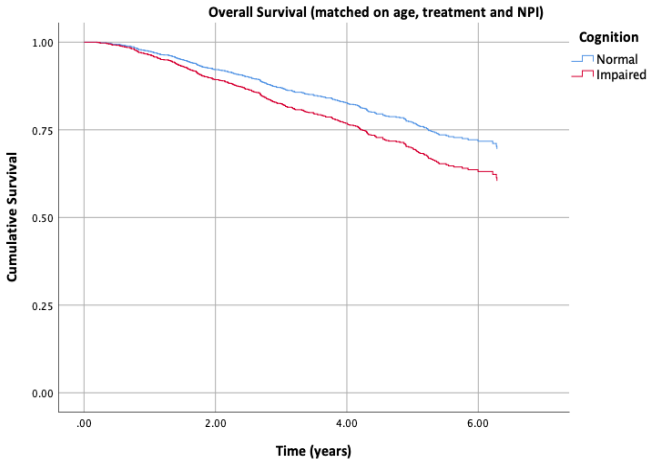


Figure 21: Kaplan Meier curve for overall survival: propensity match 1 (age, treatment and NPI)

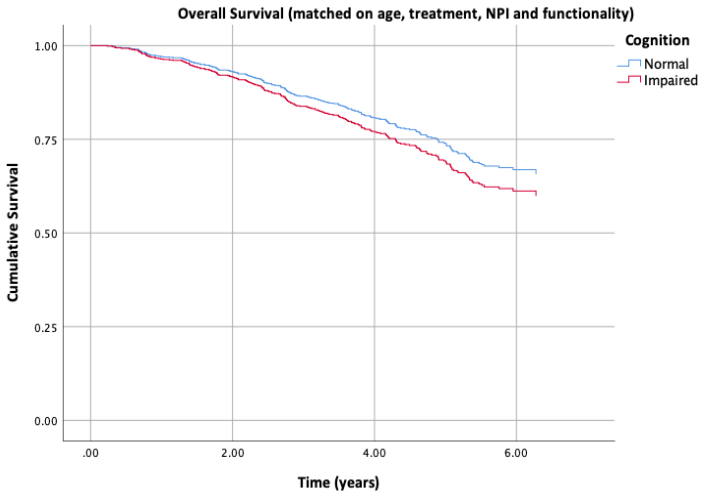


Figure 22: Kaplan Meier curve for overall survival: propensity match 2 (age, treatment, NPI and functionality)

Patients with cognitive impairment had reduced overall survival compared to those without impairment (HR: 2.10, 95% CI 1.77 to 2.5, p<0.001). The effect was greatly reduced (although not removed) when comparing patients matched for other characteristics. The effect sizes were similar for both models: matching for age, NPI, ER and treatment gave a hazard ratio of 1.38 (95% CI 1.09 to 1.76, p=0.008) whilst adding functionality, nutrition and comorbidity gave a hazard ratio of 1.22 (95% CI 0.93 to 1.59, p=142).

6.6.6.2. Breast cancer specific survival

Breast cancer specific mortality status was available for 96.9% (3310/3416) of the dementia versus normal cognition sample **(Table 44)**. The majority of patient deaths were unrelated to breast cancer (chi squared: p=0.152).

Table 44: Breast cancer specific survival for normal versus dementia sample

		Normal cognition	Dementia (mild/moderate/severe)	P value
Breast cancer specific death?	**Data available**	**(N= 2843)**	**(N= 467)**	
	Yes	208 (7.3%)	43 (9.2%)	p=0.152
	No	2635 (92.7%)	424 (90.8%)	

0 cells (0.0%) have expected count less than 5. The minimum expected count is 35.41.

Univariate analysis of breast cancer cause-specific survival gave a hazard ratio of 1.38 (95% CI, 0.99 to 1.92, p=0.060) **(Figure 23)**. The hazard ratio indicates that the

difference in breast cancer specific survival between the two groups is not statistically significant.

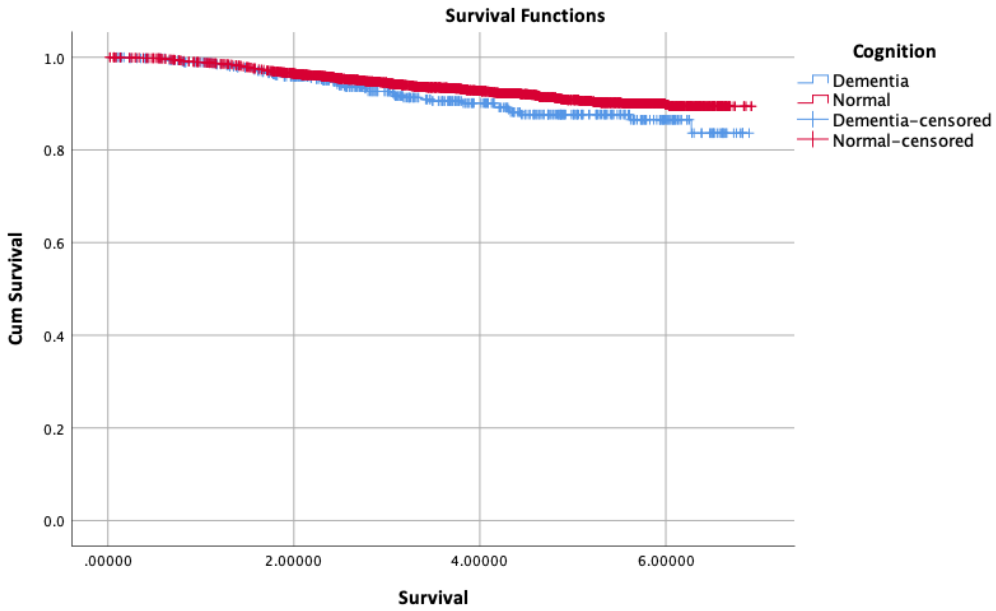


Figure 23: Kaplan Meier curve for breast cancer specific survival of patients with and without dementia in the study cohort

In the propensity score matched patients, there was no statistical difference in hazard both with and without matching, despite the differences in treatment allocation **(Table 45, Figures 24-26).**

Table 45: Breast cancer specific survival in cox regression propensity model

Comparison	Hazard Ratio (95% CI)	P value
Unmatched	1.387 (0.999, 1.926)	0.051
Matched for age, treatment, NPI	0.959 (0.614, 1.495)	0.852
Matched for age, treatment, NPI, functionality	0.931 (0.582, 1.488)	0.764

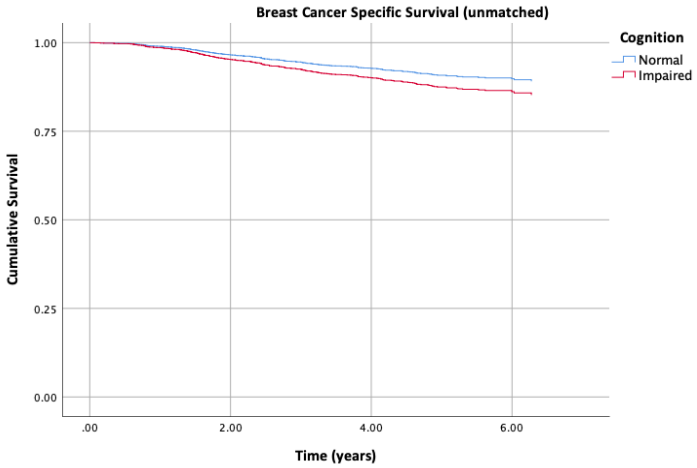


Figure 24: Kaplan Meier curve for breast cancer specific survival: unmatched analysis of normal versus dementia cohort

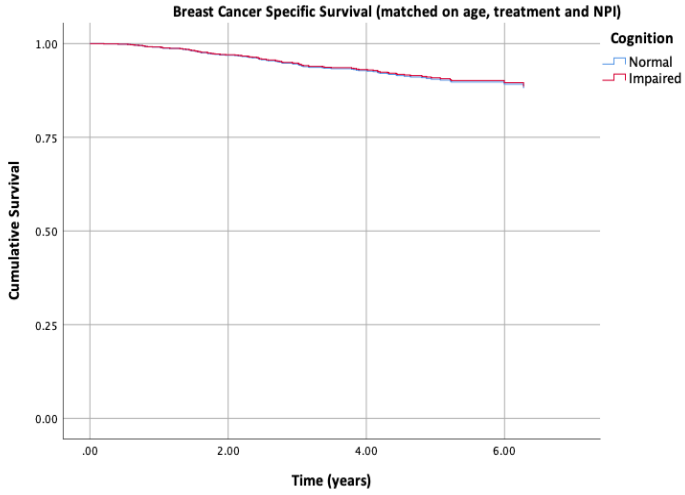


Figure 25: Kaplan Meier curve for breast cancer specific survival: Propensity match 1 (age, treatment and NPI)

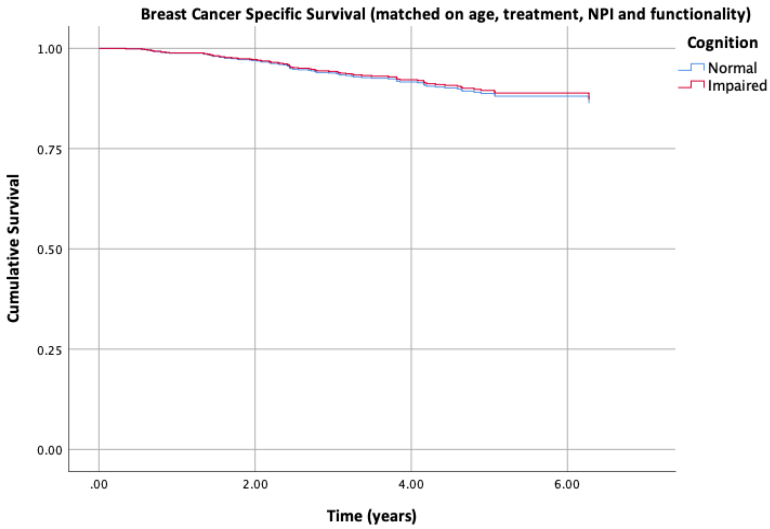


Figure 26: Kaplan Meier curve for breast cancer specific survival: Propensity match 2 (age, treatment, NPI and functionality)

6.7. Discussion

This analysis demonstrates the variation between the treatments that older women with cognitive impairment receive compared to women with normal cognitive function. The use of PET is increased in women with cognitive impairment, particularly those with severe impairment. Similar figures were found by Hooper and colleagues (125), with PET offered to 62% of patients with comorbidities (inclusive of dementia). This practice is in keeping with U.K. NICE guidelines which state that PET can be an appropriate option for women with ER+ tumours, short life expectancy or those considered too frail to withstand surgery (92).

In the sub-analysis of ER+ cases, the rate of PET use in patients with normal cognition was significantly lower than in women with cognitive impairment. These findings are reflected in other studies which present the view that in some cases, non-surgical management may be more appropriate for women with ER+ cancers (120, 126). In this study, rates of PET in patients with dementia were higher than the rate reported in the recent UK national audit (NABCOP) rate of 24% (141). However, the NABCOP audit reported all women over 70 and did not sub-analyse for a cohort with cognitive impairment.

Women with cognitive impairment were slightly more likely to undergo mastectomy compared to women with normal cognition, although this difference did not reach statistical significance. This may reflect a desire to avoid post-operative radiotherapy (267) or may be a result of larger tumour sizes seen in women with cognitive impairment. Other drivers for mastectomy may include patient or caregiver preference, the desire to optimise patient outcomes; local disease control and a reduced risk of recurrence are often perceived as more likely with mastectomy, despite evidence to the contrary (268). There may be a perception that a patient with cognitive impairment may be less concerned about body image. In contrast, it could also be argued that wide local excision is less major surgery with a lower risk of morbidity for a group of patients who are generally in poorer health.

The variation in treatment offered to older women is reflected in the lack of best practice evidence-based guidelines that take into account the heterogeneity of frailty and fitness levels in older age groups. Older women continue to be poorly represented in randomised trials (269), meaning that there is little guidance on whether surgery or PET is more beneficial for women with multi-morbidity. Where previous trials have attempted to investigate this, such as the ESTEEM trial, the recruitment of older participants has been challenging (270). As a result, there are a lack of data on how older patients tolerate treatments, and there are no models or guidelines to guide clinicians on the benefit of systemic therapies in patients over 80 years of age. There are also differences in opinion from clinicians on how women within this age group should be treated (13).

In this analysis, cognitive impairment was associated with a decreased rate of overall survival, which includes death from all causes, including breast cancer. This is to be expected as the study participants with cognitive impairments were older, had poorer functional status and higher rates of comorbidities. When propensity matched analysis was performed, the difference in overall survival is reduced, but remains significant. When breast cancer specific survival was examined, there was minimal difference in outcomes between patients with and without cognitive impairment, and this disappeared completely when matching was performed. This suggests that non-breast cancer causes of death are relatively more important in patients with dementia, and the selective use of PET in the cohort of older women with ER+ breast cancer does not increase breast cancer specific mortality.

Systematic complications reported in the trial were low, which suggests that treatment tolerance in patients with cognitive impairments is acceptable, although another explanation may be that some adverse events are underreported in cognitively impaired groups. As published previously, there were no deaths attributed to surgery in the trial (200), although there were five deaths within 90 days of surgery, which suggests that these women were over-treated. In general, those individuals at the greatest risk of surgical morbidity received PET, keeping surgical mortality to a

minimum. Follow-up at 52 months showed no difference in rates of progression free survival, and rates of local control were similar between groups.

6.7.1. Limitations

There were two main limitations. The first matching technique was relatively simple and only matched for age, tumour stage and biology and treatment type. In particular, the matching did not include other co-morbidities which may have been a source of bias when attempting to show association of cognitive impairment with survival. By contrast, the second match (which included comorbidity score and measures of functionality) may have caused overmatching, wherein the impact of dementia on outcome is diluted by including patients in the matched group that were similar in terms of underlying condition (271).

A second limitation is missing data. This was due to some patients choosing not to complete optional questionnaires (ADL, MMSE) and unavailable data on treatment, adverse events and HER2 status. The trial data does have advantages over registry data where dementia severity is not categorised and may be less fully or accurately recorded than in this prospective observational cohort study. Cognitive impairment was only recorded at baseline, which may also be viewed as a limitation of the study. Finally, follow-up of the cohort is only 52 months and longer-term follow-up will be needed to validate the survival outcomes, especially for women with ER+ cancers where events occur over several decades.

6.8. Conclusion

This analysis shows that the severity of cognitive impairment is a significant predictor of PET for older women with breast cancer, and cognition appears to play a significant part in deciding how to treat older women with breast cancer. The presence of cognitive impairment is linked to higher rates of overall mortality but has limited impact on breast cancer related death, suggesting that breast cancer is being adequately (not under-) treated in this group, despite the reduced treatments delivered. The high rate of non-breast cancer causes of death at one year after

diagnosis may suggest that some of these women may have been be over-treated. Careful consideration must be given to a more tailored approach in these women.

6.9. Chapter Summary

This chapter presented an analysis of treatment and survival outcomes for older women with breast cancer and dementia versus no dementia. There is evidence that women with dementia receive fewer aggressive treatments when compared with women with normal cognition, and further research is needed to explore why this treatment variation exists.

The next chapter will present the quantitative phase of this study, which used a postal questionnaire to explore some of these issues by sampling the caregivers who had been involved in decision-making for older patients in the 'severe' cognition category of this analysis.

Chapter Seven: Quantitative Questionnaire

7.1. Introduction

The analysis of cohort data from the Bridging the Age Gap trial highlights the variation in treatment and outcomes between women with dementia versus women with normal cognition. The questionnaire aimed to explore these disparities in more depth by capturing the views of caregivers who were involved in making treatment decisions for those patients. This chapter presents the results from the quantitative component of the study, which used a postal questionnaire to determine the role of caregivers in making cancer treatment decisions for patients with dementia.

The quantitative phase of the study met the following study objective:

- Design and apply a bespoke quantitative questionnaire to a sub-group of caregivers for patients with dementia and breast cancer, recruited to the Bridging the Age Gap trial.

The role of the lead researcher (CM) in undertaking this phase of the study was as follows: developing the initial concept; designing the questionnaire and information packs; and the analysis of results. Field testing of the questionnaire was undertaken by members of the Bridging the Age Gap steering group (Karen Collins, Lynda Wyld) and a PPI group (Yorkshire and Humber Consumer Research Panel).

7.2. Abstract

Aim: To explore the experiences of caregivers who were involved in making breast cancer treatment decisions; the information they used, the support they accessed, and the treatments they were recommended for the patient with dementia whom they provided care for.

Method: A quantitative postal questionnaire was developed and completed by caregivers who had consented a family member to participate in the Bridging the Age Gap trial, which recruited older women >70 with primary invasive breast cancer. Caregivers who had been involved in making a breast cancer treatment for a patient with a confirmed diagnosis of dementia were eligible to participate.

Results: Of the 62 women with dementia recruited by caregiver assent to the Bridging the Age Gap study, 37 patients had passed away, leaving 25 eligible caregivers. Of these, 13/25 (52%) informal caregivers agreed to complete the questionnaire. Findings focused on three areas: information needs, treatment decision-making practices, and support needs. Caregivers reported high levels of satisfaction with the level of information they received, with leaflets most useful in helping to make the treatment decision. Nine caregivers were recommended surgery for the patient (69.2%) with 4/13 (30.8%) offered PET. The majority of caregivers were happy with the decision made, yet reported high levels of stress (46.2%, agreed/strongly agreed that the decision process was stressful). Caregivers had discussions about adjuvant therapies such as chemotherapy and radiotherapy but chose not to opt for these on behalf of the patient.

Conclusion: Caregivers were happy with the level of support and information they received, and report having sufficient time to make decisions. Further research is needed to explore caregiver views on the content of information they received, and the factors that influenced treatment decisions.

7.3. Background

Proxy, or surrogate, decision-making is defined as making a decision on behalf of another person who lacks the capacity to do so themselves (171). In the context of medicine, this is enshrined in the Mental Capacity Act (MCA) (71) and utilised in situations where a person has been assessed as being unable to give informed consent to treatment. The guidance on making treatment decisions in the MCA (71) and Mental Capacity Code of Practice (272) are based on the best interest principle, which states that any decisions made on behalf of another person must be made in their best interest. This principle is referred to unless an advance decision has been made by the patient prior to losing capacity.

When an individual is faced with a new diagnosis of breast cancer, there will be a discussion of the treatment options available, taking into account both patient-related factors (age, frailty), and cancer-related factors (stage, grade and type of cancer) (92). For a person with dementia, these considerations will also include the severity of dementia, the potential for treatments to interact with the behavioural and psychological symptoms of dementia, and the level of support they currently have or may need as a result of new treatment regimens. Part of this process will also involve clinical input by undertaking comprehensive geriatric assessments (CGA) (19, 20) and guiding the patient (and their caregivers) towards making a person-centred decision.

For a patient with comorbid dementia, giving consent to cancer treatment can be complex, and not all people living with dementia are incapable of making informed decisions. Some people with mild-moderate dementia may be able to express their preferences for treatment and actively participate in shared decision-making (273-275), while others may prefer to delegate the decision to a family member or caregiver (242, 276). In scenarios where a person is unable to make this decision, through severe cognitive incapacity, and judged as not being able to weigh up the pros and cons of different treatment options, another person can be authorised to make this decision on their behalf. The legal process for this involves appointing another person with

lasting power of attorney for health and welfare, which means that under UK law, another person can consent to (or refuse) treatment on behalf of the patient (71).

Assuming a decision-making role in this context may be challenging in situations where the preferences and wishes of a patient are unknown, and an advance decision has not been made. Family caregivers often find themselves taking on a decision-making role (165), and may be best placed to assume this role if they know the patient in a personal capacity. From the evidence reviewed, it is known that caregivers play an important role in cancer treatment decision-making, although there has been little focus on how caregivers help people with dementia to make decisions, and which information resources they use or find most helpful (277). It is also unknown if caregiver input in treatment decision-making is part of their main role throughout the patient's whole dementia-cancer treatment journey (235, 278). Both breast cancer and dementia are primarily a disease of older age, and thus, with a growing ageing population, caregivers will be faced with making an increasing number of treatment decisions for people with comorbid dementia in the future.

This study aimed to explore how caregivers were involved in making breast cancer treatment decisions; the information they accessed, which treatments they are offered and recommended. The aim of this first phase of the study was to apply a bespoke quantitative questionnaire to a sub-group of caregivers who had assented an older woman with dementia and breast cancer to a U.K. cohort study, Bridging the Age Gap in Breast Cancer, which collected data on treatment outcomes for older women with early-stage breast cancer.

7.4. Methods

7.4.1. Eligibility

Caregivers who had assented a patient with confirmed dementia to the Bridging the Age Gap trial were eligible to take part in this phase of the study. The full eligibility criteria are outlined in the Study Protocol **(Appendix 1)**, and an abridged version is given here.

7.4.1.1. Inclusion criteria

- Individual aged 18 years and over, and capable of giving informed consent
- Individual is a formal or informal caregiver involved in treatment decision-making for a person with cognitive impairment (as defined by clinician) taking part in the Bridging the Age Gap trial

7.4.1.2. Exclusion criteria

- An individual who is not a formal or informal caregiver for a patient with primary operable breast cancer and has a diagnosis of cognitive impairment
- A caregiver who themselves has severe cognitive impairment and is unable to give informed consent to take part in the study

7.4.2. Study Sample

The quantitative phase of the study used a purposive sampling technique. The sampling strategy would ensure that only participants matching the key characteristics of being a caregiver and involved in breast cancer treatment decision-making would be approached to join the study. To identify the sample, the cohort of breast cancer patients within the Bridging the Age Gap trial were stratified by cognition level (n=478 identified as having a diagnosis of dementia), consent level (n=147 of these joined the study by proxy consent) and recruiting site (patients with dementia and breast cancer were recruited from n=37 breast units). In total, 37/57 breast units had recruited participants with a dementia diagnosis and were invited to join the study. Thirteen centres completed study set-up and R&D approval, meaning that 24 units were excluded **(Figure 27).**

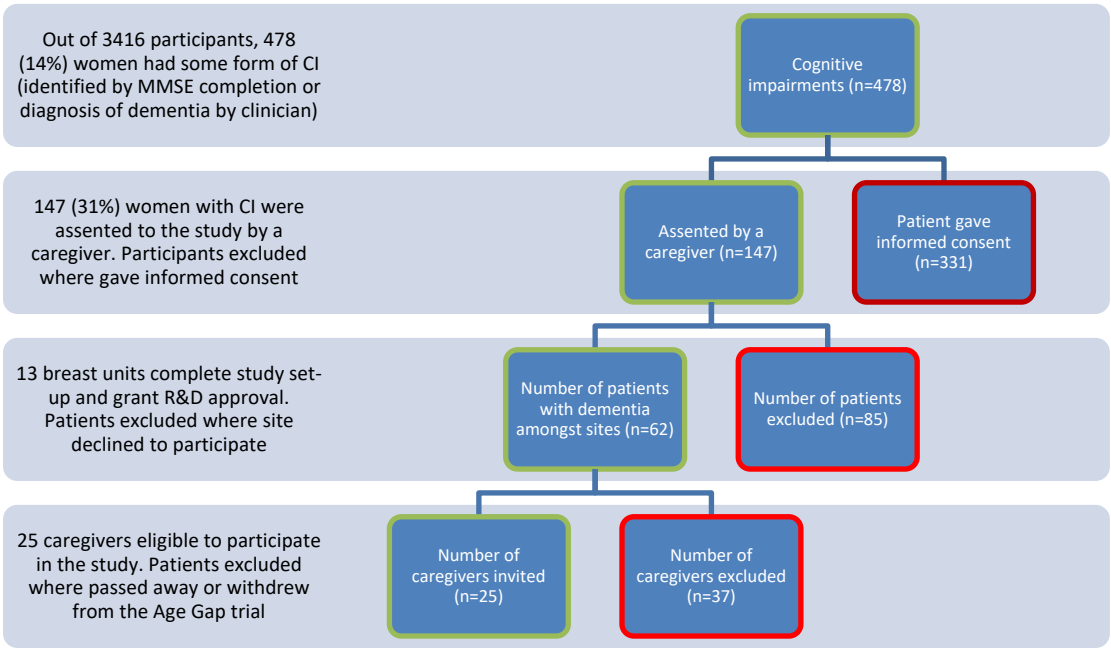


Figure 27: Identification of study population and sample

After completing set-up as participant identification centres (PIC)s, patients at each site were then scrutinised against the eligibility criteria. After data cleaning and withdrawals (patient death, loss to follow-up), a combined sample of 25 patients with dementia were identified as having a caregiver who would be eligible to join the study **(Table 46).**

Table 46: Eligible participants from PIC breast units.

Site	Number of BTAG patients with consultee form	Number of eligible participants after data cleaning/ withdrawals	Date of ethics approval
Sheffield	11	3	04.10.16
Doncaster	2	1	26.05.17
St Helens	4	3	15.03.17
Liverpool	6	2	09.02.17
Bradford	12	3	22.09.17
Cardiff	3	2	10.04.18
Wakefield	11	4	26.01.17
Brighton	2	2	03.05.17
Airedale	4	2	09.03.17
Weston General	2	0	19.01.17
Mid Cheshire/Leighton	2	1	06.04.18
Kings Mill	1	1	14.03.17
Aneurin Bevan	0	0	12.09.18
Dorset County	2	1	07.12.16
Totals	**62**	**25**	

7.4.3. Recruitment Process

Following site-specific R&D approval, the study invitation pack was posted from each PIC (n=13) to the sub-group of caregivers between December 2016 and June 2017, in England and Wales. Each pack comprised of a cover letter **(Appendix 5),** patient information sheet **(Appendix 6),** consent form **(Appendix 7),** study questionnaire **(Appendix 2),** and freepost envelope. Where sites had limited research capacity, the researcher assisted with this. Completed questionnaires and consent forms were returned to the researcher at the University of Sheffield Medical School. Informed consent was obtained by postal consent which was countersigned by the researcher on the date received.

7.4.3.1. Confidentiality

Each participant was allocated an ID number before the information pack was posted. The returned original consent forms were stored in a locked cabinet in a locked office at the University of Sheffield, Medical School. The enrolment log of participant names was stored electronically on a secure network drive separately from the original consent forms. Where a participant did not respond to the pack, it was assumed that the invite to participate was declined and no further contact was made by the research site or researcher. No participants withdrew from the study after giving consent, however, the process for withdrawal was detailed in the information sheet and study protocol.

7.4.4. Questionnaire Development

The questionnaire was developed using the themes identified in the systematic review **(Chapter Five),** field testing from a PPI group and breast cancer consultants to achieve content validity. This was due to there being no pre-existing validated questionnaires which appropriately captured the experience of making decisions for this population of older women.

The following validity considerations were addressing after field testing:

- ***Face validity:*** Expert opinion from a PPI group and breast consultants from the Bridging the Age Gap programme. Where suggestions for changes were made to the wording or omission of questions, these were addressed.
- ***Construct validity:*** The aim of the questionnaire was to gather opinions and experiences rather than measure theoretical constructs. Where suggestions were made from the PPI group on the relevance of questions to the topic, these were addressed.
- ***Concurrent validity:*** The literature did not yield similar instruments to make a comparison of the questionnaire against existing measures. Criterion validity was therefore not measured.
- ***Acceptability:*** The questionnaire was assessed to measure the approximate time of completion and test its completeness. Where the length of the questionnaire was commented on by the PPI group, it was agreed that this was acceptable due to the spacing of the answer sections rather than the number of questions, and this was deemed acceptable.

The final questionnaire **(Appendix 2)** comprised of 7 topics and a total of 40 questions:

- **Topic 1:** Demographics (5 items)
- **Topic 2:** Caregiver Relationship (11 items)
- **Topic 3:** Information Needs (7 items)
- **Topic 4:** Making the Decision (8 items)
- **Topic 5:** Types of Proxy Decision Making (3 items)
- **Topic 6:** After making a decision (5 items)
- **Topic 7:** Final Thoughts (1 item)

The questionnaire explored proxy decision-making using questions that were categorical, Likert scales, closed and open-ended. A final section at the end of the questionnaire allowed respondents to indicate if they would participate in a follow-up interview and receive the results of the study.

7.4.5. Analysis

Findings were entered into an excel sheet and exported to SPSS (Version 22) for statistical analysis. Graphs were reproduced using Microsoft excel. Descriptive analysis used median, mode, ranges, and percentages.

7.4.6. Validating the Approach

Due to the small sample of patients on the trial that could be sampled, the questionnaire was not piloted. It was however discussed and refined by the trial team and members of a PPI group with experience of breast cancer care. Validity was also not assessed as the questionnaire captured recall of decisions, opinions and experiences.

7.4.6.1. Critical Appraisal

A quality appraisal of the questionnaire was carried out using the Centre for Evidence Based Management (CEBM) Critical Appraisal Checklist (214) **(Table 47).**

Table 47: Quality Appraisal of the questionnaire

	Appraisal Question	Yes	Can't tell	No
1.	Did the study address a clearly focused question/issue?	X		
2.	Is the research method (study design) appropriate for answering the research question?	X		
3.	Is the method of selection of the subjects clearly described?	X		
4.	Could the way the sample was obtained introduce selection bias?	X		
5.	Was the sample representative with regard to the population to which the findings will be referred?	X		
6.	Was the sample size based on pre-study considerations of statistical power?			X
7.	Was a satisfactory response rate achieved?		X	
8.	Are the measurements (questionnaires) likely to be valid and reliable?		X	
9.	Was statistical significance assessed?			X
10.	Are confidence intervals given for the main results?			X
11.	Could there be confounding factors that haven't been accounted for?		X	
12.	Can the results be applied in your organization?	X		

The quality appraisal raised the following issues which were acknowledged as limitations of the study

1. The way in which the sample was obtained introduced selection bias due to the lack of random sampling. Caregivers were purposively sampled to address the study aims, objectives and answer the research question, which is focused on the experiences of this very specific set of participants.
2. The response rate achieved was 52%. It was anticipated from the small sampling frame and nature of the population that high numbers would be difficult to achieve.
3. Validity and reliability were difficult to assess as caregivers were not involved in the pilot, however, involvement from a PPI group, ethics committee comments and expert opinions from clinicians were incorporated into the development and design of the questionnaire to achieve content validity.
4. The small numbers in the study population meant that descriptive analysis was the best method of fit for the analysis (statistical significance and confidence intervals could therefore not be performed).

7.4.6. Results

7.4.6.1. Response Rate

A total of 25 questionnaires were distributed from 13 breast units in England and Wales. Recruitment by geographical region is highlighted in **Figure 28.** A total of 13 questionnaires were returned to the researcher (52% response rate) from seven sites **(Table 48).**

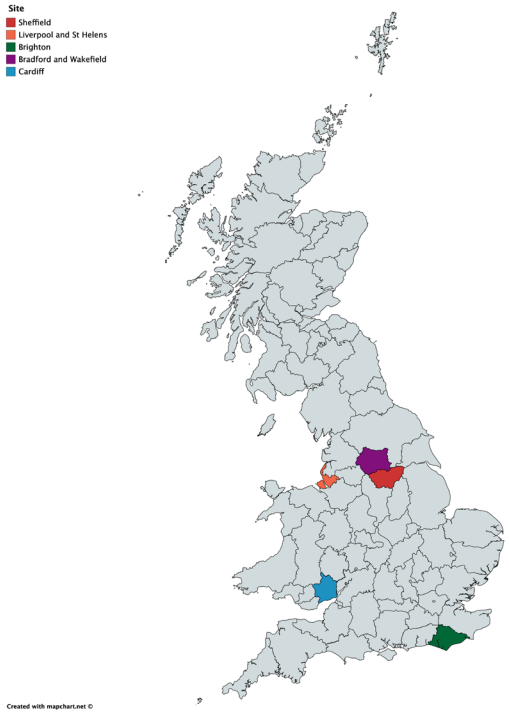


Figure 28: Recruitment by geographical location

Table 48: Number of invites sent and study response by PIC

Site	Number of packs sent (invited/approached)	Number of packs returned (recruited)
Sheffield	3	1
Doncaster	1	0
St Helens	3	2
Liverpool	2	1
Airedale	2	0
Bradford	3	3
Cardiff	2	2
Mid Cheshire/Leighton	1	0
Dorset County	1	0
Wakefield	4	3
Kings Mill	1	0
Brighton	2	1
Totals	**25**	**13**

7.4.6.2. Caregiver Demographics

Out of 13 respondents, 11 caregivers fully completed the demographics section in the questionnaire. The missing details for participant CG2 were captured during the interview. The mean age of respondents was 61 (47-77), with seven female respondents and six males **(Table 49).** The ethnicity of all participants was white

(English/Welsh/Scottish/N.Irish/British). The occupation of caregivers was mostly retired (n=6) or semi-professional job titles. In summary, all respondents were English-speaking and identified as informal caregivers for a family member or relative with breast cancer and dementia.

Table 49: Caregiver Characteristics and Demographics

Demographics	Questionnaire Respondents (n=13)
Age	
Average (range)	61 (47-77)
Gender	
Male	46% (n=6)
Female	54% (n=7)
Location	
England	85% (n=11)
Wales	15% (n=2)
Relationship to the person with dementia	
Son/daughter	77% (n=10)
Spouse	8% (n=1)
Relative-in-law	8% (n=1)
Nephew	8% (n=1)
Lasting power of attorney	
Yes	62% (n=8)
No	38% (n=5)

One respondent reported receiving financial support for providing care. Four caregivers considered themselves full-time caregivers, eight part-time, and one answering "neither." The length of time spent in the caregiver role is reported in **Figure 29**.

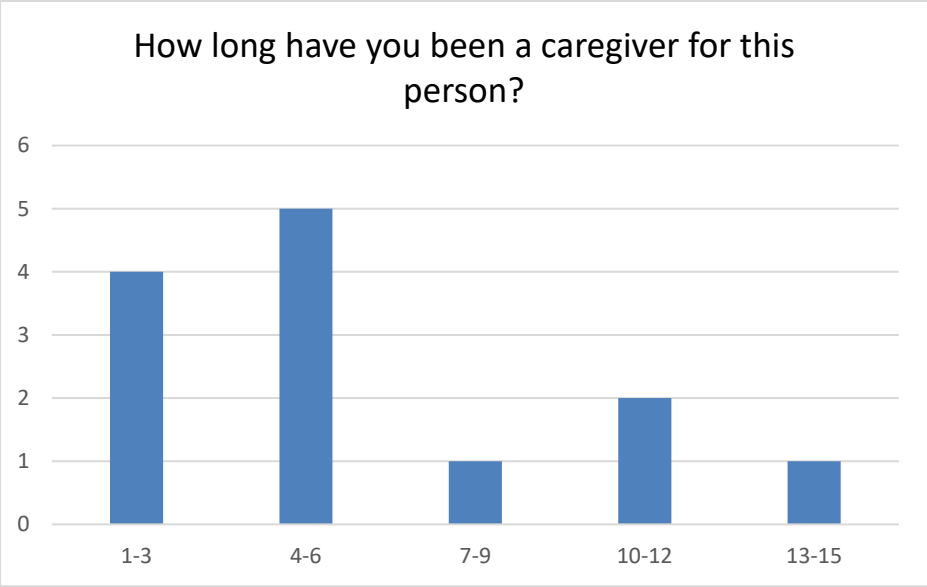


Figure 29: Length of time in years in caregiver role

Two caregivers (2/13) reported that they lived with the person they provided care for, and none of the respondents reported having caring responsibilities for another person. The number of hours a week spent providing care are reported in **Figure 30**.

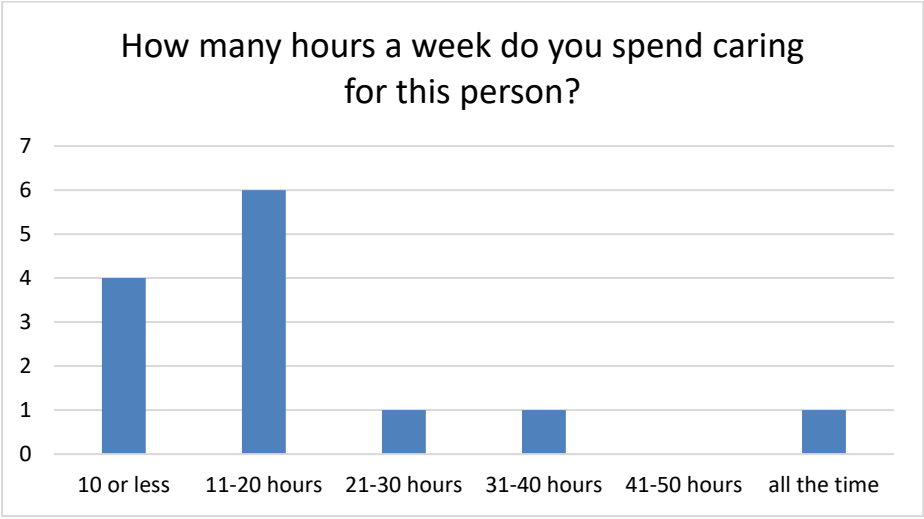


Figure 30: Hours spent providing care for the patient

On the subject of lasting power of attorney, 8/13 (62%) had this in place for the person that they cared for. Four caregivers reported that the person cared for had made an advance decision relating to a do not resuscitate (DNR) order (n=1); to have surgery (n=1); preference for accommodation/where to live (n=2).

7.4.6.3. Findings

The findings from the questionnaire have been categorised into three themes:

1. Information needs
2. Treatment decision-making
3. Support needs

7.4.6.3.1. Caregiver Information Needs

Amongst the respondents, around three quarters had prior awareness of breast cancer (76.9%, 10/13), and 69.2% (9/13) had prior knowledge of the treatments available for breast cancer **(Figure 31)**.

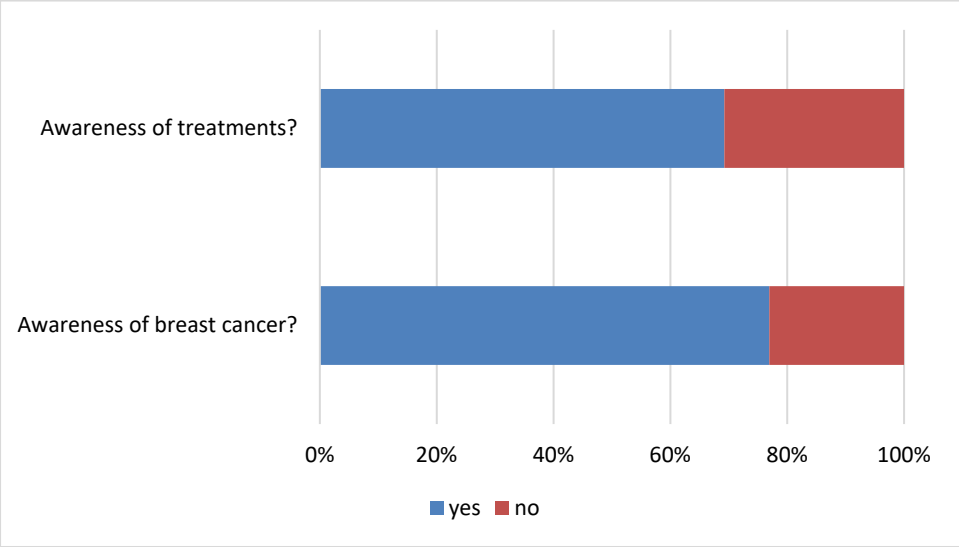


Figure 31: Caregiver awareness of breast cancer and treatments (n=13)

All thirteen caregivers (100%) reported receiving additional information from the hospital to help them make a decision, rating high levels of satisfaction with the amount of information received **(Figure 32)**.

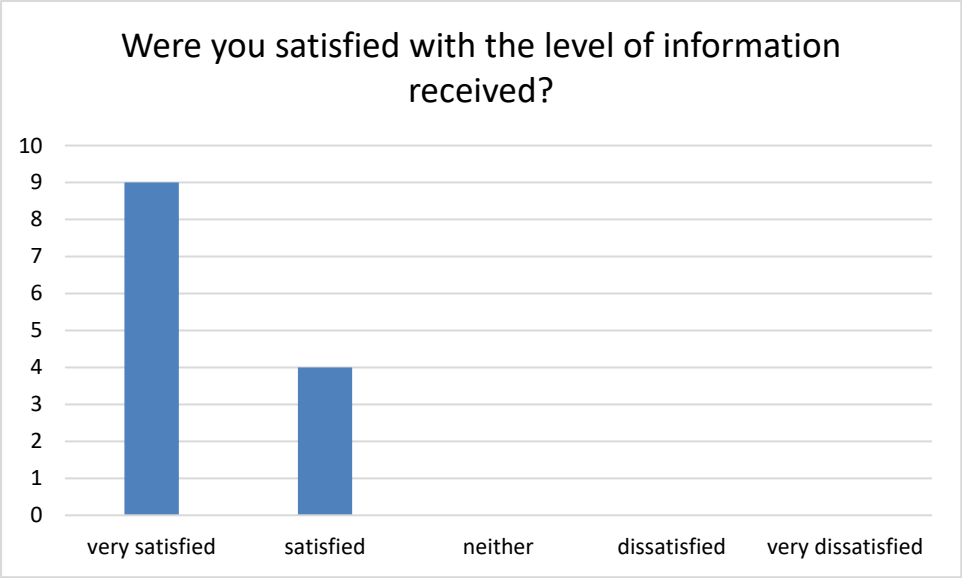


Figure 32: Caregiver satisfaction level with information received from the hospital (n=13)

All caregivers (100%, 13/13) reported that the breast clinician answered all of their questions before deciding on treatment. When asked about the resources used to help make a decision, caregivers reported that family (n=5) and leaflets (n=5) were used most to help make the decision, and out of these, leaflets (n=5) were the most useful resource **(Figure 33)**.

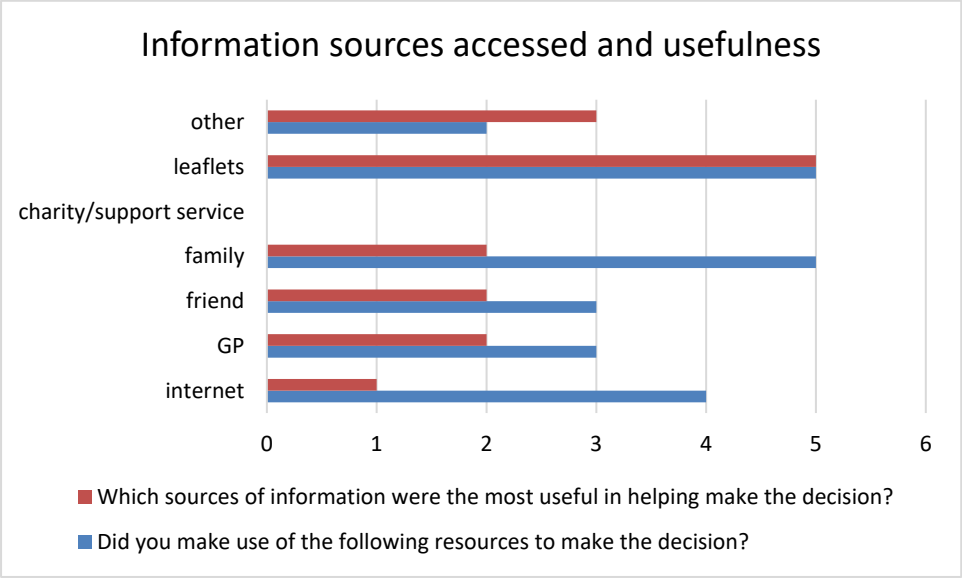


Figure 33: Information sources accessed by caregivers and their usefulness

7.4.6.3.2. Making the Treatment Decision

Respondents were asked which treatments were offered and recommended to the patient by the breast clinician. Four caregivers were offered PET only for the patient (4/13, 30.8%) and nine (69.2%) were offered surgery (with/without tablets) **(Figure 34).** Following the discussion, 5/13 (38%) of patients were recommended PET, and 8/13 (61.5%) surgery.

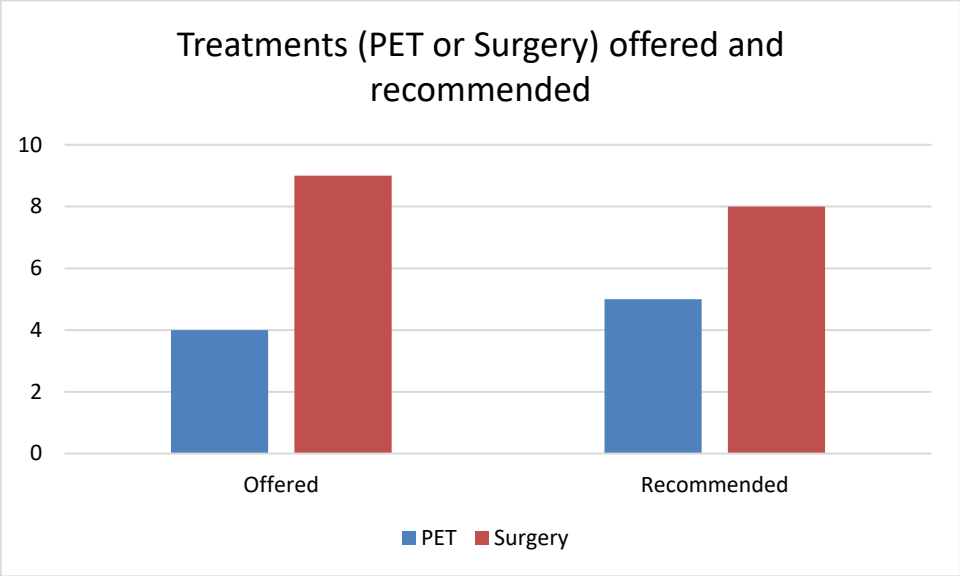


Figure 34: Treatment offered and recommended to the patient

Two patients were offered chemotherapy, and two patients were offered radiotherapy. All caregivers reported that the consultant or breast care nurse went through the pros and cons of each treatment option (100%). All caregivers (13/13, 100%) responded 'yes' to having enough time to think about the treatment decision before making it.

When asked who was responsible for making the final decision, 8/13 (61.5%) responded that a joint decision was made between either the caregiver, patient or clinician **(Table 50)**. Two caregivers reported having responsibility for the final decision (15.4%), and two patients made their own decision alone (15.4%). One caregiver reported that the decision responsibility was with the clinician (7.7%).

Table 50: Treatment decision responsibility

	Decision Responsibility	Number	%
Shared Decision Making	Caregiver and Patient	5	38.5%
	Caregiver and Clinician	2	15.4%
	Caregiver, Patient and Clinician	1	7.7%
Caregiver, Patient or Clinician	Caregiver responsible only	2	15.4%
	Patient responsible only	2	15.4%
	Clinician responsible only	1	7.7%
	Totals	**13**	**100%**

The questionnaire asked caregivers to report on which factors (multiple choice: aftercare, quality of life, and what the person would have wanted) were most important when making the treatment decision; 11/13 answered quality of life, 8/13 would place importance on the wishes of the patient, and 5/13 answered aftercare **(Figure 35)**.

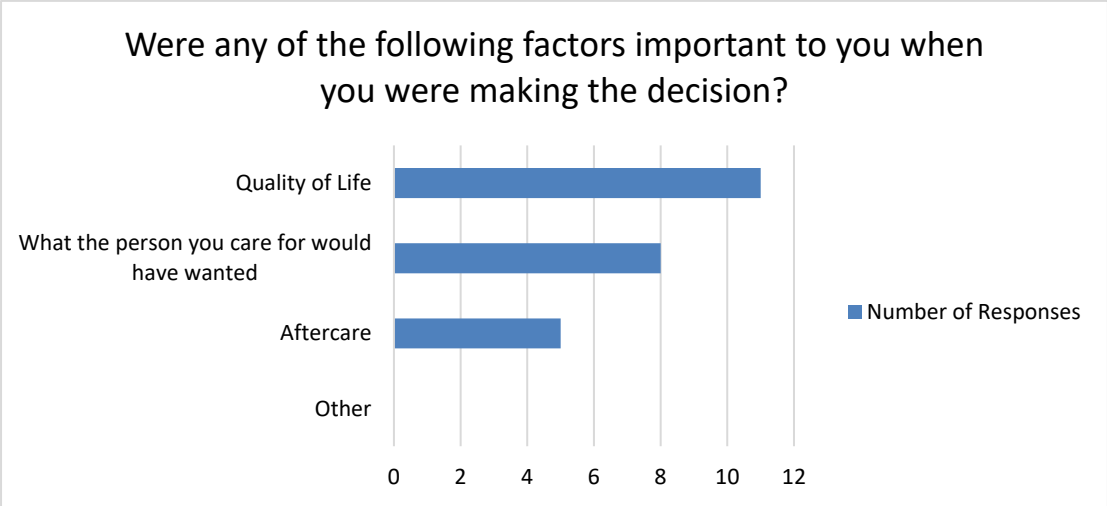


Figure 35: Important factors when making the decision

The survey asked respondents to read through three examples of types of proxy decisions (advance decision, substituted judgment and best interests) and answer questions on the type of decision made, if they would make the same decision again, and which they thought was the best decision type to use for another person. Definitions of each type of decision were provided in the glossary of the questionnaire for reference. When asked which type of proxy decision matched the type of decision that caregivers made, 2/13 answered substituted judgment, 4/13 answered advance

decision, 6/13 answered best interests, and 1/13 annotated: my mother was able to decide for herself **(Figure 36).**

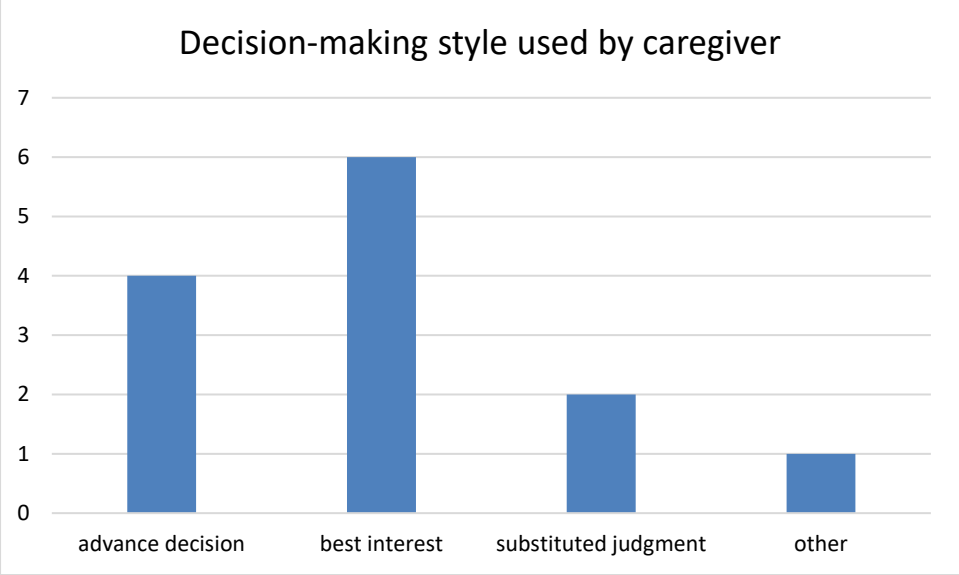


Figure 36: Caregiver response to question, "Which decision matched the one you made?"

When asked if caregivers were to make the same decision again, which decision style would they choose; 54% responded best interests; 38% advance decision and 8% substituted judgement. Finally, when asked which type of decision was best to use, caregivers responded in favour of either an advance decision (54%) or best interest (46%). When asked if caregivers would in hindsight make the same treatment decision again, 13/13 (100%) answered 'yes.'

7.4.6.3.3. Support

All caregivers (13/13, 100%) reported having enough time to think about the decision before making it, and enough access to support and information during this time (100%). When asked if caregivers had sought any support after making the decision, 2/13 (15.4%) did; with those two caregivers seeking support from their family **(Figure 37).**

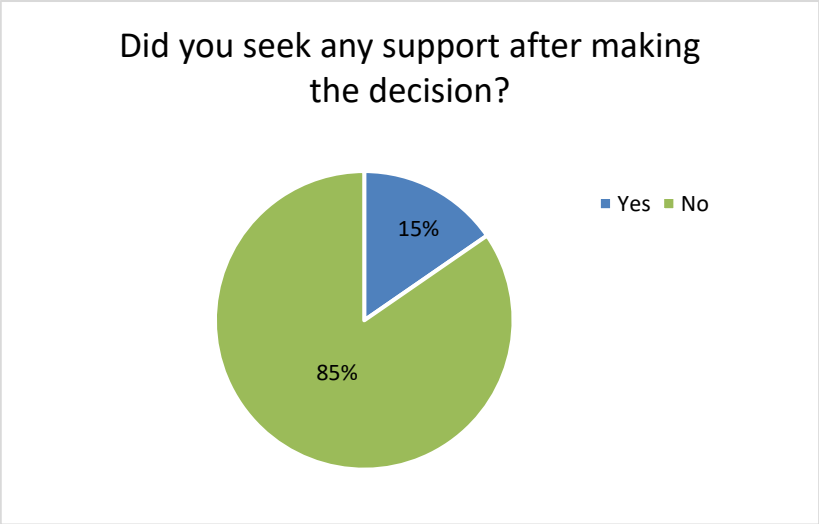


Figure 37: Seeking support after making the decision

Respondents were asked to report on their thoughts after making a proxy decision. The majority of caregivers were happy with the decision made, with all caregivers reporting either *"strongly agree"* (n=9, 69%) or *"agree"* (n=4, 30.8%) **(Figure 38)**. In terms of stress and seeking support: When asked *"Did you find the process of making a decision stressful?"* on a scale of 1-5 (1 being strongly disagree, 5 being strongly agree), 46.2% of caregivers reported either *"strongly agree"* (n=3, 23.1%) or *"agree"* (n=3, 23.1%).

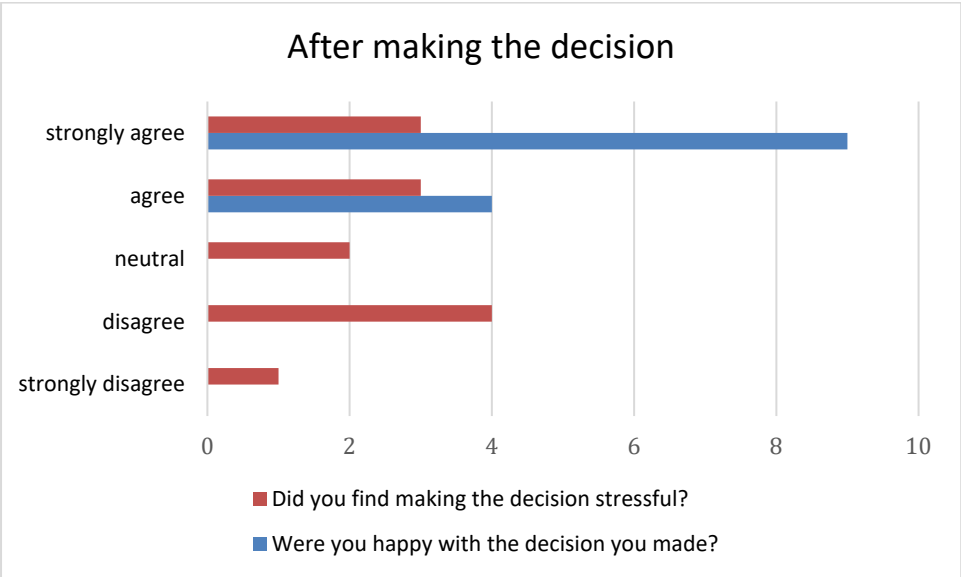


Figure 38: Decision satisfaction and stress

The final section asked respondents for any final statements in a free text format. Four (4/13) respondents completed this section.

Responses to this section commented that the questionnaire did not take into account the level of patient incapacity, as one patient was able to take part in making the decision, guided by the doctor and family. Another caregiver reported feeling that being the only relative made making the decision easier, as having siblings that disagree could delay the decision. Another caregiver highlighted there being a 'one fit' approach from the hospital, referring to "lumbering the patient with treatments."

7.5. Discussion

The aim of the questionnaire was to explore the role of caregivers who had been involved in making breast cancer treatment decisions. In the wider literature, the carer-patient relationship was viewed as the key element for a "successful" consultation, particularly in cases where the caregiver was known to the patient in a personal capacity (242, 243). The caregivers in this study were all family-related and middle-aged; some making a treatment decision for the first time, whilst others had been making decisions for a long period of time. The majority of caregivers were unpaid for the care they provided, which is in keeping with the wider literature on how family members are most likely to assume an informal caregiving role when an older relative develops cancer or dementia (165).

The questionnaire focused on the treatment choice between PET and surgery as this was the main outcome of interest, and eligibility criterion, for participants enrolled to the wider Bridging the Age Gap trial (of which this study sampled). The finding that 69% of patients were offered surgery as part of their treatment plan was unexpected, as the wider literature notes that women with dementia are treated less aggressively (153, 250). However, of those who were offered surgery, few had discussions about adjuvant chemotherapy and radiotherapy. In the literature, there is wide variance in rates of both surgery and chemotherapy in older populations (279, 280), and using chemotherapy in a patient with dementia would be complex in terms of the risk of side effects. The finding that quality of life was an important factor is in keeping with

another study where the impact of treatment on the patient's quality of life was a key consideration for caregivers (156). An overwhelming majority of caregivers reported having enough time to think about the decision before making it, which differs from other studies highlighting that more time and planning was needed for discussions (156, 244).

The majority of caregivers perceived the treatment decision as being in the patient's best interest. This view held when asked which proxy decision type they would choose if they were to make the decision again, and only changed when asked which type of decision they thought was the "best" one to use. This finding suggests that decision-making styles may not be consistent over time, and that there is a difference between the type of decision style that caregivers may use in practice, compared to what they may think is ideal. Guidelines for making decisions on behalf of a person who lacks the capacity to decide for themselves is outlined in the MCA (272). The caregivers who responded to the questionnaire rarely accessed guidelines, and none of the patients they provided care for had made advance decisions in respect to their breast cancer treatment. This is also reflected in the wider literature on the inconsistent application of the MCA in practice (281).

Caregivers in this study were largely satisfied with the level of information they received from the hospital, finding leaflets most useful for making decisions. This conflicts with other studies which found that written information and leaflets were oftentimes not tailored towards a patient with dementia and cancer (242, 243), with caregivers seeking further information to supplement that which was received from the clinician (243). The questionnaire did not ask caregivers to comment on whether the information they received was adapted towards a patient with dementia, and this will be explored in the interviews.

Caregiver burden and stress is reported in much of the wider literature on decision-making, with caregivers for people with cancer and dementia reporting higher levels of burden compared to others (244, 282). Caregivers in this study reported high levels

of stress at the time of making the decision but chose not to access any support after making the decision. Where support was sought, caregivers chose to rely on family. These findings will be explored further in the qualitative interviews.

7.6. Limitations

There were two limitations, the first being that the response rate of questionnaires was low despite the large Bridging the Age Gap population of patients with dementia. A high number of units recruiting to the trial declined participation, presumably feeling that the study would potentially be intrusive and difficult to recruit to (sites that agree to recruit to a portfolio study must meet targets set, or they are penalised). Another explanation for the low response rate was the use of a postal questionnaire. Without any prior face-to-face contact, the researcher was dependent on the recipient reading the instructions on the questionnaire and the participant information sheet. There may have been an implicit distrust of receiving a postal questionnaire from a researcher unknown to the participant and the care their relative had received. This is in keeping with the literature, where the approach of contacting patients prior to posting questionnaires increased response rates (283). It was an option for centres to recruit patients face-to-face, and those that did report discussing the study with potential caregivers in advance (Brighton, Wakefield and Bradford) had higher levels of response.

The second limitation was recall and selection bias. Caregivers were asked to retrospectively recall a treatment decision that in some cases may have been made some time ago. Therefore, the caregivers' subjective memories of the decision-making style they used may not be reliable due to the amount of time that had passed. The characteristics of respondents who completed the questionnaire may differ from non-respondents (response bias). There was also selection bias where only caregivers with a living relative received an invitation to participate. The implication of this is that the questionnaire did not capture the experiences of caregivers for a relative who had passed away; and their experiences and decisions may have been very different from those that are still alive. Assumptions cannot be made about whether the participants who responded truly represent this population of caregivers.

Finally, the lack of control over sending out the packs directly to caregivers meant that the researcher was reliant on the research nurse sending out the packs as promised to the correct addresses. The restrictions placed on the study from the ethics committee meant that the researcher was unable to follow-up non-respondents with a reminder and to view non-completion as the participant declining to take part in the study. This also meant that the researcher could not ask those who did not return their questionnaire their reasons for declining the study.

7.7. Conclusions

Caregivers were generally satisfied with the level of information received and the amount of time given to make the decision. These findings have provided some useful insights into the types of information that caregivers access, what they found most useful, and the factors they consider important when making a treatment decision. The process of making treatment decisions was found to be stressful for some caregivers, and their decision-making approaches were varied. The findings from the questionnaire give insight to the caregiver experience of making breast cancer treatment decisions.

7.8. Chapter Summary

This chapter has presented the findings from the quantitative questionnaire, which focused on how caregivers made treatment decisions for a patient with breast cancer and dementia. The next chapter will present the qualitative phase of the study, which used semi-structured interviews to further explore the treatment decision experiences of a sample of questionnaire respondents.

Chapter Eight: Semi-structured Qualitative Interviews

8.1. Introduction

This chapter will present the findings from the qualitative component of the study, which involved undertaking semi-structured interviews with caregivers who had been involved in making a proxy decision for a relative diagnosed with dementia and breast cancer. The aim of the interview phase was to determine the role and support needs of caregivers involved in making breast cancer treatment decisions.

The qualitative phase of the study met the following study objective:

- Undertake qualitative interviews with caregivers for older patients with dementia to explore the experience of decision-making and caring for a relative with dementia and breast cancer.

My role in undertaking this phase of the study included: developing the initial concept for the study; designing the topic guide; undertaking all interviews; analytical framework development; analytical interpretation. Anne Shrestha (AS) assisted with

the initial interview. Maria Burton (MB) independently reviewed transcripts for quality control and assisted with the development of the analytical framework. Lynda Wyld (LW) helped to develop the initial concept for the study, reviewed the topic guide and themes included in the final analysis.

8.2. Abstract

Aim: To explore the views of caregivers on making treatment decisions for a relative with dementia and breast cancer.

Method: The study recruited caregivers of women with dementia and breast cancer who had been recruited previously to the Bridging the Age Gap in Breast Cancer study. Semi-structured interviews were conducted with family caregivers who responded to the postal questionnaire, face-to-face (n=4) and by telephone (n=4). Caregivers who completed the postal questionnaire and had made a treatment decision for a patient with confirmed dementia were eligible to participate. Interviews were transcribed and coded using NVivo software. The Framework Approach was used to analyse the interviews.

Results: Of the 13 informal caregivers who responded to the study questionnaire, eight (62%) agreed to take part in a follow-up interview. Despite the small sample size, saturation of themes was achieved. Four themes were generated: clinical interactions, accessing information and support, decision-making involvement, and treatment influences. Receiving consistent advice from clinicians was essential for caregivers to feel informed and reassured in their role facilitating the treatment decision. Information was not always tailored to towards people with dementia and caregivers described supplementing this information with their own research or knowledge. Treatment choice was influenced by advice from clinicians, perceptions of the person's ability to understand treatment regimens and their age.

Conclusion: The findings demonstrate some of the key challenges that caregivers face when navigating cancer treatment options, their interactions with clinicians, and the caregiver role in supporting their relatives.

8.3. Background

As previously discussed, there are evident differences in the screening, treatment and survival rates of breast cancer patients with dementia compared to those without. For patients with dementia, breast screening may involve a trade-off between benefit and harm (133, 147) and there is a higher likelihood of diagnosis at a later stage (148). Compared to women without dementia, breast cancer patients with a pre-existing diagnosis of dementia receive non-standard treatments (153), higher rates of primary endocrine therapy (PET) (284), and have inferior breast cancer specific survival rates (10).

When a patient with dementia is faced with a new diagnosis of cancer, caregivers are often relied upon for support and care needs, such as facilitating treatment discussions (243), providing emotional, physical and practical support (285) and communicating the needs and history of the patient in the consultation (244). The demands on the caregiver role will increase as the person they provide care for begins their breast cancer treatment. For some caregivers, this role is often unrecognized (242) or marginalised (244) by clinicians.

To date, there has been very little research on treatment decision-making in the context of breast cancer and dementia, and few studies have explored the lived experiences of caregivers who have been involved in making breast cancer treatment decisions. In part, this reflects the challenges of recruiting the caregivers of dementia patients to research studies (286). Our systematic review identified three themes that reflected the caregiver experience of making treatment decisions in this context; the role of the clinician; treatment discussions, communication and information needs; and the caregiver-patient relationship (277). Two previous reviews suggested that a diagnosis of dementia was associated with poorer cancer outcomes for patients (234), concluding that further work is needed to establish new practice guidelines for managing patients with cancer and dementia (235). This study aimed to address the gap in knowledge around making cancer treatment decisions for older women living with dementia and explore the caregiver experience in- depth.

8.4. Methods

8.4.1. Eligibility

Respondents to the questionnaire component of this study could indicate their willingness to take part in a follow-up interview. The eligibility criteria were the same with the addition of two criteria:

1. Respondent must have completed the questionnaire prior to the interview
2. Respondent must be willing to participate in either a face-to-face or telephone interview

8.4.2. Topic Guide

The interview topic guide **(Appendix 8)** was discussed and refined by members of the steering group, and a PPI group. As the recruitment criteria and primary outcome of the wider Bridging the Age Gap study focused on the choice between PET and surgery, this influenced the decision to focus primarily on these treatments in the topic guide.

The topic guide asked caregivers to recall the breast cancer treatment journey of the family member whom they cared for and built on their responses to the questionnaire in more depth. The questions asked were open-ended, allowing participants to elaborate on their answers in a conversational manner. A pragmatic approach was taken, whereby some questions were adapted for the interview based on the answers given in the questionnaire (i.e., where the caregiver's relative was treated with PET, the questions around surgical complications were omitted). Other questions were interchanged where the respondent had already responded in part to a previous question, to avoid repetition. Where there were inconsistencies in the questionnaire, these were explored for clarification. The topic guide followed a historical timeline which began at the point where the caregiver became involved in making treatment decisions for the patient and ended with the patient's post-treatment recovery.

8.4.3. Study Sample

The qualitative phase of the study used a volunteer response approach to recruit caregivers to participate in a semi-structured interview. This strategy meant that only

caregivers who completed the questionnaire were recruited to participate in an interview. Eight out of 13 (61.54%) questionnaire respondents expressed an interest in taking part and agreed to participate. Figure 39 shows the study flow diagram.

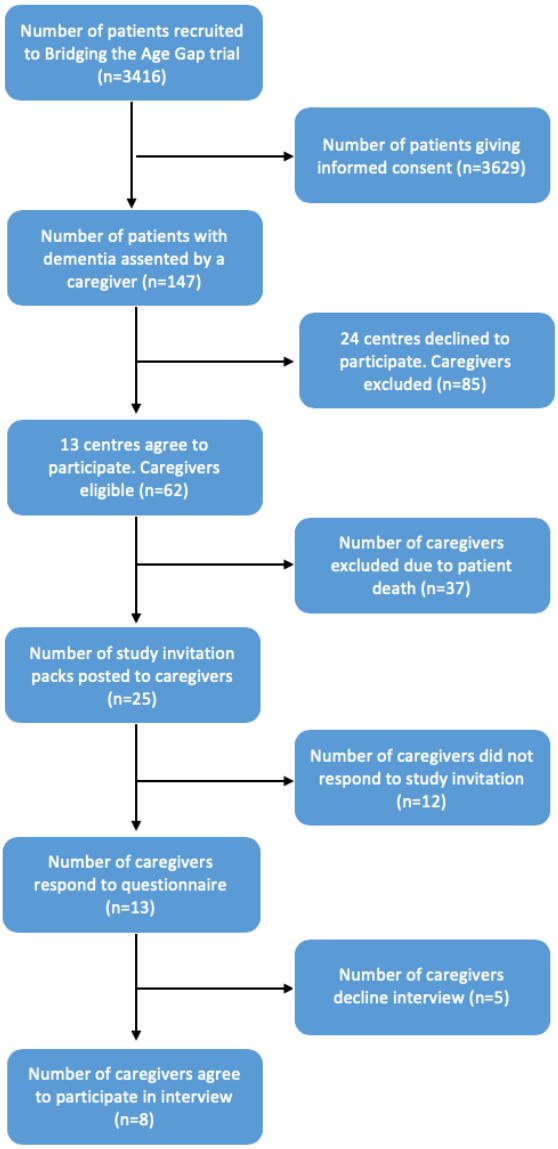


Figure 39: Participant flow diagram

The advantage of having a small number of responses meant that the researcher was able to interview all the caregivers who expressed interest, as time constraints and geographical limitation was not a barrier. Site recruitment and mode of interview is shown in Table 51.

Table 51: Duration and geographical location of interviewees

Unique Identifier	Interview Type	Duration/minutes
CG1	Face-to-face	32:29
CG2	Face-to-face	36:12
CG3	Face-to-face	49:03
CG4	Face-to-face	19:40
CG5	Telephone	01:00:40
CG6	Telephone	38:49
CG7	Telephone	48:20
CG8	Telephone	45:45

8.4.4. Recruitment

Caregivers were recruited from breast clinics participating in Phase 1 of the study. A study information pack was posted to caregivers of patients who were previously assented to the Bridging the Age Gap trial. The interview expressions of interest were received between 2016 and 2017 from caregivers residing in England and Wales. The researcher contacted all respondents directly who had expressed interest in participating in the interview by either telephone or email, and the participant information sheet was reiterated. Consent to recording was either obtained verbally (where a telephone interview took place, witnessed oral consent was given by reading out the points of the consent form to the participant) or written consent, where the interview was conducted face-to-face. The patient information sheet detailed the conduct of the interview, the recording and how it would be stored **(Patient Information Sheet, Appendix 6; Consent Form, Appendix 7).** Participants were reminded that the interview would be confidential and that they were free to withdraw from the study at any time without giving any reason.

8.4.5. Interview Conduct

The PhD researcher undertook all semi-structured interviews. The first interview was assisted by a second PhD researcher (AS) with a clinical background in breast cancer and familiarity with the study. The following prompts were respected before undertaking each interview:

- Introduction of the researcher, the aims and objectives and purpose of the study
- Reiteration of the procedure for withdrawal and confidentiality

- Ask the participant if they have had time to read the information sheet and know what is expected of the study
- Take consent
- Ask if there are any questions
- Confirm permission to audio record the interview

8.4.6. Confidentiality

Each participant was allocated an enrolment number during the questionnaire phase of the study. The transcripts and audio files were stored electronically on a secure network drive.

8.4.7. Analysis

Eight interviews were transcribed by the researcher verbatim from the audio-recordings and imported into NVivo software for analysis along with any analytical field notes. The length of the recordings ranged from 19-60 minutes. The analysis was conducted in accordance with Ritchie and Spencer's (223) Framework Analysis approach and guided by Gale et al (239)'s seven stage interpretation of this approach. The Framework Approach was chosen over other data analysis methods in view of the flexibility to incorporate field notes and reflexive annotations; the ability of the framework matrix to manage and visually deal with qualitative datasets; and how the approach is not typically aligned with any one theoretical perspective (meaning it would be suitable for a mixed method approach).

8.4.7.1. Framework Analysis Approach

The transcripts were reviewed independently by two researchers. The first reviewer (the author, CM) designed the topic guide and study set-up. The second reviewer (MB) had significant experience of undertaking both qualitative interviews and mixed methods research and was a co-supervisor of the PhD student. The PhD supervisors (LW and MB) were both involved in discussing the final themes; the lead PhD supervisor is a consultant breast surgeon, and second PhD supervisor has undertaken research into decision making for older women with breast cancer. This meant that

there were a number of multidisciplinary perspectives involved in the analysis of the interview data. The steps followed are presented in Table 52.

Table 52: The Framework Approach steps followed in the analysis stage

Stage	Step
Stage 1: Transcription	Interviews transcribed by the researcher within a week of taking place. Doing this enabled an examination of the transcripts on an ongoing basis and ensured that these were written up in a similar format and style. The main focus of the transcripts was on the content of each interview, with pauses, 'um's' and 'ah's' largely omitted. During this process, any identifiers such as names and locations were pseudonymised or redacted before importing the transcript into NVivo.
Stage 2: Familiarisation with the interview	After transcribing, the researcher read through each interview transcript numerous times to immerse within the data. Any handwritten notes that were taken before, during and after the interviews were used to supplement the interviews. During the familiarisation process, first impressions of the data were noted in the margins of each transcript. A two-page summary of each interview was produced as a writing exercise to immerse the researcher in each interview.
Stage 3: Coding	Initially, the first three transcripts were coded, ensuring that the analysis was data-driven rather than confined by a pre-defined framework. Another researcher (MB) undertook a second comparison of the initial codes. These codes formed the basis of the working analytical framework.
Stage 4: Developing a working analytical framework	Each code was reviewed for interpretation and meaning. Together with the second researcher, the codes were discussed, and any links back to the topic of treatment decision-making, the study aims and objectives, and answers to the research questions. Where passages were interpreted differently, the researchers revisited the transcript and came to an agreement over which code fit the data better.
Stage 5: Applying the analytical framework	The working analytical framework was applied to each transcript using NVivo software. This involved systematically reading through each transcript and highlighting text, which was attributed a code from the framework.
Stage 6: Charting the data into the framework matrix	After coding was completed, this was summarised in a framework matrix. This process involved exporting themes from NVivo into an excel spreadsheet, with interviews on the rows, and themes in the columns. A full version of the framework matrix is included in Appendix 9
Stage 7: Interpreting the data	To generate the final themes, the matrix was reviewed in detail to identify any patterns across the participants and their interviews. This process was guided by the research aims and objectives, keeping in mind the overarching research question.

Source: Adapted from Gale et al (239)

After completing the final stage, four key decision-making themes, and two contextual categories were generated from the interview data (Table 53).

Table 53: Final interview themes and subthemes

Contextual Information	Subtheme

Caregiver Context	• Age
	  ○ Age and treatment options
	  ○ Priorities for older patients
	• Dementia
	  ○ Unawareness of screening and breast changes
	  ○ Impact of dementia symptoms on discussions and treatment

Patient Context	• Carer-patient relationship
	  ○ Caregiver and family involvement
	  ○ Living arrangements
	• Caring Duties
	  ○ Practical and emotional support
	  ○ Caregiver outlook

Decision-making themes	**Subtheme**
Clinical Interactions	• Receiving professional advice from clinicians • Clinician awareness of dementia diagnosis and dementia friendly services
Accessing information and support	• Advance care planning and decision-making guidelines • Seeking additional information
Decision-making involvement	• Caregiver role in making the treatment decision • Involving the patient in the treatment decision
Treatment Influences	• Reasons for choice of PET • Reasons for choice of Surgery

8.4.8. Validating the approach

To appraise this process, Spencer and colleagues' (227) *Quality in Qualitative Evaluation: A Framework for Assessing Research Evidence* approach was adopted **(Table 54)**.

Table 54: Quality appraisal of framework

	Appraisal Question	How I addressed this
Findings	How credible are the findings?	The interview recordings and transcripts are available for further scrutiny (example of a transcript in **Appendix 10)**. Samples of data and quotes are organised in the framework matrix (**Appendix 9).**
	How has knowledge/ understanding been extended by the research?	These findings have been linked back to the systematic review and any new contributions are presented in the discussion
	How well does the evaluation address its original aims and purposes?	The discussion links back to overarching aims and objectives of this study
	Scope for drawing wider inference.	The use of a volunteer response sampling approach means that inferences cannot be made to the wider population
	How clear is the basis of evaluative appraisal?	The basis of the evaluation has been presented honestly and clearly in this section
Design	How defensible is the research design?	The study has used rigorous techniques at all stages where possible.
Sample	How well defended is the sample design/target selection of cases/ documents?	The sampling rationale is described in **Section 8.4.3.** and the justification of methodological design is given in **Section 4.4.**
	Sample composition/case inclusion – how well is the eventual coverage described?	The inclusion and exclusion criteria are defined in the study protocol **(Appendix 1)** and detailed in **Section 7.4.2**. Recruitment limitations are discussed in this chapter.
Data Collection	How well was the data collection carried out?	The methods for data collection are described in **7.4.** All participants were interviewed by the lead researcher and interviews transcribed verbatim.
Analysis	How well has the approach to, and formulation of, the analysis been conveyed?	The Framework Approach was followed, and data was organised and analysed using NVivo software which is frequently used for organising qualitative data.

	Contexts of data sources – how well are they retained and portrayed?	The context of data has been portrayed to the best ability of the researcher.
Reflexivity & Neutrality	How clear are the assumptions/theoretical perspectives/values that have shaped the form and output of the evaluation?	Reflexivity is discussed in **Chapter ten.**
Ethics	What evidence is there of attention to ethical issues?	The ethical issues are described in **Section 4.6.1.**
Auditability	How adequately has the research process been documented?	The research process has been documented thoroughly throughout the thesis

8.5. Results

8.5.1. Sociodemographic characteristics of caregivers

Of the eight informal caregivers who agreed to take part in the interview there was an equal split of male (50%) and female (50%) interviewees **(Table 55)**. All caregivers identified as informal family caregivers, who were related to the person they were involved in making decisions for; husbands (n=1), daughters (n=4), sons (n=2), and one nephew. The caregivers were all in some capacity the primary decision maker, although some did share a Health and Welfare LPA with other family members. The interviews took place either face-to-face (n=4) or by telephone (n=4). Each interview followed the same topic guide, which reflected the key stages in the breast cancer care pathway.

All of the patients the caregivers represented had a formal diagnosis of cognitive impairment caused by either dementia or stroke. Amongst this group of patients, some were living with mixed dementia, Parkinson's and dementia, Vascular dementia and mixed dementia; all at varying degrees and stages which affected their lives in different ways.

Table 55: Characteristics of interviewees

Interview	Gender	Relationship to patient	Type of dementia (if known)	Treatment for breast cancer
CG1	Male	Son	NK	Surgery (mastectomy)
CG2	Female	Daughter	Stroke	Surgery (mastectomy)
CG3	Female	Daughter	NK	PET
CG4	Male	Husband	NK	Surgery (WLE)
CG5	Female	Daughter	Mixed	Surgery (WLE)
CG6	Female	Daughter	Parkinson's + dementia	Surgery (mastectomy)
CG7	Male	Son	Vascular	Surgery (mastectomy)
CG8	Male	Nephew	NK	PET

Of the people with dementia that the caregivers were involved in making decisions for; two patients received PET and six patients received surgery (n=2 wide local excision, n=4 mastectomy + tablets) **(Figure 40).**

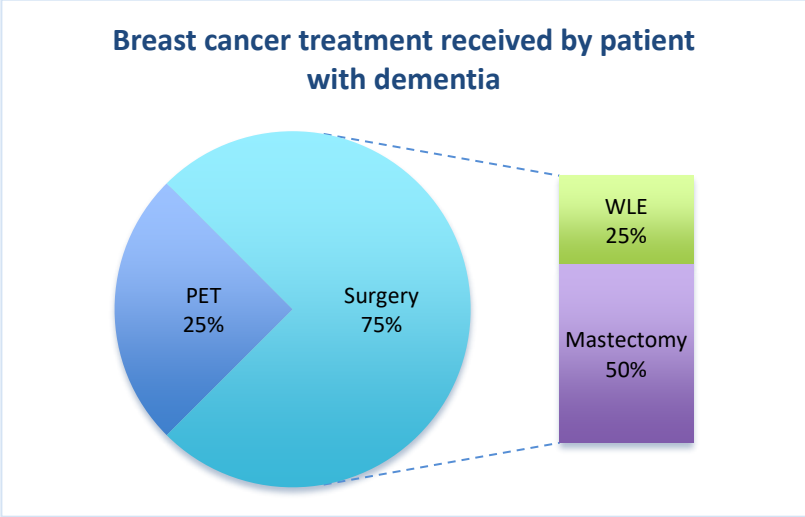


Figure 40: Treatment type received by the patient with dementia

8.5.2. Findings

Interviews were analysed iteratively to determine when saturation of themes had been reached. After eight interviews, saturation of themes was achieved, and in light

of the comments from the ethics comment, the study did not progress beyond this, with no further recruitment.

Four decision-making themes were developed from the interviews; clinical interactions; accessing information and support; decision-making involvement and treatment influences. Framing these four themes were two overarching contextual findings relating to the patient and the caregiver **(Figure 41).**

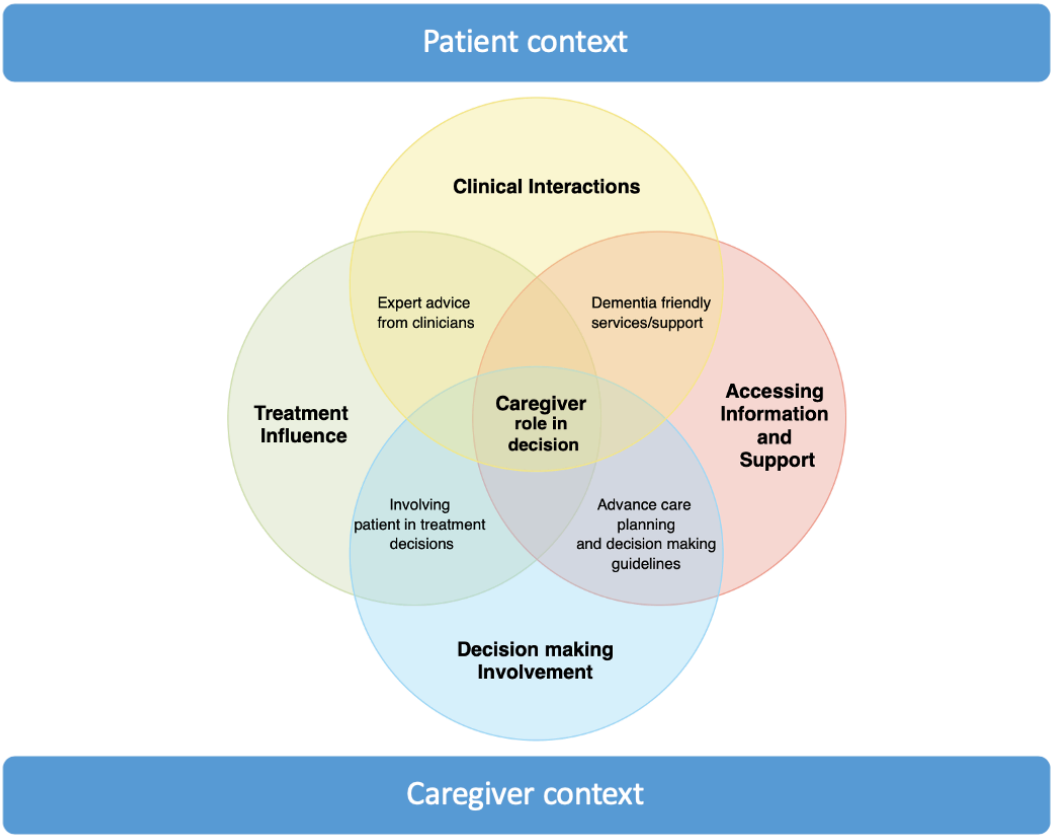


Figure 41: Diagram of study themes

The next section will detail the contextual factors and findings from the interviews. Key quotes denote the caregiver ID number and treatment received by the person with dementia in brackets.

8.5.2.1. Contextual Findings

8.5.2.1.1 Patient Context

The individual circumstances of the person with dementia and breast cancer underpinned the decision-making process and had a subtle influence on the caregiver's decision-making **(Table 56).**

Table 56: Patient Age and Dementia

Contextual Factors	Sub-context	Codes
Age	Age and treatment options	Perceptions of age; treatments and ageism.
	Priorities for older patients	Priorities for old v younger patients; co-morbidities.
Dementia	Unawareness of diagnostic examinations and breast changes	Understanding treatment; coping with screening, biopsy and examinations; ongoing breast monitoring.
	Impact of dementia symptoms on discussions and treatment	Memory issues; retaining information; dependency; coping.

8.5.2.1.1.1. Age

Age and treatment options

Prior to discussions with the treating clinician, the patient's age was perceived as a factor that may limit treatment options. Amongst caregivers there was a perception that for older patients, a palliative approach, rather than a curative approach would be offered:

> *"My thoughts were that she's just going to have some kind of domiciliary package, maybe a long-term hospice or something and try and make her as comfortable as possible. That was my thought, simply because of her age"* **(CG1, Surgery)**

> *"She was 90 when she got it, which is, it's different if somebody's 30 isn't it? Or even 50, 60, but at 90 you think to yourself, well, I just thought "that was it""* **(CG3, PET)**

Caregivers expressed an initial perception that some treatments would be unsuitable for older patients, and feeling surprised when the clinician presented the option of surgery:

> *"I just thought with her age, her health, I thought they would just want to go for [...] the easy option, I suppose, without sounding a bit cruel, of just letting my mum be as comfortable as possible. I didn't even contemplate the surgery. I just thought they wouldn't do it at her age."* **(CG1, Surgery)**

Where the clinician presented examples of successful surgical treatments for older patients, the caregiver's initial impressions of available treatment options shifted.

> *"I was gobsmacked, pleased, and the surgeon turned around to me and said something along the lines of, he'd operated on a 94-year-old lady only weeks before, he'd said, you know, age is no barrier."* **(CG1, Surgery)**

Priorities for older patients

Alongside living with dementia, many of the patients were dealing with a wide range of co-morbidities which impacted greatly on all aspects of their lives. Common across this sample of patients were:

- Visual impairments
- Hearing loss
- Mobility issues
- Polypharmacy (warfarin, blood pressure tablets, calcium tablets)

Caregivers recognised that the preferences for older patients may differ from younger women:

> *"No disrespect she's 83, it's not like she's got 50, 60 years to go… somebody who's younger who may be diagnosed as a young lady would have a totally different outlook on that, I imagine"* **(CG1, Surgery).**

Two caregivers who opted for surgical intervention for their relative acknowledged that older patients may not have the same concerns about their body image:

> *"Unless you're very body conscious the best one is to get rid of it, especially at mam's age"* **(CG7, Surgery).**

> *"…Maybe if somebody who's younger who is probably more bothered about how they look and feel about themselves from a woman's perspective, they might feel that going through medication they would do first to take that risk of not having to have the surgery. But my mum is at a time of life where that's not at the top of her agenda"* **(CG1, Surgery).**

8.5.2.1.1.2. Dementia

Unawareness of diagnostic examinations and breast changes

Caregivers were aware that breast screening programme invitations stopped at the age of 70 but were surprised that this cut-off applied to women with dementia. One caregiver remarked his concern about the "void period" between the patients' last screening and diagnosis, and lack of formalised monitoring for breast changes:

> *"You get this perfect storm coming, of people's mental capacity slowing down."* **(CG7, Surgery)**

The same issue was raised by another caregiver who expressed his concerns over the patient's ability to notice symptoms and changes in her breasts,

> "*…my aunty wouldn't have thought of, you know, self-diagnosis of breast cancer or anything like that. So really, it's the GP service that would have been your only hope […] but my aunt's mental state was such that she wouldn't have bothered."* **(CG8, PET)**

The patient's unawareness and cognitive understanding of why they were undergoing diagnostic examinations was another key concern for caregivers. A scenario was described where the patient exhibited acute feelings of confusion, pain and discomfort during the biopsy:

> *"It was difficult because mum didn't understand what was going on, except she was, I mean it was like taking a child for an injection but worse. And she couldn't understand, but she was in pain while they took the biopsy. And of course, she was frightened."* **(CG3, PET)**

In contrast, another patient was able to cope well during their breast examinations and biopsy, although the caregiver later acknowledged that the ease of coping may have been a feature of the dementia:

> "*The biopsy was a bit daunting, but I don't know whether it was my mum's dementia, but she didn't flinch at all. She just went with the flow."* **(CG6, Surgery)**

Impact of dementia symptoms on discussions and treatment

The cognitive symptoms associated with dementia, such as memory loss, meant that some patients lacked the capacity to retain information on their treatment options and the ability to remember the decisions made in the consultation. Several patients were able to take an active part in the discussion, but then struggled to retain information about the decision that was made:

> "*mam will talk through things and she will immediately forget what she's said."* **(CG7, Surgery).**

Memory impairment had an impact on the independence of patients with dementia, particularly when attending the clinic. Caregivers stressed the importance of accompanying their relatives at appointments to offer support, gather information on their behalf, and comfort them during their treatment and examinations:

> *"…if mum went to any hospital appointments, she'd come out and say oh it all went fine, and she hadn't got a clue what had happened. So that's why it's important to go with her."* **(CG5, Surgery)**

> *"…because she had dementia, I went with her in the morning and I didn't leave her, I stayed there all day […] my mum can't really speak for herself and explain how she's feeling, I didn't feel comfortable leaving her by herself."* **(CG6, Surgery)**

In two scenarios, the patient failed to remember the treatment they received. This resulted in a caregiver periodically going through the cycle of re-living the experience with the patient.

> *"Now and again she'll just go […] I want to talk to you; I've got a lump. Yeah, dear that's why the nurse comes. Does she? She comes every three months. Oh OK. And then we go through that again."* **(CG3. PET)**

> "*she didn't understand what was going on. I don't think she even noticed her breasts had been removed"* **(CG6, Surgery).**

This view was articulated by two other caregivers, who suggested that the patient's dementia may have played a role in their ability to cope with their treatment:

> *"And even if I did tell her, which I have done once, she forgets about it […] Now I think that's marvellous because you and I would be petrified wouldn't we? We'd be worrying about the future, you'd be, am I on the right tablets? Blah, blah, blah. She hasn't a care in the world because she forgets, which I think is great. So, in that respect I think the dementia is great that she can't remember she's got breast cancer."* **(CG3, PET)**

> *"My mum, she took it in her stride, didn't bat an eyelid to be honest. She never mentions it. It doesn't bother her. And it hasn't done ever since it happened."* **(CG1, Surgery)**

8.5.2.1.2 Caregiver Context

The caregiver's relationship to the patient and knowledge of their support needs framed the treatment decision **(Table 57)**.

Table 57: Carer-patient relationship and caring duties

Contextual Factors	Sub-context	Codes
Carer-patient relationship	Caregiver and family involvement	Family relationships; networks.
	Living arrangements	Place of residence
Caring Duties	Practical and emotional support	Support needs; physical; emotional.
	Caregiver outlook	Reflections; feelings; caregiver role.

8.5.2.1.2.1. Carer-patient relationship

Caregiver and family involvement

The carer-patient relationship gave an insight into the extent of their involvement in the patient's care and the wider family networks which helped them to cope. Except in the case of one patient cared for by her husband **(CG4),** all patients were widowed, which meant their subsequent care and treatment decisions relied on other family members. All interviewees defined themselves as the main decision-maker in terms of the health and welfare of the patient and described either taking on their role due

to other family members either passing away or other family members unable to help. Two caregivers **(CG3, CG8)** described feeling isolated from not having siblings or family close-by to assist with the patient's care:

> *"We used to go and see all her relatives who unfortunately have all passed away. That's another sad thing when you reach 90-odd, you know, everybody else has gone."* **(CG3, PET)**

> *"The main thing that I began to get worried about is my own health deteriorated as I got older and that I wouldn't be able to provide that sort of backup."* **(CG8, PET)**

Living arrangements

The eight patients with dementia and breast cancer lived in a range of settings; Independently or at home with their spouse**;** sheltered living or residential care. Of the patients who lived independently or in sheltered accommodation, this was often local to the caregiver or other family members, with adaptions made to their homes which enabled them to live on their own. These arrangements involved both formal and family caregivers visiting to help with shopping and medicine adherence.

Caregivers described the decision to move their relative into a care home as one of the most difficult decisions they had to make. When equated with the breast treatment decision, the resolution to move the patient into care was viewed as more difficult because it had been against the patient's wishes.

> *"It was only me and there were no close relatives that could help […] at the age of 95 we had to make the horrible decision of putting her in a care home. Which she still asks every day when we go, why am I here and why I can't come home?"* **(CG3, PET)**

> *"They could no longer meet her needs basically, so we had to move her. But she seems to be OK there [...] It wasn't an easy… decision, but it had to be done."* **(CG6, Surgery)**

Another caregiver **(CG8, PET)** described having to move his aunt to a care home as a result of his own diagnosis of cancer and the uncertainty of what the future would hold. Another patient was placed in a care home because the lack of continuity in

respect to formal caregivers (who would visit daily) became difficult for the patient to cope with:

> *"…for somebody with dementia and had got eight different people every day and all she wanted was me, because that's somebody she knew, instead of helping me it was actually hindering."* **(CG3, PET).**

8.5.2.1.2.2. Caring duties

Practical and emotional support

Alongside their dementia diagnosis, the patients in this study had extensive social care needs, some of which were undertaken by the primary caregiver, and others by formal caregivers. When asked to report the level of care provided, this ranged from making financial decisions, organising care packages to taking the patient shopping, to hospital appointments and cleaning. One caregiver was emphatic about his responsibility to *"virtually organise everything, have done for a number of years."* **(CG1, Surgery).**

When asked for their views on the informal care they provided for the patient, the caregivers conceptualised this as a 'duty' or 'paying back' what their relative had done for them in the past, rather than viewing their caring as a 'burden.'

> *"It's my duty to be doing this."* **(CG6, Surgery)**

> *"…it was sort of like payback time."* **(CG8, PET)**

> *" I was just repaying what she'd done for me."* **(CG3, PET)**

> *"I never wanted to say it was a burden because it wasn't a burden, but it was difficult […] the part I enjoyed was that I could be there for my mum. You know, I could do it."* **(CG6, Surgery)**

Alongside physical support, the caregivers described the emotional support they provided to the patient, particularly throughout the time during which they were undergoing treatment. One caregiver explained this role involved "boosting" the spirits of her mother with visits:

> *"Because when you're in the house by yourself all the time you can dwell on things. And they're little things, they're not big problems, but when you're 88 it can fester. And I can go sometimes, and I can see she's quite down or she's not feeling well and boost her up"* **(CG2, Surgery)**

For caregivers who did not live close-by to the patient, this support was sustained remotely from a distance. One caregiver described pre-empting problems and being prepared with instructions:

> *"The photos on my phone are bizarre. I've got a collection of remotes, the alarm panel, to try and pre-empt what she's going to have a problem with next to sort out over the phone."* **(CG5, Surgery)**

The notion of pre-empting problems was not just a concern where patients lived in the community or independently; this was also a source of apprehension where the patient resided in a care home. One caregiver emphasised the worries about her mother's level of care, describing these as a 'new set of worries' after the patient moved to a care home.

> *"…yes, they might take her to the toilet, and they put her to bed, but there's still all these little things that you have to keep on top of, because she's your mum! You don't want her with huge fingernails with jam and marmalade all underneath the nails."* **(CG3, PET)**

Caregiver outlook

The caregivers reflected on their role and the challenges involved in providing care for another family member with cancer and dementia. None of the caregivers reported receiving payments for the care they provided, which signified that they did not associate the caring they provided as a formalised role. One caregiver remarked that she did not identify as a caregiver, but as a family member first and foremost.

> *"I don't consider myself a carer; just a daughter really"* **(CG2, Surgery).**

In most cases, the patient had received their diagnosis of dementia some time ago, and the new diagnosis of breast cancer was viewed as another hurdle to overcome. When asked to describe their feelings towards being a caregiver, a range of emotions were described:

> *“Very emotional as you can tell. It’s very tiring. There’s no easy way I’ll be honest with you. I used to get, frustration as well, somebody else is going through it. You also get resentment. You get a horrible spectrum of feelings: guilt, resentment.”* **(CG3, PET)**

> “*I wouldn’t say I enjoyed it, but I never begrudged it. I never saw it as a burden. But I did used to get frustrated."* **(CG6, Surgery)**

Another caregiver reflected on being an only child and a male caregiver to his mother, through describing the “uncomfortable” discussions about his mother’s breast care. While he acknowledged that these discussions might have been easier for a mother and daughter to talk about, he described a sense of resilience of having to ‘get on with it,’

> *"I suppose the only thing from my point of view that gets uncomfortable sometimes is because it’s my mum. There are times when there’s probably discussions and things that I’ve had to have that I probably didn’t want to have about my mum, which might have been easier if I’d have had a sister. But other than that, no, I’ve just got on with it."* **(CG1, Surgery)**

Another male caregiver spoke with candour in respect to addressing his mother’s care needs in a ‘bloke’s manner:’

> *"If there’s any issues I just deal with it. I just deal with it in a bloke’s manner which is, there’s a problem let’s get it sorted. We go off and get it sorted and I don’t do any wishy-washy stuff, just like right, you’ve got a problem mam, we’re going to the doctor, we get it sorted.”* **(CG7, Surgery)**

This frankness was in stark contrast to the perspective of a female caregiver who described the impact that caring for her mother had on her life, highlighting that not all caregivers shared the same ease of making decisions:

> *"Looking after my mum? Yes, you want to do it, but then when it gets really, really bad and your life, you haven’t got a life, that’s when you feel guilty and resentful."* **(CG3, PET)**

8.5.2.2. Decision-Making Themes

8.5.2.2.1. Clinical Interactions

The first decision-making theme centred around the clinical interactions between the patient, caregiver and clinicians at the breast clinic (Table 58).

Table 58: Theme one: Clinical interactions

Theme	Subthemes	Definition of sub-theme
Clinical Interactions	Receiving professional advice from clinicians	Receiving advice; continuity; knowledge; conflict
	Clinician awareness of dementia diagnosis and dementia friendly services	Dementia tailored services; dementia (un)friendly.

Receiving professional advice from clinicians

Caregivers described positive interactions with breast clinicians, which left them feeling reassured in respect to their relative's prognosis, and the treatment options that would be available to them.

> *"…Listening to the surgeon, and the nurses that we spoke to when we came out of the consultation, her reassuring that women of my mother's age and older had gone through this operation and it's been a success."* **(CG2, Surgery)**

> *"The only thing I was worried about because obviously I'm not a doctor was not understanding all the options but the guys at [REDACTED HOSPITAL NAME] did such a good job of synthesising or rationalising the treatment options. They literally put it into bloke's language which was these are your options."* **(CG7, Surgery)**

Clinician continuity was important, with caregivers feeling more reassured when the results of investigations were delivered by the patient's primary consultant. One caregiver reflected on a scenario where conflicting treatment advice was given by two different clinicians involved in the patient's care.

> *"…we went along on the first meeting, it's surgery, we're not doing radiotherapy, you'll stay on the hormone [tablets], these are the reasons, do you agree? And it felt right. What threw us off keel was the following meeting post-surgery where the MDT team are making a decision as to whether you need radiotherapy and we thought we've already […] said this or agreed not to have it."* **(CG5, Surgery)**

Having comprehensive advice was important for caregivers, as they acknowledged the knowledge differential between their role as a caregiver and the medical professional. Caregivers relied on professional opinions to make the 'right' decision:

> *"They're experts, you've got to trust them, haven't you?"* **(CG7, Surgery)**

> *"She [the patient] was very trusting of the medical staff and myself, and in a way I'm sort of trusting in the medical staff because, you know, they're there to help you."* **(CG8, PET)**

Some caregivers stated the treatment decision rested heavily on the options presented by the clinician, describing the decision as 'taken out of my hands,' and 'this really is the only option.'

> *"They more or less just said we think we can treat it with drugs. So really, I was kind of, part of it was taken out of my hands wasn't it, because I was talked around. Which I had no problem with."* **(CG3, PET)**

The implication of some consultations was that shared decision making was not achieved but rather the patient and caregiver were encouraged towards one or other treatment option.

Clinician awareness of dementia diagnosis and dementia friendly services

Caregivers highlighted the complexities involved in making the dementia status known in the breast consultation. Caregivers described scenarios where after learning their relative had dementia, the consultant would switch towards acknowledging the caregiver rather than the patient.

> *"Some of the doctors in the hospitals talk, if you're there they talk to me not to her, and then she just disengages from the conversation."* **(CG5, Surgery)**

When asked if the information given by the hospital was tailored towards people living with dementia, one caregiver reported,

> *"No nothing. We didn't have anything like that. […] No. No, it was just all general."* **(CG6, Surgery)**

Caregivers reported that hospitals would send text message reminders to patients including details of their upcoming clinic appointments. This service was not tailored appropriately towards a person with dementia:

> *"…they send you texts to remind you of the appointment, and you confirm that you'll attend your visit, they sent one to mum's home number and it just so happened that my sister was there at the time. Because there was no way that mum would have been able to cope with an automated message and pressing things on the pad* […] *they should have contacted me anyway."* **(CG5, Surgery)**

Another scenario was described where follow-up involved the person with dementia accessing an online 'self-management group' website. The caregiver remarked,

> *"Mum's not even on the internet and wouldn't know how to use a computer, and at 90 with dementia, so it's something that my sister and I can do on her behalf."* **(CG5, Surgery)**

8.5.2.2.2. Accessing information and support

The second decision-making theme centred around the information, guidelines and support that caregivers accessed while making the treatment decision **(Table 59)**.

Table 59: Theme two: Accessing information and support

Theme	Subthemes	Definition of sub-theme
Accessing information and support	Advance care planning and decision-making guidelines	Advance care planning; guidelines; LPA; best interests; informed consent.
	Seeking additional information	Information offered; information format; additional information sought.

Advance care planning and decision-making guidelines

In the context of breast cancer care, none of the caregivers interviewed described having an advance decision (AD) for treatment preferences in place. When asked if having an AD in place would make treatment decision-making easier, one caregiver responded:

> *"Yeah, even if I'd have had some little clue that that's what my mum wanted yeah it would have. But there was just no way, she didn't know."* **(CG6, Surgery)**

Five caregivers had lasting powers of attorney (LPA) for their relative, which covered health and welfare, and finance and property. Often the LPA had been put into place

around the time when the person was diagnosed with dementia, designating the caregiver as the main decision-maker. One caregiver described that having an LPA in place allowed them to take an active role in the discussion and patient's support package.

> *"The fact that I've got an LPA for health and welfare, and the fact that she's now deemed to not be able to make decisions for herself, I was able to override that – because I was able to come up with the care package that was deemed sufficient."* **(CG1, Surgery)**

Two caregivers noted some inconsistencies in how clinicians made assumptions about a person's capacity to make decisions and give consent to treatment:

> *"Quite often they then get her to sign things, or a couple of doctors have actually refused to let her sign and let me sign […] I'd say some of them jump to a conclusion and just think she's incapable of making a decision, whereas others, perhaps they're rushing to get through."* **(CG5, Surgery)**

> *"In my aunt's case on the dementia front, when she went into the care thing with the care company, I was put down as the sort of contact and so as if I had powers of attorney which I hadn't, and I didn't."* **(CG8, PET)**

When asked if caregivers accessed any formal guidelines, such as the Mental Capacity Act (MCA), or ethical frameworks to guide decision-making, the majority responded either being unaware or choosing not to use them. Where two caregivers had expertise in decision-making guidelines and later life planning, these were referred to during the time they made decisions. When prompted, several caregivers spoke about making decisions using the best interest principle, although this was not explicitly stated as a 'best interest decision' as defined in the MCA:

> *"I just kind of always tried to do things for mum's best interest. It was as easy as that."* (**CG2, Surgery)**

Seeking additional information

When asked to recall the format of information received from the breast clinic, caregivers reported receiving leaflets, booklets or verbal discussions with the breast care team. One caregiver recalled only being presented with verbal information, with the clinician stating that treating with PET would be 'the best thing:'

"I wasn't offered any information sheets, I think I was just told we think this is the best thing, and then mum was put on the medication and that was it." **(CG3, PET)**.

Three caregivers recalled the additional information they accessed online following their relative's diagnosis. They described searching for statistics, *'worst case scenarios,'* and probabilities, which were absent in the information provided at the clinic. For some, this research was motivated by worry, and others, a desire to confirm survival statistics while making the decision:

"Yeah, I did actually go online and do a bit of my own research mainly because you're scared aren't you and you think, you look for the worst-case scenario […] I didn't want to lose my mum, so I was looking at statistics and things like that whereas the leaflets you get they don't tell you that, it's just basics." **(CG6, Surgery)**

"I went away and analysed it, did a little bit of research, checked it all out that it was as it should be […] we did this little dance about probabilities. Eventually I came to the conclusion they weren't going to give me a probability of longevity after the operation because what will be, will be." **(CG7, Surgery)**

Another caregiver described joining an online support group, which enabled her to talk to other women who were going through similar experiences. The caregiver stated how it was helpful to discuss dementia-related issues with other group members.

8.5.2.2.3. Decision-making involvement

The third decision-making theme centred around who was involved in the treatment decision and their role (caregiver and patient) (Table 60)

Table 60: Theme three: Decision-making involvement

Theme	Subthemes	Definition of sub-theme
Decision-making involvement	Caregiver role in making the treatment decision	Facilitating; supporting patient; decision stress/burden.
	Involving the patient in the treatment decision	Patient involvement; shared decision-making.

Caregiver role in making the treatment decision

Caregivers described the way in which patients would rely on them to communicate their decisions. Their role as a facilitator was critical in cases where the person with dementia had difficulties with hearing and speech. One caregiver described a negative experience at a pre-operative appointment where she felt excluded from the discussion.

> *"My mother's partly deaf and the nurse wouldn't let me participate in the conversation, and I found that very, very bad. Really, I feel I should have reported it, but I didn't."* **(CG2, Surgery)**

Prior to being involved in treatment decision-making for their relative, caregivers described an awareness of breast cancer through the experiences of friends or family members they knew who had been diagnosed in the past. Caregivers described how their relative would rely heavily on their opinion to make decisions on their behalf. One caregiver described her attempts to give her mother a choice in the decision:

> *"She goes 'I'll do what you think is best,' and she's always said that to me […] it gives me a bit of comfort, because she'll still say, I'll still offer, although she's got the dementia, choices or I'll tell her things, you know, and I'll go well the decision is yours. And she'll go no dear I'll just do what's best, what you say, like that –"* **(CG3, PET)**

The reliance on the caregiver to adopt the main decision-maker role was emphasised in another interview, where the patient would look to the caregiver for their opinion on which treatment to choose:

> *"They spoke to her and sort of said, now we're thinking of doing this, how do you feel about that? And she'd sort of use this OK, sort of shrug and turn to me like that, as if what do you think?"* **(CG8, PET)**

When asked how the caregiver felt during the time when the treatment decision was made, some described this as straight-forward and for others, a challenge. For two of the caregivers, the decision-making process was described as,

> *"…fine. I mean I've been making decisions all my life in the medical world, so it wasn't a problem, no. I didn't find any difficulty."* **(CG4, Surgery)**

Similarly, another caregiver explained,

> *"I've got the moral framework that I've got, and it would be one of these things that as a family we've been facilitators to help mam make a decision. It's not us imposing our decision on mam. So, from that perspective it was fairly easy because we've just done what mam wanted to do."* **(CG7, Surgery)**

Conversely, other caregivers described the experience of making the decision as "hard," "difficult," and "stressful."

> *"You just feel, are you making the right decision? So, I found it hard."* **(CG2, Surgery)**

> *"It's difficult, and you try and remember what you think your parent would have wanted if they had full capacity. That's all you can do is think that you're doing the best for them."* **(CG3, PET)**

> *"The most stressful thing about it was having it on your head that you weren't making the right decision and it's a big decision to make and just thinking oh what if I've made the wrong decision, that was the most stressful part of it."* **(CG6, Surgery)**

Involving the person with dementia in the treatment decision

Despite lacking capacity, there were still instances where people living with dementia were able to actively participate in decision-making. One caregiver described their role in facilitating the decision, which was then ultimately made by the person with dementia:

> *"I see my role as a facilitator. Now, mam will talk through things and she will immediately forget what she's said […] the final decision was mam's, because it was going to be supporting mam in her decision."* **(CG7, Surgery)**

When probed further on how decisions were made together with the patient, the caregiver described the process -

> *"She took a decision and we asked her several times. We didn't overrule any of mam's decisions but the only bit for me was I wanted to make sure."* **(CG7, Surgery)**

Many of the caregivers described having a wider family support system, or shared responsibility of decision-making with other family members. This was often the case where the caregiver had siblings. One caregiver described how the whole family would

be involved in decisions and supported the patient at appointments. They described their process of decision-making was to look at the options and then support the patient to make her own autonomous decision:

> *"As a family we looked at the different options and the family said various different things and then the final decision was Mam's."* **(CG7, Surgery)**

When asked if the caregivers believed that the patient would make the same decision about their choice of treatment if they had the capacity to do so, most agreed that their decision reflected what they perceived the patient would choose for themselves:

> *"Yeah, I do, because my mum wouldn't have wanted the upheaval of more medication, more hospital visits, going to the GP; she would have wanted to go for the option that said right, this has got a higher percentage chance of working. So yes, I do, I do think she would."* (**CG1, Surgery)**

> *"I think she would, yes I think she would, because she wasn't hesitating."* **(CG2, Surgery)**

8.5.2.2.4. Treatment Influence

The final decision-making theme centred around the factors that influenced the primary treatment received for the patient's breast cancer (PET or surgery) **(Table 61).**

Table 61: Treatment influence

Theme	Subthemes	Definition of sub-theme
Treatment Influence	Reasons for choice of PET	Reasons given for choosing PET over surgery.
	Reasons for choice of Surgery	Reasons given for choosing surgery over PET; type of surgery.

Reasons for choice of PET

Two of the eight caregivers interviewed chose PET for the patient. Both patients also resided in a nursing home**.** The key factors that led to the person with dementia receiving PET were perceptions about their age, advice from the clinician and caregiver preference. Caregivers maintained the belief that surgery 'wouldn't be right,' for a person with dementia, in their 90's, dealing with multi-co-morbidities:

> *"Because of her age they basically more or less said we wouldn't consider surgery. Because of her age and she was 90, and she'd already got the dementia, and they said we don't think it would be right to put somebody through that."* **(CG3, PET)**

Where the clinician presented PET as the only option, one caregiver described the decision as being *"taken out of my hands"* but admitted that this was also in line with her own preference for her mother to not undergo surgery,

> *"…they basically more or less said we wouldn't consider surgery […] they then said it was a slow, it wasn't an aggressive cancer, and they more or less just said we think we can treat it with drugs […] I had no problem with that because I'd thought straightaway, there was no way she was going to have surgery."* (**CG3, PET)**

Another reason for choice of PET was the rationale that taking a tablet would be easily understood by the patient.

> *"I was quite relieved, I just thought well mum can understand that. That's another thing, she can understand just taking a tablet, you know, it's quite easy isn't it? She might not understand what the tablet actually does for her, but to my mother it's just a tablet isn't it?"* **(CG3, PET)**

Reasons for choice of surgery

Six of the interviewees opted for their relative to undergo an operation. Patients either lived independently with support from formal and informal caregivers or lived with their caregiver. The key factors were advice from the clinician, the desire to prolong life, and preference of the person with dementia. For those treated with surgery, caregivers noted the positive way that surgery was presented as a treatment option. Where caregivers were initially apprehensive about surgery for older patients, this view was changed after listening to the advice of clinicians:

> *"…surgeon turned around and said this is what we're going to do, we're going to operate, we're going to do a mastectomy, I was gobsmacked."* **(CG1, Surgery)**

Having reassurance from the surgeon that surgery would be successful was another factor:

> *"…listening to the surgeon, reassuring that women of my mother's age and older had gone through this operation and it's been a success, so that reassured as well."* **(CG2, Surgery)**

Prolonging life was also a concern for caregivers, acknowledging the clinician's advice that it would be safer to have surgery earlier rather than later (when the patient would be older and potentially experiencing more ill-health).

> *"Our main concern is to get her to be able to live as long as possible, and that was the reason we took it because we just thought that's going to as much as you can put an end to it as much as possible and prolong her lifespan."* **(CG1, Surgery)**

> *"We decided that she should have surgery because if she had to have surgery in the future when she wasn't perhaps as well –"* **(CG4, Surgery)**

Another influencing factor for choice of surgery was the rationale that the patient would be able to understand the surgery. Caregivers presented this option to the patient as "getting rid" of the cancer:

> *"With mam's oncoming dementia, that influenced the kind of treatment we were leaning towards which was get rid, because it's the least management option after that."* **(CG7, Surgery)**

> *"I think mum's understanding of it was if it's cancer and it's a lump you've got to get rid of it."* **(CG5, Surgery)**

Finally, patient and caregiver preferences were also motivating factors for choice of surgery.

> *"Mam said no she'd prefer just to have the cancer out."* (**CG7, Surgery)**

> *"The consultant left it up to us really. But we, I think, we made our decision there and then. But we were given a choice."* (**CG4, Surgery)**

8.6. Discussion

The aim of the qualitative interviews was to explore the experiences of caregivers when making cancer treatment decisions for patients living with dementia, and the

context within which proxy decisions are made. The second aim was to further explore and expand upon the responses to the quantitative questionnaire.

The interviews highlighted some of the key challenges faced by caregivers when making cancer treatment decisions for another person with dementia. These findings are in line with other studies which highlight the lack of guidance for treating older patients with dementia and cancer (156, 235), and underscored areas where the cancer care pathway could be improved to address the needs of caregivers (244).

Caregivers described being heavily influenced by clinicians in terms of the treatment options presented to them. They acknowledged that clinicians possessed expert knowledge, although there were instances where caregivers reported unmet information needs. Clinician continuity and consistency of advice were identified as key barriers to decision-making, causing unnecessary stress and confusion for both the patient and their caregiver. Where clinicians were consistent, and gave positive examples of treatment, caregivers felt reassured. These findings support the need for dementia-specific awareness and training for cancer clinicians, as highlighted in other studies (242, 243, 285).

Similar to experiences described in other studies (244), caregivers viewed their role as a facilitator, whom the patient relied upon for support and opinions on the available treatment options. This reliance appeared pertinent for the two patients who were treated with PET. Some caregivers remarked on feeling excluded from discussions in consultations; echoing similar findings from other studies (244, 287), which highlighted instances where caregivers felt marginalised from discussions.

Caregivers described some shortcomings in services such as the use of appointment reminders and online patient management systems that did not consider the complex needs and requirements of people living with dementia. In addition, caregivers reported the lack of information tailored specifically towards people with dementia, as seen in other studies (242, 243). A key principle of the Mental Capacity Act (MCA)

is that when providing information to patients, this should be tailored to their needs and be sufficient enough to allow informed decision-making. These findings suggest that improvements could be made to adapt existing services to ensure they fully address support needs of people with dementia and their caregivers.

Some of the positives highlighted in the interviews were the caregiver attempts to involve the patient in the treatment decision as much as possible. These findings demonstrate the ways in which caregivers facilitate discussions and supporting their relatives to input their opinions and take part actively in consultation discussions. This came through strongly in one of the interviews where the family collectively supported the patient to make the final decision. The rationale that the treatment regimen would be understood by the patient was important to the caregivers; demonstrating the level of details and care taken to ensure the patient fully understood their treatment plan and would be able to adhere to the requirements.

Where caregivers had knowledge and expertise of LPA frameworks, this was useful in terms of asserting their role in making the treatment decision and organising their relative's care and support. Similar to the questionnaire findings, the majority of caregivers rarely accessed guidelines to frame the decisions made, which could be explained by the inconsistent application of the MCA and advanced care planning (ACP), as seen in the wider literature (281, 288). Whilst some caregivers did describe making best interest decisions, this was not explicitly stated in the context of the MCA and ACP.

The analysis focused on the choice of PET or surgery in women with breast cancer, as this was the inclusion criteria for patients recruited to the Age Gap trial (of which this study sampled). While increasing age is associated with the use of PET in older (>70) women with breast cancer (257), these findings show positive examples of older women who did undergo surgery, and highlight the factors that influenced this decision. One key finding was that the two patients who resided in care homes were treated with PET, whereas those who either lived with a caregiver, or independently

in the community with care support were treated surgically. The ability to function in the community could be taken as an indicator that the stage of dementia for those patients was not as severe in comparison to the patients who had moved into residential care. It is also true that lack of independent living is an independent prognostic factor for short life expectancy, and some surgeons may view this as indicative of higher surgical risks and a higher risk of over treatment. The women who received surgery were more collaborative with their caregivers when making the treatment decision, whereas the women who received PET were more passive and relied on their caregiver. This could indicate that women with higher care needs and who are unable to live in the community are less likely to receive surgery, and more likely candidates for PET. This also suggests that a treatment choice was not offered to the least fit.

8.7. Study Limitations

The interviews generated rich descriptive data on caregiver experiences, however, there are some limitations to note. The study could not recruit caregivers where the patient they made the decision for had passed away, which means there is an inherent bias within this sample, where those with poorer outcomes were not captured in this study.

The second limitation is recall bias, as caregivers were recruited quite some time after making the treatment decision, which means that some were retrospectively recalling discussions that had in some cases occurred more than a year prior to participating in the interview. The severity of dementia was not formally captured in the interviews; therefore, it is not fully known if dementia stage complicated the treatments available or skewed caregivers towards a different treatment pathway.

Finally, due to the study design and sample size, the conclusions cannot to generalised to the wider population (although this was never the intention of the qualitative phase of the study). The small sample size and recruitment of caregivers was limited in part to ethical restrictions and willingness on part of breast units to join the study. Despite these forthcomings, there was saturation of themes at eight interviews. The decision

to cease recruiting beyond this point took into consideration to the complex nature of accessing the caregiver group (286) and the advice of the ethical committee not to continue recruiting beyond theme saturation.

8.8. Conclusions

These findings have underscored the role of family caregivers in facilitating treatment decision-making, gathering information and supporting their relatives to participate in treatment discussions. The interviews suggest that dementia awareness could be improved in three areas: communication (such as appointment reminders and patient follow-up care), the information they received (which was not tailored towards people living with dementia), and the lack of consistency and continuity of advice from clinicians.

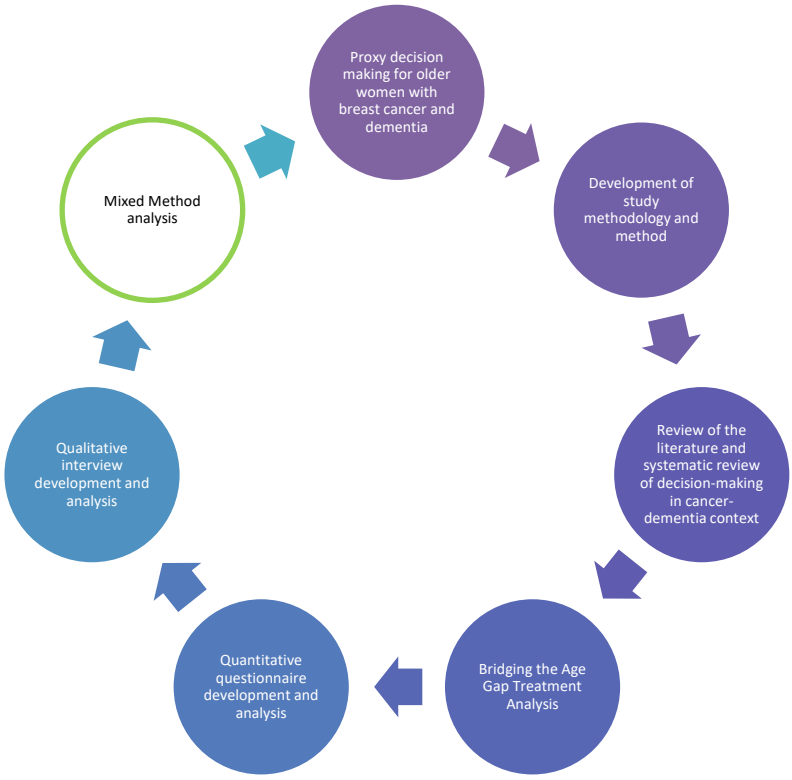
8.9. Chapter Summary

This chapter has presented the qualitative component of this study and the findings from the semi-structured interviews. The next chapter will integrate these qualitative findings with the results from the questionnaire, cohort analysis and the systematic review, as a mixed method synthesis.

Chapter Nine: Mixed Method Synthesis

9.1. Introduction

This chapter integrates the systematic review, cohort data analysis, interview and questionnaire findings as a mixed method synthesis. The aim of undertaking a mixed method synthesis was to address the research questions of the thesis and determine the support needs and role of caregivers involved in making cancer treatment decisions for people living with dementia.



9.2. Objective

A triangulation protocol was used to synthesise the study findings and address the following study objective:

- Perform a mixed methods synthesis of quantitative and qualitative findings to gain an in-depth understanding of the challenges facing patients with dementia and breast cancer.

9.3. Method

The background to mixed method research and the triangulation approach used is outlined in **Chapter Four**. This approach will be used to triangulate the findings from the systematic review, cohort data analysis, questionnaires and interviews as a mixed synthesis **(Figure 42)**.

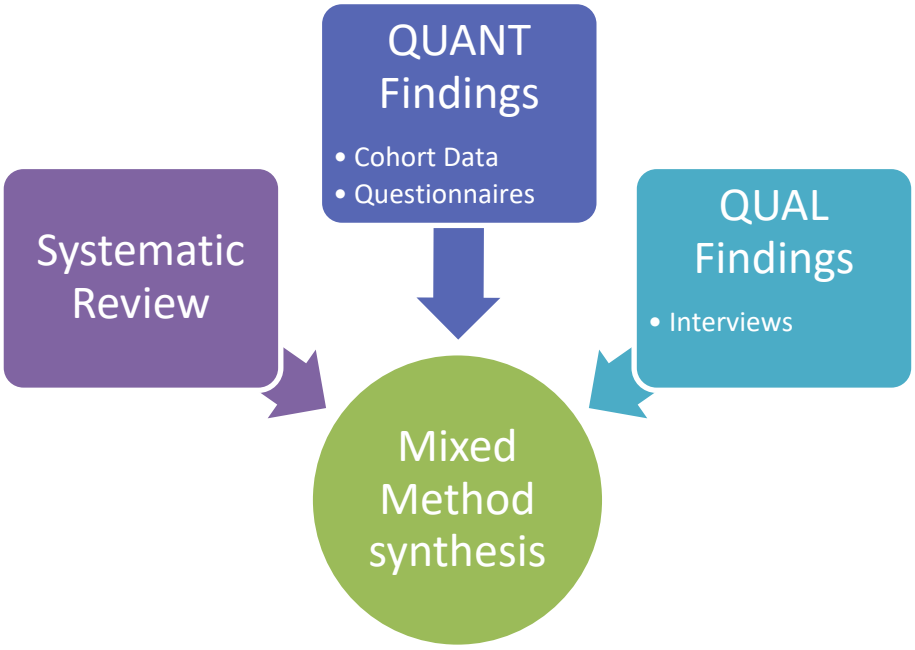


Figure 42: Mixed method schema

9.3.1. Triangulation Protocol

The triangulation protocol was developed using Farmer and colleagues' (228) six step process. A summary of this approach is detailed in **Section 4.5**. Findings from the four study components were organised in an excel sheet. As the systematic review and the questionnaire findings informed the development of the topic guide, the four decision-making themes developed from the interviews were used to construct a working analytical framework. The framework was used to draw the findings of each data set together.

- Clinical Interactions
- Accessing Information and support

- Decision-making involvement
- Treatment Influences

A matrix was created to answer each of the three study questions:

1. What is the impact of a cancer diagnosis on the treatment and outcomes for patients with dementia?
2. Which factors influence the treatment decision making process from the perspective of caregivers for patients with dementia and cancer?
3. What is the role of caregivers in making decisions for patients with a diagnosis of breast cancer and dementia?

The four data sources (systematic review, cohort data, questionnaire data and interview findings) were reviewed to assess complementarity and divergence **(Table 62).**

Table 62: Convergence Coding Criteria

Coding Label	Definition
Agreement	Agreement across all data sources
Partial Agreement	Partial agreement across some but not all data sources
Dissonance	Disagreement between data sources
Silence	Absence of theme in sources

Source: Based on Farmer et al (2006)'s Triangulation Protocol

9.4. Mixed Method Findings

Three over-arching meta-themes were developed from the framework matrix **(Tables 63, 64, 65)**.

1. Caregiver role in making decisions
2. Expert knowledge
3. Influence of dementia diagnosis

An overview of each meta-theme in answer to the three research questions is presented here, along with a discussion of each finding.

Table 63: Findings that address research question 3: *What is the role of caregivers in making decisions for patients with a diagnosis of breast cancer and dementia?*

Meta Theme: Caregiver role in making decisions				
Sub-theme	**Systematic Review**	**Questionnaire/ cohort data**	**Interview**	**Convergence Code**
Collecting information on behalf of the patient	Studies describe caregivers as *facilitators*, gathering information from the clinician and negotiating on behalf of the person living with dementia. Clinicians happy to conduct the consultation with the caregiver taking a lead role.	All caregivers reported gathering additional information.	Caregivers described gathering information during (and after) the consultation on the range of treatment options and referring to expert opinions.	Agreement
Communicating background knowledge on the patient	Caregivers were the key to a successful consultation; especially where they knew the patient well. Otherwise, memory loss became a 'barrier.' Some caregivers felt their role was marginalized by the HCP; some examples where judgements and knowledge questioned.	Not addressed in the questionnaire or cohort data.	Caregivers described highlighting the patient's dementia diagnosis to the HCP during the consultation. An issue was raised where one caregiver attempted to provide information on behalf of the patient during a pre-op consultation but was marginalized by a breast nurse.	Agreement

Making the dementia diagnosis known to the clinician	The patient's cognition status not always known to the HCP, prior to the consultation. Memory problems often reliant on caregiver disclosures.	Not addressed in the questionnaire or cohort data.	One caregiver described a complex scenario when trying to make the dementia diagnosis known to the HCP, without upsetting the patient. Where the patient was known to have dementia, the HCP switched towards acknowledging the caregiver instead of the patient.	Partial agreement

Table 64: Findings that address question 2: *What factors influence the treatment decision making process from the perspective of caregivers for patients with dementia and cancer?*

Meta-theme: Expert knowledge				
Sub-theme	**Systematic Review**	**Questionnaire/ cohort data**	**Interview**	**Convergence Code**
Professional Knowledge	Dominance of clinician/expert knowledge in the consultation. Caregivers guided by clinical recommendations on decisions to treat and screen the patient.	5/13 caregivers reported that the patient's clinician was involved in making the treatment decision. 10/13 caregivers had prior awareness of breast cancer. 9/13 caregivers had prior awareness of treatments.	Caregiver reliance on expert opinion to make the "right" decision. Some decisions "taken out of my hands" and "this really is the only option." Caregivers recognised the knowledge differential between the caregiver and medical professional.	Agreement

Familiarity and continuity of advice	Highlighted the need for clinician familiarity to avoid repetitive recall, frustration and anxiety for patients and their caregivers. Studies in favour of having a 'continuous link' (i.e., A designated dementia nurse) to coordinate care and provide dementia-specific support.	Not addressed in the questionnaire or cohort data.	Caregivers reassured when results were presented by same consultant. Continuity and consistent advice important; breast consultant not always consistent. Breast nurse often continuous. One scenario where conflicting advice on the extent of MDT input in final treatment decision resulted in upset for the caregiver and the patient.	Agreement

Table 65: Findings that address question 1: *What is the impact of a cancer diagnosis on the treatment and outcomes for patients with dementia?*

Meta-theme: Influence of dementia diagnosis				
Sub-theme	**Systematic Review**	**Questionnaire/ cohort data**	**Interviews**	**Convergence Code**
Patients with dementia are treated differently to women with normal cognition	Patients with dementia likely to receive less treatment. Reasons included: toleration of side effects, life expectancy, and ability to deal with complex treatment regimens. Caregivers for women with mild-moderate dementia more likely to choose aggressive treatments. In some studies, comfort care suggested for patients with severe dementia.	*Cohort analysis:* patients with dementia were more likely to be offered PET. *Questionnaire:* 9/13 patients offered surgery with or without tablets. 12/13 offered tablets (4 of these tablets only). 2/13 offered chemotherapy, 2/13 offered radiotherapy.	Consultants presented positive examples of older women undergoing successful surgeries. 6/8 received surgery; 2 treated with PET. Chemotherapy and radiotherapy ruled out due to patient's ability to cope with side effects. Surgery *"wouldn't be right"* for a patient with dementia, in their 90s, and dealing with multi-comorbidities. Patients treated with PET resided in nursing homes; surgical candidates lived	Partial agreement

			independently or at home with support.	
Caregivers for people with dementia have unmet information needs	Unmet needs where information not adapted specifically to patients with a cancer-dementia diagnosis. Extra time needed. Caregivers happy with the level of information but had to seek out further information after the consultation.	13 (100%) caregivers had enough access to support and information. Ranged from satisfied (4/13) to very satisfied (9/13) in terms of information received. Leaflets were the most useful information format (5/13)	Caregivers felt the level of information received was adequate. Caregivers did own research online to find out more on statistics and probabilities. Information was not specifically tailored towards people with dementia.	Dissonance
Lack of dementia-specific support in the consultation	Tendency to focus on cancer-related discussion rather than dementia-related. HCP not always able to give on advice on the impact cancer treatment would have on the patient's dementia. Dementia awareness training highlighted for cancer HCPs. Extra support needed for patients with dementia – clearer signage, staff to accompany.	13/13 questionnaire respondents reported that the breast clinician answered all of their questions before deciding on treatment.	Some caregivers relied on the patient's dementia nurse for advice. Appointment reminders sent to the patient and not the caregiver. Electronic reminders and online patient management systems not tailored towards patients with dementia.	Partial Agreement

9.4.1. Caregiver role in making treatment decisions

The caregiver's key role was concerned with gathering information on behalf of the patient and communicating detailed background information during the consultation. This often involved disclosing the patient's dementia diagnosis to the breast clinician.

The systematic review and interview data describe the caregiver as a 'facilitator,' tasked with gathering information on behalf of the patient (156, 242, 243). Similarly, the interviews highlight the importance of this role in collecting information during and after the patient's hospital appointment. In the questionnaire, all caregivers reported supplementing the information received from the hospital which emphasises the scope of their role in helping to weigh up the pros and cons of treatments offered to the person they care for.

Another important aspect of the caregiver role involved making the patient's past medical history and preferences known to the clinician during the consultation. Studies included in the systematic review described caregivers as the key to a successful consultation (242, 243), and were best placed to represent the patient where they possessed knowledge of their preferences. In scenarios where the caregiver had limited knowledge of the patient's history, memory loss became a barrier (242).

In the systematic review, HCPs were happy for the caregiver to assume the lead decision-making role and would address them directly in the consultation (242). In the interviews, caregivers described how following the disclosure of the patient's dementia diagnosis, the clinician's approach of switching towards addressing the caregiver could at times lead to the patient feeling excluded from the discussion. The systematic review and interviews highlighted some of the tensions where caregivers themselves had also felt excluded from discussions, including scenarios where their judgments and knowledge was questioned by the HCP (244). This led to some caregivers feeling marginalized during discussions, which was similarly described in one of the interviews where a caregiver attempted to speak on behalf of the patient and was reprimanded by the breast nurse. Scenarios such as these led to caregivers feeling uncertain of the level of responsibility expected from them in consultations and discussions (156).

Another facet of the caregiver role involved disclosing the patient's dementia diagnosis or memory problems to the breast clinician or consultant. Both the literature (243) and interviews raised examples of where cognition status was unknown to the HCP in advance of the consultation. In the interviews, one caregiver emphasized the complexities of communicating the dementia diagnosis to the breast clinician in the presence of a patient who was in denial of their cognitive problems. This was also highlighted in the literature, where the disclosure of memory problems would often be reliant on the caregiver (243).

9.4.2. Expert knowledge

Across all three data sources, the HCP or treating clinician's knowledge was highlighted by the caregiver as influential when making the treatment decision.

In the wider literature and interview findings, caregivers were influenced by both the screening and treatment recommendations given by the HCP (241), with 38% of questionnaire respondents reporting that the patient's clinician was involved in making the treatment decision. In the interviews, caregivers explained this process in more detail, describing their reliance on the HCPs 'expert' opinion to make the 'right' decision. Caregivers in the interviews recognized the knowledge differential between their role as caregiver and the breast clinician, although in the questionnaire, 77% and 69% reported already having a prior awareness of breast cancer and treatment respectively. In the interviews, the treatment decision was described as 'taken out of my hands,' with caregivers placing their trust in expert opinions and the options presented to them by the breast clinician.

The literature and interviews underscored the need for familiarity in the breast consultation. The advantage of seeing the same HCP throughout the pathway would avoid repetitive recall of patient details, which often resulted in unnecessary stress and anxiety for patients and their caregivers (244). The interviews reinforced this point, whereby caregivers felt more reassured when results were presented by the patient's assigned consultant and this avoided conflicting advice on treatment plans.

In one interview, a scenario was recounted where the patient's post-operative results were delivered by a new consultant, who then gave advice which contradicted the decision to rule out radiotherapy, which had been discussed with the patient's initial consultant. This led to anxiety and upset for both the caregiver and patient who were uncertain over whether the decision responsibility lay with the caregiver or the MDT.

Both the interviews and literature highlighted the need for clinician continuity from the onset of the patient's breast cancer journey. This ensured that the advice received was consistent. In the interviews, continuity was often provided by the breast nurse, who was often assigned at the start of the pathway and contactable during treatment and follow-up. The literature referred to the need for a co-ordinated central figure to provide dementia-specific support from the initial appointment (243, 244).

9.4.3. Impact of dementia on decision

The presence of a dementia diagnosis impacted on the patient's cancer diagnosis in three key areas; the treatment they received, unmet information needs and lack of dementia-specific support throughout the cancer pathway.

There was partial agreement across the data in regard to the treatment of women with dementia compared to women with normal cognition. In the literature, it was remarked that patients with dementia were more likely to receive fewer treatments than patients without dementia (242). Some of the reasons for this included toleration of side effects (241, 243) and the ability of the patient to deal with complex treatment regimens (242). Likewise, the analysis of cohort data suggested that women with dementia were more likely to be treated with PET, and that this treatment choice increased in line with the severity of dementia. For patients who had mild-moderate dementia, rates of surgery were higher. This finding was also seen in the interviews, where patients who resided in residential care were treated with PET, whereas patients treated surgically still lived in either the community or with the caregiver. For the two patients who received PET, surgery was ruled out as not being right for a patient with dementia in their 90s and dealing with multi-comorbidities.

The majority of questionnaire respondents reported having discussions around surgical treatment options and 62% were recommended surgery, which is the gold standard for all women with primary operable breast cancer. Some respondents did recall having chemotherapy and radiotherapy discussions but did not go on to pursue these adjuvant therapies. In the interviews, chemotherapy and radiotherapy was ruled out for one patient on the grounds that they may not have the ability to cope with side effects. The impact of side effects on the treatment decision was also highlighted in the literature review (242, 243).

There was agreement between the literature and interviews in respect to the absence of dementia-specific information on treatment options. Studies included in the review found that information was not always adapted for patients with a cancer-dementia diagnosis (243, 244). Leaflets were the most useful information format for questionnaire respondents, although the interviewees remarked that these were not always tailored towards the needs of patients with dementia. Caregivers from one study included in the review (156), and those interviewed, described supplementing much of the information they received by searching online for survival probabilities which could not be found in the information supplied by the clinician. Despite these misgivings, caregivers across all three sources were satisfied with the level of information they received at the clinic.

The literature review and interviews highlighted the tendency of the consultation to focus on cancer-related issues, rather than dementia-related discussions (242), which suggests there may be some need for dementia awareness training amongst cancer clinicians (243). Some of the caregivers interviewed chose to rely on the patient's dementia nurse contact for advice on the impact that cancer treatments may have on the patient's dementia diagnosis. In the literature review, there were also some issues documented where HCPs were unable to advise on whether some cancer treatments may potentially exacerbate the patient's dementia symptoms (242). Despite this, all questionnaire respondents within the study reported that the breast clinician was capable of answering any questions prior to making the decision (100%, 13/13).

Both the literature and interviews highlighted opportunities for improving the 'dementia friendliness' of cancer services. Caregivers in the study by Witham and colleagues (244) described scenarios where unclear signage and absence of staff led to some patients missing their appointments. In the interviews, where the hospitals sent out appointment letters and reminders, copies of these often did not reach the caregiver. Where electronic appointment reminders and online follow-up systems were in place, these were not appropriate for the patient to use without assistance from the caregiver.

9.5. Conclusions

Across the data, the role of the caregiver was central to making treatment decisions. This role included gathering information on behalf of the patient and communicating their preferences and dementia diagnosis to the HCP. Clinician continuity was important, as this reassured caregivers that the advice received was consistent and inclusive of the patient's preferences. There was much variation found in the treatments offered to women with dementia; patients with mild-moderate dementia were more likely to have surgery compared to those with severe dementia (or those living in residential care) were more likely to be treated less aggressively with PET. Most caregivers had unmet information needs in terms of untailored information, although on the whole were satisfied with the level of information received from the patient's treating clinician and the breast clinic.

9.6. Chapter Summary

This chapter has synthesized the findings from the systematic review, cohort analysis, questionnaire and interview components of the study. Together, these findings will be discussed in the context of the entire thesis in the final discussion chapter.

Chapter Ten: Discussion

10.1. Introduction

The findings from this mixed method study sit within the wider Bridging the Age Gap programme, which explored breast cancer treatment outcomes in older women. This study has built on the aims and objectives of the trial by analysing the treatment and survival outcomes of patients with cognitive impairments, and explored the experiences and support needs of caregivers who were involved in making those treatment decisions. This chapter will discuss the results from the study, how the aims were met, reflexivity, the justifications for exploring this area of research and its contribution to the existing knowledge of treatment decision-making in breast cancer care.

10.2. Discussion of Findings

This discussion focuses on the key issues raised from the systematic review, the analysis of cohort data from the Bridging the Age Gap trial, and the mixed method synthesis. The aims of the study were:

1. To determine the oncological outcomes for older women with early breast cancer when also affected by cognitive impairment
2. To determine the role of informal caregivers in making cancer treatment decisions for patients with cancer and dementia
3. To determine the support needs and wishes of informal caregivers in the breast cancer care setting

The following procedures were used to address the study aims.

- The systematic review explored the role of caregivers in making cancer treatment decisions for people living with dementia
- Statistical analysis of cohort data determined the oncological outcomes (treatment and survival) of patients with breast cancer and cognitive impairment

- The bespoke quantitative questionnaire was completed by caregivers who had been involved in making cancer treatment decisions, to determine their role in supporting breast cancer patients with dementia
- Semi-structured qualitative interviews were undertaken with caregivers to explore in-depth their experience of cancer decision-making and supporting a relative with dementia and breast cancer through treatment
- A triangulation protocol was used to synthesise the study findings, gaining an in-depth insight into the support needs and experiences of caregivers when making cancer treatment decisions

10.3. Key findings

Patient age and co-morbidities influence cancer treatment decision-making

For caregivers and the cancer clinician, the patient's age and co-morbidities were both influential factors when making treatment decisions. The cohort analysis of treatment outcomes demonstrated that age, and the presence of comorbidities, were associated with a higher rate of PET use in women with breast cancer and cognitive impairment. These findings were in keeping with other studies reporting on the difference in treatments for older women with co-morbidities (10, 136, 153). Reasons for the lower rates of surgery in the cognitively impaired groups may include clinicians offering PET due to a perceived risk of co-morbidities and age, patient and caregiver preferences for what is perceived as a lower risk/lower morbidity option in women with lower life expectancy, and a wish on the part of the patient's caregivers to optimise quality of life.

The patient's age and perceptions around their ability to cope with complex treatments were common themes across the study components. Where patients were treated with PET, caregivers framed the decision as a clinical recommendation from the patient's cancer clinician. Elsewhere in the literature, cognitive impairment has been shown to be a significant clinician driver for non-surgical treatment (14). The two patients within the interview study treated with PET were both aged 90+ and resided in residential care; although severity was not formally recorded in this study, it

appeared that the severity of dementia had reached the stage where the patient was unable to live independently at home. Taking into account the risks involved with surgery (and subsequent adjuvant therapies), the combination of being in the 'old-old' age category and severity of dementia, guided caregivers towards PET for these patients.

Updated registry data on mortality and recurrence was available for 11 out of the 13 patients cared for by questionnaire respondents. Eight patients have since passed away, including all those treated with PET (n=3). Only one death out of eight was breast cancer related (patient treated with PET). The remaining three patients still alive at a 5-year median follow-up were treated surgically. There were no recurrences recorded for the 11 patients with follow-up data available. In keeping with the wider literature (10, 11, 289), the cohort analysis found that compared to women with normal cognition, cognitively impaired patients had reduced overall survival. This included death from all causes.

Cancer clinicians play an important role in supporting treatment decision-making

Caregivers were heavily reliant on the patient's breast clinician for expert advice on the ambiguities of cancer treatments, although discussions around the patient's dementia diagnosis were largely absent from these conversations. In some cases, clinicians were unaware of the patient's dementia diagnosis, as also found in other studies (242, 243). The systematic review highlighted gaps in the HCP's breadth of knowledge regarding dementia-related issues, particularly during cancer consultations (277). This finding resonated within the interviews, where caregivers reported feeling unclear at times regarding the impact of cancer treatments on the patient's dementia. Despite this, caregivers were highly satisfied with the level of breast cancer information received from the clinic and the treatment decision they subsequently made. Caregivers recognised the knowledge differential between themselves and the cancer clinician; trusting their expert opinion to guide them towards the 'right' decision. Following the initial discussion of treatment options with the cancer clinician, caregivers appeared to shift their preconceptions of treatment if

they were presented with successful examples of older women undergoing complex surgeries. This finding highlights the importance of informed decision-making; ensuring that both the caregiver and patient are aware of all available treatment options and challenging ageist treatment preconceptions.

The questionnaire and interviews highlight the nuances of decision-making, and the support needs of caregivers varied widely. When making decisions, some described almost second-guessing what the patient may choose for themselves, while balancing this with their best interests and expert recommendations. When asked if having an advance decision in place would make this process easier, caregivers agreed that this would be useful to allow insight into what the patient would choose for themselves. This was echoed in other studies, where caregivers highlighted the need for access to support and tailored information to help guide them towards making decisions (74).

Supporting caregivers throughout this time is important. Caregivers gave detailed insight into the level of dementia-related support they provided and their relationship to the person they cared for. Together with the patients' other ongoing health problems, these issues gave context to the wider framework within which caregivers made their decisions. Many of the caregivers within this study described keeping to their own support systems, relying on families or friends, being either unaware of external support or choosing not to access it. While most caregivers were reticent to talk about their role as a burden, they did go on to describe the stress, guilt and emotions that come hand in hand with seeing a relative in pain or distressed during biopsies or treatment (290). They described the breast care nurse as being the continuous link throughout the patient's treatment journey, whereas the consultant (or cancer clinician) would sometimes interchange; often leading to inconsistences and misunderstandings over the course of treatment, and when to speak up on behalf of the patient. These findings highlight the need for co-ordinated care, such as having a designated dementia clinician to offer continuity and support to the caregiver from the onset (242-244, 285).

Adapted cancer care services and tailored information is needed

For caregivers who are already encumbered with caring for a person with a dementia diagnosis, navigating services that lack specialist dementia input was highlighted as an area for improvement. Much of the breast care pathway was generically structured, such as using text message reminders and electronic follow-up systems. Most, if not all of the caregivers described how the patient would be unable to attend appointments alone unsupported, and worried that the patient would forget to relay the discussions later. These findings were similarly shown in another study which highlighted the importance of the caregiver's role in accompanying the patient to their treatment appointments (244).

In the questionnaires and interviews, caregivers reported being highly satisfied with the level of information they received, although they did go on to supplement this with further research, such as using online forums to speak with others who had similar experiences. Caregivers described searching for additional information to anticipate the impact of cancer treatment on the patient's dementia, which was absent in the information they received in the clinic. There was no mention of tailored breast cancer information for people living with dementia, which was also reflected in other studies (235, 243).

10.4. Reflexive Account

Reflexivity is a method for ensuring rigour and quality in research (291). Reflexive practice involves examining the contextual similarities and differences between the research and the participants to increase the credibility of findings (292). The next section will reflect on my experiences of working on this research and examine the methods used in the study.

10.4.1. Researcher reflexivity

The development of this study drew from my multi-disciplinary background based in clinical trial research, social sciences and public health. Prior to this study, I already had a research interest in treatment decision-making and medicine adherence in the context of patients with impaired capacity; in particular, proxy decision-making. At the

stage when I began developing my study protocol, I was working as the Clinical Trial Monitor and already had early insight into the nuances of the patient data that the Bridging the Age Gap trial was collecting on women with cognitive impairments and breast cancer. At monitor visits, I had many anecdotal discussions with local research nurses and breast consultants on the treatments offered to this cohort of older women, and my curiosity around how dementia impacted on treatment decisions grew from there.

During this time, I worked alongside a team of research fellows, surgical consultants and breast nurse specialists on the Bridging the Age Gap Trial from 2012-2020. Planning this study involved exploring the wider literature and methods that had been used in studies with similar populations. I also had an awareness of the challenges involved in recruiting older populations to research studies and the potential sample size of older women on the trial who would fit the study criteria. This knowledge gave me a good starting point for considering which research methods would be most suitable for meeting the aims and objectives of the study, while also taking into account the complexities involved in researching older populations, particularly those with cognitive impairment.

10.4.2 Reflexive discussion of methods

Using a pragmatic mixed method stance allowed me to mitigate some of the issues described thus far by using a 'what works best' approach such as:

- Where the systematic review yielded few results, I broadened the search strategy from my original criteria.
- Allowing participants to take part in the study in a flexible way (for example, offering the choice of a face-to-face or telephone interview; allowing caregivers to take part in the questionnaire and not the interview).

Using a sequential mixed method approach to data collection had the following advantages:

- Where data was missing in questionnaires, I was able to follow this up and capture this at the interview stage
- Where responses in the questionnaire were unclear or ambiguous, I was able to clarify and explore this in more detail in the interview
- The interviews allowed an elaboration of the responses given in the questionnaire
- Where the study sample was smaller than expected after data cleaning, I was able to integrate the findings from four components of the study to produce a synthesized analysis and gain a more complete understanding of the research.

10.4.2.1. Quality assessment of Mixed Method approach

In their paper on the quality of mixed method studies, O'Cathain and colleagues (230) produced the 6 item Good Reporting of A Mixed Method Study (GRAMMS) framework. The following section will reflexively address the GRAMMS quality guidelines in the context of the study, as part of the reflexive process.

1. Describe the justification for using a mixed method approach to the research question.

The justification for using a mixed method approach in this study was explained in Chapter Three, with a detailed section on the data collection methods for each phase of the study in Chapter Four. The study objectives detailed how the aims would be met by undertaking a systematic literature review; statistical analysis of cohort data; descriptive analysis of questionnaire data; and thematic analysis of interview findings. I outlined the complexities of undertaking research into caregiver populations and the few studies that have explored this topic.

2. Describe the design in terms of the purpose, priority and sequence of methods

The purpose was to add to the existing knowledge base and fill in the knowledge gaps around treatment decision-making in a cancer-dementia context, as highlighted in the literature review (Chapter Five). The priority of the research was to identify the

challenges and support needs of caregivers and give a voice to their views and experiences. The sequence of methods and data collection in both phases of the study were influenced by the study time scales and access to the population, which was sampled from a cohort study which recruited within a specific time frame. Ethical restrictions were also a factor in how the study recruited. These choices have been detailed in Chapter Four.

3. Describe each method in terms of sampling, data collection and analysis

Both phases of the study used non-probability sampling techniques (purposive, volunteer response) to collect qualitative and quantitative data, which is detailed in Chapter Four. This approach was influenced by the complexities of the study population, which is hard to reach, both for practical reasons and as an ethically challenging subject matter. The analysis for each stage of the study was guided by the methods chosen. A thematic analysis of the systematic review was undertaken due to the nature of the studies found in the search strategy. Meta-analysis was not possible due to the heterogeneity of studies. Statistical analysis (hazard ratios, p values, univariate) of cohort data was undertaken due to the large data set, which permitted a more complex analysis of patient treatment and survival analysis. Conversely, the small data sample in the questionnaire component of the study meant that descriptive analysis was performed. The Framework Approach was used to analyse the interview data as this was the best fit for organising and exploring rich in-depth qualitative data. Details of all the analysis techniques have been outlined in Chapter Four.

4. Describe where integration has occurred, how it occurred and who has participated in it

Data integration occurred in three instances. The first was the use of the systematic review findings to design the qualitative questionnaire and interview topic guide. The second stage was the use of the questionnaire results to inform the topic guide. The third level of integration involved triangulating the data as a mixed method synthesis to address the research questions and study objectives. Integration of data occurred

sequentially. The researcher, a PPI group, breast experts and caregivers participated in different aspects of the study.

5. Describe any limitation of one method associated with the presence of the other method

One key limitation is that the interview component of the study depended on the completion and response to the study questionnaire. Following the recommendations from the ethics committee, I was unable to send a reminder to participants who did not reply to the questionnaire, nor was able to invite caregivers to the study where the patient cared for had passed away. This meant that many of the options for maximising recruitment (such as sending reminders or follow-up calls) could not be used and constrained the ability to recruit.

6. Describe any insights gained from mixing or integrating methods

The insights gained from undertaking a mixed method study were greater than what could have been achieved from using a single method approach. By combining a number of approaches to explore a complex under-researched topic, I was able to overcome the limitations of using one method alone. One example was using interviews to build on the questionnaire findings to give more depth and nuance to the decision-making process.

Based on the GRAMMS framework, this study was of good quality, and attempted to provide an honest account of the challenges involved in researching treatment decision-making for a complex group of patients and their caregivers. Throughout the study I have aimed to be transparent about the way in which data was collected and integrated, providing an honest account of 'real world research.' The methods chosen achieved the aims and objectives of the study. The next section will give a reflexive account of each study component and reflect on the strengths and weakness of each approach.

10.4.3. Systematic Review reflexive account

The paucity of studies included in the literature review reflect the small amount of literature exploring decision making in a cancer-dementia context. Since 2019, there have been more studies focusing on this topic, highlighting the relevance of the disparity in care received by people with dementia and cancer (285). My key learnings from this component of the study were to be flexible in terms of searching the literature in order to maximise the reach of the search. The initial scoping of the literature was important as this indicated the small amount of literature that specifically focused on breast cancer and dementia, which led to broadening the search criteria to include studies with all cancer types.

During the scoping phase, it was clear that caregiver experiences and perspectives were mostly captured in qualitative and mixed method studies, as demonstrated by similar reviews of caregiver decision-making in cancer care (234, 235). To maximise the search, I opened up the criteria to include a range of study designs, which meant that I retrieved more studies to address my search question. The disadvantage was that I would be unable to draw direct comparisons between studies or conduct a meta-analysis of findings.

10.4.4. Cohort analysis reflexive account

The Bridging the Age Gap trial is the largest prospective cohort study of treatment and outcomes in patients over the age of 70, and uniquely collected detailed data on cognitive status by permitting proxy consent of patients with cognitive impairment. In addition, the study collected detailed baseline health and fitness status, allowing the analysis to tease out the contribution of impairment from other comorbidities, frailty and older age, which often confound these analyses. The objective of the Age Gap study was to gather data on women treated with either PET or surgery and determine the variables which predict optimal outcomes from these treatments. This aim influenced the choice to focus on PET or surgery as primary treatments.

The spread of data indicated that the cohort study recruited relatively more women over age 70 at the younger end (70-74) of the age range, and relatively fewer at the older range (90+) compared to registry data age distributions. This could mean that the oldest and frailest women were excluded from the analysis, which may restrict the generalisability of the findings. There are also some limitations to the categorisation of patients by severity of cognitive impairment, as proxy consent patients were not expected to complete a MMSE form. Cognitive severity was also not formally assessed for those where dementia was only indicated on the Modified Charlson Score form (unless they had also completed an MMSE form).

10.4.5. Questionnaire reflexive account

Postal questionnaires are frequently used; for ease and as a cost-effective way to collect research data (293). In terms of practicality, this reduced the pressure on research nurses at each PIC as they would not be tasked with recruiting participants face-to-face. Caregivers had also been involved in the wider Bridging the Age Gap study, which indicated that they were familiar with the wider programme of research. The low response rate in questionnaire completion was a key issue for this component of the study, which limits the generalisability of results to the population (although this was never the intention). Reflecting on this component of the study, there were some key issues which may have impacted on the response rate and completion of the questionnaire.

The first issue was the exclusion of units within the Bridging the Age Gap trial with high numbers of eligible participants who declined to participate in the study. The rationale of recruiting through the Age Gap trial was that this would enable access to a representative population of caregivers who had specifically been involved in making treatment decisions for an older woman with breast cancer and dementia. It was thought that the caregivers may be open to participate in research having previously given assent for their relative to join the breast cancer trial and having completed baseline questionnaires by proxy.

Some of the trial sites agreed in principle but then did not reply to the invite or progress forward with R&D approval. A number of breast units with a high turnover of research nurse staff were reticent to take part in view of not having the time to look-up the caregiver address, while others had concerns over burdening caregivers with additional research while supporting a relative through their cancer treatment. I was also aware of the possibility that gatekeeping may be an issue within this group of patients and caregivers (286). The packs were provided in a way that meant an address and caregiver name could simply be attached to the envelope and cover letter. A key learning from this part of the study would be to carry out a capacity assessment prior to applying for ethics approval to anticipate any barriers to study set-up and the study sample.

A key challenge for this study was the ethical considerations of undertaking research with a vulnerable group. Following the recommendations from the ethics committee, I was unable to send a reminder to participants who did not reply to the questionnaire, nor was I able to invite caregivers to the study where the patient they made decisions for had passed away. This means that only experiences of caregivers for the typically "healthier" participants in the dementia cohort were captured, and this introduces a bias to the findings reported.

The final issue is that a full pilot of the questionnaire was not possible due to the lack of access to caregivers and the failure of the initial focus group. The questionnaire content was developed together with cancer clinicians and a PPI group, however, there was a lack of caregiver perspectives in the pilot to measure face validity. The use of a validated instrument would have been ideal for a postal questionnaire, if one indeed did exist. A key learning from this would be to start involving PPI input much earlier on and organise multiple focus groups in the event of cancellations.

10.4.6. Interview reflexive account

The use of qualitative interviews for exploring experiences, opinions and perspectives are increasingly being used to research caregiver experiences (156, 244). The

interview topics were partly driven by the treatment choice of PET or surgery, as this was an inclusion criterion for participants joining the Bridging the Age Gap trial.

Over half of the questionnaire respondents agreed to participate in an interview. Despite general low uptake, this meant that I had the capacity to interview all those who initially expressed interest in taking part, with no selection bias based on location. Recruiting until saturation of themes meant that there was a trade-off between meeting the requirements of the ethics committee and being able to more fully understand the issues faced by caregiver. A key learning from this part of the study would be to establish face-to-face contact with participants at the point of consent and recruitment to the study, in place of relying on centres to post out packs.

Another key consideration is retrospective recall. The duration of time from diagnosis and questionnaire completion varied, meaning that some caregivers were retrospectively recalling events that took place up to a year prior to the interview. The nature of a semi-structured interview is that some interviews will be more in-depth than others, depending on how off-topic the conversations go. During the analysis stage, it became clear that in terms of consistency, not all questions were asked to each interviewee. This was often at the discretion of the researcher where it was clear that the interviewee was becoming upset, and the interview was paused or a change in topic was initiated to maintain the flow of the interview. A key learning from this component of the study was that caregivers appeared to be more at ease talking in detail over the telephone rather than face-to-face, as the telephone interviews were often more in-depth and longer in duration. The anonymity afforded by speaking on the telephone may have allowed participants to 'open up' more, particularly as the researcher was not known to the caregiver prior to the interview.

Another issue was selection bias, as the caregivers for patients who had passed away were excluded from the study population. This decision was based on points raised at the REC meeting, which advised against exposing caregivers to undue harm and distress, particularly where a patient had passed away in the timeframe between

completing the questionnaire and taking part in the interview. In my position as a researcher, I agreed with this approach and felt it may cause unnecessary harm to ask caregivers to reflect on decisions which may have led to their relative passing away. As a result of this decision, this may have skewed the study findings, as only caregivers with a relative who was still alive took part in both phases. The caregivers interviewed were self-selected using a volunteer response method, which means that the characteristics of the sample may be different to the five caregivers who returned the questionnaire but did not take part in the interview.

Prior to the interview, I took care to revisit the answers given in the caregiver's questionnaire as part of the planning exercise for the interview. I felt this approach would avoid asking the caregiver irrelevant questions and allow them to feel that their responses in the questionnaire had been heard and acknowledged. I was prepared for the possibility that because of the sensitive nature of the topic, caregivers may not necessarily feel comfortable disclosing the truth, for fear of what may happen if they disclosed what may be perceived as an unethical decision. Being aware of the study aims, caregivers may also simply have reported what they presumed I wanted to hear. I kept these reflections in mind when analysing the transcripts. The findings generated represent my interpretation of the subjective experiences of caregivers. To reduce research bias, I discussed emerging findings with other researchers, including my PhD supervisors, and agreed mutually on the themes constructed from the data.

Throughout the interviews I was aware that the caregivers were revealing their personal thoughts and sensitive information to me about the person they provided care for. Prior to beginning the interview, I established rapport between myself and the respondent, to ensure that they felt at ease when sharing their stories and experiences with me. In terms of discussing the topic of treatments and breast care, I was mindful of giving my own personal opinions or judgments in case this would unduly influence or bias the responses from participants. I was also careful not to express an opinion on the treatments or decisions they made, as the focus of the interview was to find out their opinions, not to make judgements on their decision-making.

10.5. Dissemination and communication of findings

A lay summary of the study findings was posted to the caregivers who took part in the study and provided their details for future contact.

Presentation and publications of findings:

- Publication of the cohort analysis in the Journal of Geriatric Oncology, 2020
- Publication of the systematic review in Psycho-oncology journal, 2019
- Poster presentation at the Dementia Futures conference in 2019
- Poster presentation of treatment analysis at the NCRI conference in 2018
- Poster presentation of methodology at Medical School Research Day 2017

Chapter Eleven: Conclusions

11.1. Summary of thesis findings

The aim of this study was to explore the experiences of caregivers involved in making treatment decisions for older women with breast cancer and dementia. The wider literature highlighted some of the key concerns regarding the management of patients with a dementia-cancer diagnosis and the complex issues that influence treatment decisions. The cohort treatment analysis found evidence of higher PET use amongst women with severe dementia, suggesting that cognitive impairment may play a significant role in deciding how to treatment older women with breast cancer. Caregivers who participated in this study were generally satisfied with the level of support, time and information they received while making treatment decisions, although information was rarely tailored towards the needs of a patient with cognitive impairment.

11.2. Conclusion

Making cancer treatment decisions for older women with dementia remains a complex issue. This study provides new insights into the role of the caregiver in facilitating discussions, their information needs, and the factors that influence treatment decisions.

11.3. Implications for clinical practice

This study highlights some key areas for improving the experiences of caregivers and people with dementia. As shown in this study and the wider literature, older people with dementia have additional needs which should be met through careful planning prior and during the cancer consultation. Having adequate information about the patient's diagnosis of dementia and additional background information may address the stress burden on caregivers who are tasked with highlighting this to the cancer clinician. The lack of dementia-cancer information provided to caregivers suggests that a more tailored and personalised approach should be used when discussing treatments.

In terms of clinical practice, this study highlights the need to avoid taking a generic approach toward the care of older people living with dementia, in order to optimise their treatment plans. This includes challenging ageist perceptions that some people are considered “too old” to undergo certain treatments. There are few guidelines in place for treating women with dementia, and in the literature, there is division amongst breast clinicians on how they should be treated. There is a clear need for evidence-based guidelines that can be referred to when treating women in this group.

Finally, dementia awareness training for breast cancer clinicians would address issues that are specific to the needs of cancer patients who are living with a dementia diagnosis. Training clinicians to be aware of these needs would also increase the visibility of their caregiver within the consultation and make better use of their knowledge and judgments. Areas to focus on include being able to recognise the needs of patients with dementia and being able to advise on how their breast cancer treatments may potentially interact with their dementia treatment. This could also be achieved by having a specialist cancer-dementia nurse in clinic to advocate on the behalf of people living with dementia, give tailored advice about their treatments, and signpost their caregivers towards support services available to them.

11.4. Recommendations for future research

This study has highlighted some key areas for further research. The first is the need to undertake more research into the lived experiences of people with dementia and their caregivers in a cancer context. Exploring these experiences can be used to help shape services that best meet their needs and develop a nuanced understanding of the level of support needed to make breast cancer treatment decisions. The study highlights some of the study design issues involved in researching and recruiting vulnerable groups where sensitive topics are discussed. Ethics committees are very aware of these problems and it is for those reasons that research into vulnerable people is a sensitive area that requires an experienced researcher and sometimes taking a different approach.

Some suggestions for addressing these needs include trialling tailored breast care specific information aids, factsheets or guidelines that are relevant to the concerns of dementia caregivers. This was recently explored by the Bridging the Age Gap trial, which trialled a combination of decision support tools including an online tool, patient facing booklets and an option grid aimed at older women. The long-term aim of the Age Gap study was to establish an online decision support tool, which can now be used free online (agegap.shef.ac.uk). It would be useful to build on these tools to address the needs of caregivers and support proxy decision-making as a component of shared decision making.

Finally, the study highlighted that some women with dementia are more likely to be treated differently when compared to women with normal cognition. Further research could explore the clinician perspective on the treatments they recommend and identify the ways in which dementia training could be incorporated into the breast cancer care pathway.

Appendix

12.1. Appendix 1: Study Protocol

Proxy decision making for older women with cognitive impairments and breast cancer

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Lay Summary

One third of all breast cancers in England are diagnosed in women over the age of 70 (129).

The UK's ageing population is growing rapidly, with 1 in 6 people now aged over 65 (294). Within this demographic, the prevalence of dementia is around 10.5% (34), with the implication being that approximately 1260 women with cognitive impairment each year are likely to present with breast cancer.

Older adults with late-stage dementia are likely to lack mental capacity to make decisions regarding their breast cancer treatment, and subsequently treatment decisions may rely on a proxy (i.e., their formal or informal carer making a decision on the patient's behalf). This is an important area of research as studies have found that older women with breast cancer are generally treated less aggressively than younger women (135, 295) and are less likely to receive gold standard care for their cancer (surgical intervention, chemotherapy, radiotherapy) (111). Little is known about how decisions are made for this sub-population of older women with co-existent dementia, and there are limited decision-making recommendations tailored specifically towards older women with dementia and a breast cancer diagnosis.

This study will use a pragmatic sequential explanatory mixed method approach to explore the experiences of caregivers who are involved in making a proxy treatment decision. The purpose of this study will be to understand how proxy decisions are made and the factors that impact on carers.

The results from this study will contribute to the wider literature addressing the needs of caregivers and guide best practice towards proxy decision-making in breast cancer care.

Background

Ageing Population

The most widely accepted chronological age definition of an older adult in the developed world is 65 years old (1). In the UK, 1 in 6 people are aged over 65, with a projected life expectancy of 78.8 years for males and 82.2 for females (294). The UK population has experienced a rapid demographic change over the past 25 years in response to the rise in living standards, treatment advances and control of chronic disease in the elderly. People are living longer than ever before, and Britain is now faced with an ageing society with all the complex comorbidities and disease burdens this brings.

According to NHS guidelines, when planning treatment it is best practice to acknowledge that older adults are a diverse population with varied needs and preferences (17). Within this demographic, older adults are a very heterogeneous group: some with limited health needs who live independently, and others with high levels of dependency and complex care needs (296). Advancing age is also associated with frailty, which is not a diagnosis, but a common syndrome (297) that increases the risk of falls, disability and mortality in older people (298). To ensure that older people receive appropriate treatment, a Comprehensive Geriatric Assessment (CGA) is viewed as the gold standard for assessing an older patients' needs (299). This is an interdisciplinary diagnostic process that includes assessments such as the Eastern Cooperative Oncology Group (ECOG) Performance Status, Mini Mental State Examination and Geriatric Depression Scale (300). Despite having a strong evidence base for its effectiveness (301), delivering a CGA is a lengthy process that can be difficult to implement in clinics (302), and consequently may not always be used when assessing older adults.

Dementia

In the UK it is estimated that around 800 000 people suffer from some form or degree of dementia (303), costing the UK economy approximately £23 billion each year (304). Longitudinal data from the past 20 years indicates that the prevalence of dementia varies demographically between age-subgroups and by gender (35). Age is a primary risk factor, however it is a misconception that dementia is a normal side effect of the ageing process (29).

Dementia describes a syndrome characterised by a long-term (>6 months) loss of cognitive capacity, of varying aetiology, in someone of previously normal intellectual function. The International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) are primarily used as diagnostic criteria for dementia subtypes in the UK. The diagnostic process will usually begin in primary care, when symptoms present via a GP. Following assessment, the patient will then be referred to a specialist service where a specific diagnosis will be made (75). An early diagnosis of dementia is vitally important as it allows people the opportunity to access

timely treatments and support (305), as well as empowering people to plan ahead for their future care while they still have capacity to make decisions (306).

Dementia may be static or progressive and of variable severity. In its mildest stages, individuals may function relatively well in society, while at its most severe they may require 24-hour personal care. Many forms of dementia are progressive, and treatment varies according to onset, sub-type and aetiology. The most common causes of late-onset dementia are Alzheimer's disease, vascular occlusive disease and dementia with Lewy bodies (307), while frontotemporal dementia is more often associated with young-onset (under 65s) dementia (308).

Caregiving

It is estimated that there are around 670 000 unpaid carers for people with dementia in the UK (303). Family caregivers are most often the main source of informal provision (17), providing the day-to-day support that allows people with dementia to continue residing at home. Some carers may even be old and frail themselves. The reality of caring for an older person with complicated care needs can be complex both emotionally and psychologically (296), with some carers adopting the role of 'carer' in the early stages of the disease when the person may not need as much help (309). In cases where caring for an older person becomes too challenging (both financially and physically), the involvement of patient advocates, support workers and paid carers may be involved in care provision. This is often the case when functional decline becomes severe, and in the late advanced stages of dementia, patients may eventually be moved into residential or nursing care homes.

In its later stages, some individuals with dementia require 24-hour personal care, and so it could arguably be in their best interests to reside in a care home if their treatment and care needs cannot be met within the community. The majority of nursing homes operate under a 'person-centred' principle, allowing input from both patients and their caregivers in their treatment plans (75). Within this domain paid professional care staff are able to assist with a wide range of physical and personal support, depending on the level of care needed.

Breast Cancer

Breast cancer occurs predominantly in women, with one third of all breast cancers occurring in women over the age of 70 (86), representing 12 000 women in the UK annually. In this age group of women, the prevalence of dementia is around 10.5% (34) with the implication being that approximately 1260 women with cognitive impairment each year are likely to present with breast cancer in the UK.
There are numerous risk factors associated with breast cancer development, the strongest of which is age (310). Other risk factors add to this, such as a lifetime of exposure to carcinogens, environmental factors and lifestyle choices (90). Older women are also more likely to have a delayed breast cancer diagnosis due to lack of breast awareness (311) and lower screening uptake in the over 70s (131, 312). Comorbidities and age are also known to influence the type of breast cancer

treatments that older women receive and impact on their survival after breast cancer (10, 139).

Research shows that older women are generally less breast aware than younger women, check their breasts less often and many do not attend screening after the age of 70 (131). Most western countries do not routinely offer breast screening to women over the age of 70, although the NHS is currently running a randomised controlled trial to extend screening to the age of 73 (129, 130). In the UK, although women over this age can request screening with no upper age cut-off; most are either unaware of this facility, forget to attend or have a perception that they are no longer at risk (131). Such perceptions may contribute to older women presenting later with higher stage/grade breast cancer (313) and a poor survival rate (314). This may impact on both treatment needs and long-term survival outcomes.

Treatment for Older Women with Breast Cancer

In practice, it is recommended that older women (>70 years) should be considered for the same gold standard treatment (surgery, radiotherapy and systemic therapy) as younger women (315). For women who are unsuitable for surgery (such as those with oestrogen receptor (ER) positive tumours and either a short predicted life expectancy, or who are considered too frail to tolerate surgery), primary endocrine therapy may be offered as an alternative to surgery (126).

Despite these recommendations, evidence shows that these guidelines are not being followed (316) and that older women with breast cancer are generally treated less aggressively than younger women (135, 295). Furthermore, a lack of cohort data on local disease control in older frail patients indicates that new recommendations for management are needed (120, 317). Evidence-based International Society of Geriatric Oncology (SIOG) Guidelines recommend that surgery should not be denied to patients on the basis of age alone, although older women continue to have a lower surgery rate than younger women (10, 318). This is despite the significant advances in successful surgical intervention for older populations (319).

Co-morbidities are much more likely to complicate the treatment options of people with cancer, particularly the old and frail, and there is evidence that suggests older people with comorbidities, particularly dementia, are less likely to undergo aggressive cancer treatments than younger women (153). This may result in an inferior prognosis for this population of women (10). The practical implications of dementia in cancer care means that some treatment pathways will be very challenging to administer. At its simplest level, women taking anti-oestrogen tablets may need supervision to ensure that they take their daily medication orally. Systemic treatment such as chemotherapy, which is often given as an outpatient delivered intravenous regime, requires significant home care to manage side effects and in some cases may need to be delivered in an inpatient setting. Chemotherapy has unpleasant side effects such as vomiting, joint pain and nausea, and so older people with co-morbidities will require substantial support mechanisms in place if they live independently. Some of the most severe chemotherapy side effects can also cause severe and life-threatening

neutropenic sepsis, cardiac failure, rashes and allergic reactions (320). In the UK, adjuvant chemotherapy for breast cancer is rarely if ever given to women over the age of 80 years regardless of their level of fitness for these reasons (111).

Following a cancer diagnosis, treatment and care must take into account the stage and grade of cancer, and involve a clinician providing the patient with enough information to help make an informed treatment decision (321). This should include actively involving patients in shared decision-making, considering their information needs and supporting them to make a fully informed choice (315).
If a patient is deemed unable to make an informed decision, there are various laws and ethical issues relating to the assessment of mental capacity and making a decision on behalf of another individual (proxy decision-making) (168).

Proxy Decision-Making

In England and Wales, informed decision-making is enshrined in the Mental Capacity Act (MCA) (71), which seeks to safeguard individuals who are unable to make their own treatment decisions. This code of practice is underpinned by the principle that capacity must be assumed unless it can be established that a person lacks capacity to make his or her own decisions (166). One of the well- established side effects of dementia is the reduced ability to make rational decisions (167); meaning that at some point a proxy decision-maker may have to take over this responsibility. In some cases, caregivers assume the role of both a decision-maker and service provider (such as a clinician or paid carer) and this will involve navigating which services and treatments are most appropriate for patients (169).

In medical ethics, there are a number of philosophical approaches to making treatment decisions. In terms of proxy decision-making, Buchanan and Brock (171) define three main models that underpin this process: advance decisions, substantiated judgement and best interests.

Advance Decisions

A key principle of the MCA is to optimize self-determination by allowing patients the opportunity to make an autonomous decision (where and if they can). Autonomy is the capacity of an individual to use his or her own agency to make an informed decision free from coercion (170), however for individuals with dementia, this capacity to be autonomous declines over time. In instances where an individual has diminished capacity (such as mild cognitive impairment) the patient may still be capable of making a rational decision, and this can be achieved by advance care planning (ACP) (173).

An ‘advance statement’ describes any written statement or discussion where a patient has expressed the type of care they wish to receive in the future. An ‘advance directive’ is a legally binding document that instructs the refusal of life-sustaining treatment (such as a ‘do not resuscitate’ order) (166). The philosophical basis for ACP is that it extends the notion of patient autonomy into the future by allowing patients to actively make decisions about their treatment and care while they still can. ACP

therefore empowers patients to state their care preferences in the event of losing capacity, and designate an individual as a health care proxy to make decisions on their behalf (174). One value of ACP is that it relieves some of the burden on caregivers (175), whereby an advance decision can help guide proxies towards a particular treatment that best represents the patient's wishes before losing capacity.

Substituted Judgement

Substituted judgement is a decision-making framework that is often used when there are no advance directives in place to inform treatment decision-making. This involves making a decision based on what the patient would want if they could decide for themselves (176). Making this judgement entails gathering information about the patient's previously expressed preferences, values, attitudes and beliefs, and considering any advance decisions made by the patient before losing capacity (166). The fundamental underpinning of the substituted judgment model is that the patient's right to self-determination should be upheld - and if individuals with dementia do not have an advance directive, substituted judgment is often used to make important decisions around care and treatment.

Lasting Powers of Attorney (LPA), established in UK law under the MCA, allow patients to legally appoint an individual with the power to make decisions on their behalf in both substituted judgement and best interest models (177). In the UK, a Health and Welfare LPA is commonly used to give or refuse consent to treatment and make decisions about care and living arrangements. Evidence suggests that older adults with dementia prefer that close family are involved in the decisions about their treatment and care (178), as they will have access to the patient's biographical narrative and allow them to make decisions that are consistent with the patient's preferences. Substituted judgement also allows proxies to 'frame the decision as the patient's own choice,' relieving some of the psychological burden entailed in making a choice for the patient themselves (179).

Best Interests

The best interests model differs from substituted judgement in that it requires the proxy decision-maker to base a decision on an assessment of the individual's 'best interests' (166). This model is often accessed when there is limited information about the wishes and preferences of the patient. The application of this approach rests on the principles of beneficence (positive benefit of treatment) and non-maleficence (avoiding unnecessary harm) (170) to promote the patient's best interests. In practice, this involves weighing up the risks and benefits of treatment available, with the law stating that any decision should not be motivated by a desire to bring about the death of someone with incapacity (71). Section 4.6 of the MCA stipulates a statutory checklist of factors to consider when making a proxy decision, specifying that decisions should take into account the patient's past and present wishes, and beliefs (71, 177).

For any complicated decisions such as a procedure that may have both beneficial and harmful consequences for the patient (for example, surgical risks associated with

general anaesthetic for an elderly frail individual) a best interests meeting is usually held. This is a documented formal meeting that can be attended by anyone concerned with the patient's welfare, such as family, formal carers, close friends or other health care professionals. Independent Mental Capacity Advocates (IMCAs) may also be invited to best interests meetings if there is conflict over the patient's care, or there is no close family to make decisions based on their treatment (180).

The literature shows that there is little evidence of research that has explored proxy decision-making within this population, and even less on the psychosocial impact or emotional effect on caregivers. This demonstrates the need for research in this field. The following research study will attempt to explore some of the issues taken into account by caregivers and proxy decision makers in relation to older women with impaired mental capacity when considering their breast cancer treatment options.

Aims and Objectives

Research Question

How do caregivers make proxy treatment decisions for older (>70 years) cognitively impaired women with breast cancer?

Aims

To explore the views and opinions of caregivers towards making a proxy decision.

To investigate how proxy decisions are made for older (>70 years) women that lack the capacity to make a treatment decision themselves.

To determine the psychosocial and emotional effects involved in making a proxy decision and how this impacts on caregivers.

Objectives

To review the current literature focused on breast cancer decision-making for people with cognitive impairments and the psychosocial impact on caregivers.

Use of a quantitative questionnaire to investigate how proxy decisions are made. Statistical analysis will be used to quantify proxy decision-making processes.

Use of qualitative semi-structured interviews to explore in-depth the subjective experiences (including psychosocial effect and emotional effects) of caregivers involved in proxy decision-making.

Synthesis of themes using the Framework Approach will establish the types of decision-making models used and how proxy decision-making impacts psychosocially on caregivers.

Research Design and Methodology

Pragmatic Approach

This research study will use a pragmatic sequential explanatory mixed method approach to explore the experiences of caregivers responsible for making a proxy decision. A pragmatic approach has been chosen as this will allow the use of any well-established research techniques typically associated with quantitative and qualitative methods to optimally explore the research question (190).
Qualitative, quantitative and mixed method approaches

The field of mixed methods incorporates components of both qualitative and quantitative paradigms to form a multi-method approach (322). Qualitative methods such as interviews and cohorts are now being used more often in health research, as they are able to generate rich detailed information on subjective experiences; reaching areas that cannot always be achieved by using quantitative methods alone (323). Qualitative research is also useful for studying small samples in-depth (324) and interviews are valuable for investigating the meaning and perceptions behind decisions (325). Quantitative research is an empirical method of inquiry that involves generating numeric data through standardized processes to draw statistical conclusions. Randomized control trials and questionnaires are often performed in this way as they have the potential to generate robust statistical analysis (187).
The development of mixed methods emerged as a response to the shortcomings of using one method (192), combining multiple approaches so that the overall strength of a study is greater than using one method alone (190). The recent surge of international interest in combining qualitative and quantitative methods has led to the publication of the *Journal of Mixed Methods Research* and significant attempts have been made to establish mixed methods as the third paradigm (188, 326). As a result, mixed method approaches are now widely advocated in the health and social research field (327, 328) and best practice guidelines have been developed by Creswell et al (329) to assist mixed method researchers within this field.

Study Design

The mixed method strategy to be used for this study is a *sequential explanatory* design (187), which involves the collection and analysis of quantitative and qualitative data in two separate consecutive phases (Figure 1).

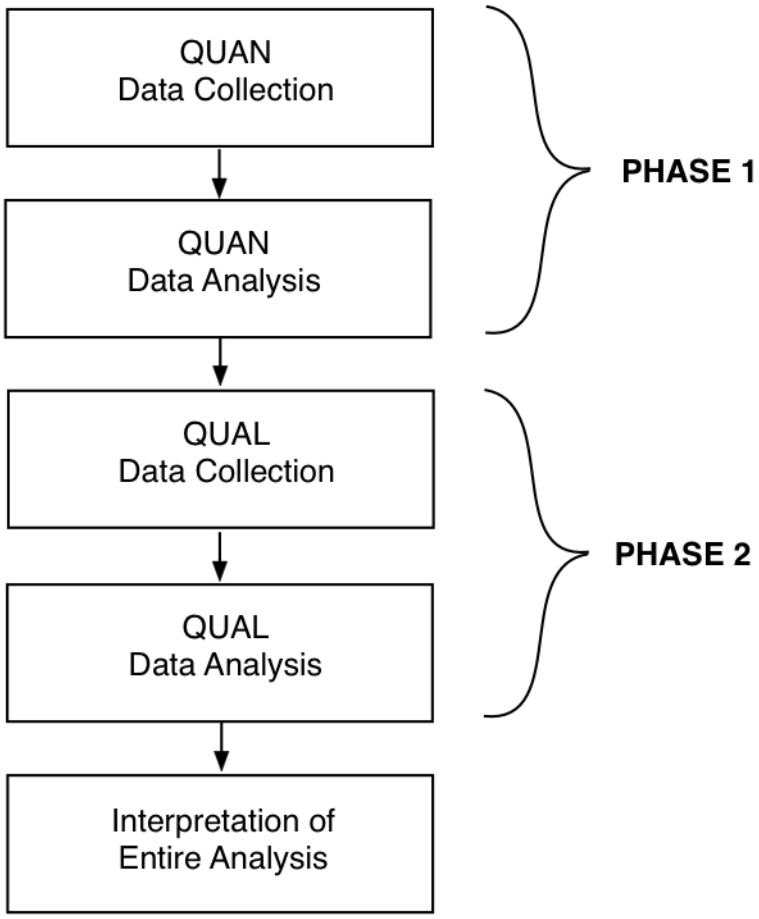


Figure 1: Sequential Explanatory Design. Source: Figure 7.4. Sequential Explanatory Design, p180. (193)

Phase 1 of the study will involve quantitative data collection using a structured questionnaire followed by Phase 2, which will sample a subset of questionnaire respondents with a semi-structured qualitative interview. Data analysis of Phase 1 will inform the design and refinement of a semi-structured interview schedule through direct interaction of quantitative and qualitative strands of the methodology.
The results from both phases will be combined to provide an integrated mixed method analysis (330).

The key areas that will be covered by the questionnaire will include:

Section 1: Demographics (details about the caregiver)
Section 2: Caregiver Relationship (details about the relationship to the person they care for such as how long they have provided care for)
Section 3: Information Needs (any information accessed and provided by the hospital while making a decision)
Section 4: Making the decision (recall of the types of treatment that were recommended and which treatment the caregiver chose)
Section 5: Decision Making Models (asking the caregiver to identify which decision-making model (advance decision, substituted judgement, best interest) best matched the decision made.

Section 6: After making the decision (asking for detail about decision regret)
Section 7: Final thoughts (any additional information on proxy decision making)

The qualitative interview will explore each topic in more detail, focusing on psychosocial and emotional impact involved in decision-making.

Pilot and PPI Involvement

Subject to necessary ethics and governance approval, the Phase 1 questionnaire will incorporate involvement from local carers based in Sheffield and the North Trent Consumer Research Panel. This will ensure that the design of the questionnaire works in practice, and identify any issues relating to the appropriateness of questions and the time taken to complete. The pilot will sample a small population of carers for people with dementia, however these will not be included in the final sample or any published analysis. The final questionnaire will be submitted as an amendment when finalized.

Diagram of Study Design:

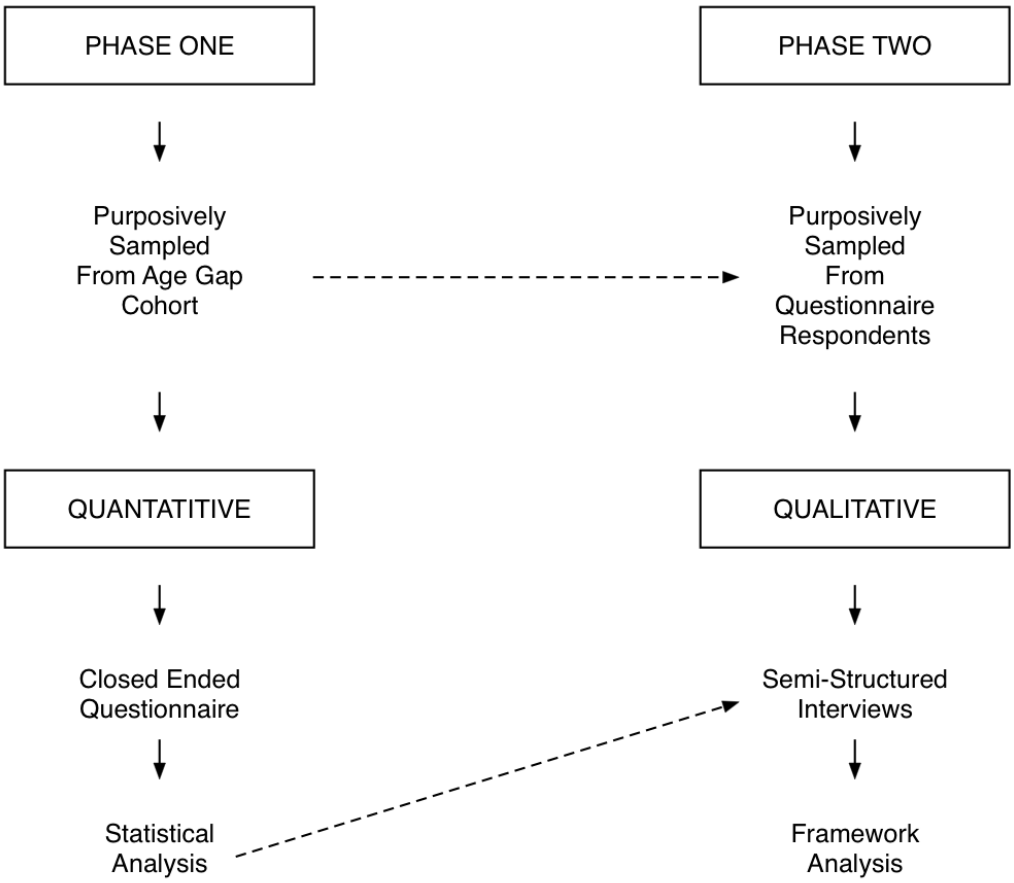


Figure 2: Study Sequence.

Study Sample

A purposive sample of caregivers will be taken from a UK cohort study, *Bridging the Age Gap*, which is a NIHR funded study of cancer outcomes in older women >70 years (201). The eligibility criteria for *Bridging the Age Gap* includes older women with cognitive impairments who have been assented to the study by a close friend or relative able to give informed consent on the patient's behalf. This is a good indicator that the person giving consent will have been involved in the care and decision-making for an older woman with breast cancer.

Quantitative Sample

All caregivers for cognitively impaired women taking part in the *Bridging the Age Gap* dataset will be invited to complete a quantitative questionnaire (for inclusion criteria and recruitment details see Phase 1: Quantitative Method). Around 9% of patients enrolled to *Bridging the Age Gap* have been assented by a consultee and therefore approximately 109 caregivers would be eligible to take part. Caregivers that complete the questionnaire will be asked if they wish to take part in a qualitative interview and permission for the PhD researcher to contact them directly.

Qualitative Sample

Caregivers that opt to take part in Phase 1 will be invited to participate in a qualitative interview (for inclusion criteria and recruitment see Phase 2: Qualitative Interviews), based on the completion of the quantitative questionnaire and consent given to take part in an interview. Purposive sampling will be used to select caregivers to participate based on location and convenience. Qualitative research is not overly concerned with statistical representativeness, and so the rational for using a convenience sample will address the impracticalities where one PhD researcher is undertaking both the qualitative data collection and analysis.

Data Analysis

Quantitative Analysis

The questionnaire will consist of structured close-ended questions utilising Likert Scales (331) and checklist type questions. This design has been chosen as responses will be easy to code, evaluate and statistically analyse. Analysis of questionnaire data will be undertaken using statistical analysis (descriptive statistics, inferential statistics and effect sizes) to analyse responses. This will then facilitate the selection of participants and interview design for the follow-up qualitative phase.

Qualitative Analysis

The interviews will consist of structured and open-ended questions using an interview guide approach (332). This strategy has been chosen in order to explore interesting or ambiguous survey responses and emergent themes in depth. Thematic analysis of

interview transcripts will be approached using a Framework Approach (224, 239). This involves using a 5 stage process (223) to organize and categorize qualitative data for themes using a coding scheme in NVivo.

Interpretation of Entire Thesis

Qualitative and quantitative analysis will be integrated using an iterative analytic approach to create a comprehensive dataset. The combination of survey and quantized interview responses will be integrated through simple statistical measures such as chi-square to statistically compare and validate the data collected separately.

Phase 1: Quantitative Method

Recruitment

All research sites that agree to participate will post an information pack to caregivers who have assented a participant to the *Bridging the Age Gap* study. The PhD researcher will identify participants by cross-referencing the assenting caregiver with the corresponding contact details listed in the patient records. Caregivers over the age of 18 years old, from any ethnic background and gender are eligible to participate if they have been involved in the decision making of a patient's cancer treatment and meet the inclusion criteria below. The information pack will comprise of a cover letter, participant information sheet, a postal consent form, decision-making questionnaire and a pre-paid envelope. The local research team or the PhD researcher can undertake this role of posting information packs on site.

Inclusion Criteria

- An individual who is an adult caregiver with the following characteristics:
- Aged 18 years and over
- A formal or informal carer for an older woman (>70 years) with cognitive impairment
- Capable of giving informed consent
- No known cognitive impairment
- An individual who is a caregiver for a patient with the following characteristics:
- Female
- Aged over 70 years of age at the time of diagnosis of cancer
- Primary operable (TNM categories: T1, T2, T3, N0, N1, M0) invasive breast cancer.
- Formal diagnosis of cognitive impairment (ICD-10 categories: F00.0-F00.9, F01.0-F01.9, F02.0-F02.8, F03) or an MMSE score indicating severe cognitive impairment.
- Incapable of giving informed consent to their breast cancer treatment
- An individual who is involved in the treatment decision-making for a person with mild/moderate/severe cognitive impairment (as defined by clinician).
- An individual who is willing to complete a questionnaire

Exclusion Criteria

- An individual who is a not a formal or informal caregiver for a patient with primary operable breast cancer and has a diagnosis of cognitive impairment.
- A carer who themselves has a severe cognitive impairment and is unable to give informed consent to take part in the study.
- Individuals who are unable to complete a questionnaire in English language.

Data Collection

Questionnaires

The quantitative phase of this study will involve completion of a decision-making questionnaire that measures the opinions and attitudes of caregivers who have been responsible for making a proxy decision. The questionnaire will be developed by the PhD researcher, as there are currently no other validated tools that can be used to measure this specific area of decision-making. The purpose of using a questionnaire will be to obtain statistical quantitative results from a purposive sample of caregivers, and follow-up with an interview to explore the responses in more depth.

Safety endpoints

An information sheet will be attached to the questionnaire outlining how to answer questions and a contact number to get in touch with the PhD researcher if there are any issues. Participants will be allocated an enrolment number by the local research team and the identity of patients will not be disclosed to the PhD researcher unless they agree to take part in a qualitative interview in Phase 2.

Some of the questions will refer to personal care of another person and may be interpreted as intrusive. To minimise this burden, the questionnaires can be completed in the participant's home and posted back to the researcher, and the information sheet will remind participants that they are not obligated to answer any questions that they feel uncomfortable with. If the carer does not wish to complete the questionnaire, this will be respected, and they can choose not to return the questionnaire if they wish.

Phase 2: Qualitative Interviews

Recruitment

Participants will be purposively selected from caregivers that agree to take part in the quantitative phase of the study and give consent to be contacted directly by the PhD researcher. The PhD researcher will contact the caregiver within 3 months of expressing interest to reiterate the aims of the study and confirm that he/she is still happy to proceed with the interview. The caregiver and researcher will then agree on a convenient time/place to take part in a semi-structured interview. Only those caregivers who indicated willingness to take part in the interview phase of the study will be contacted in this way.

Inclusion Criteria

- An individual who is an adult caregiver with the following characteristics:
- Aged 18 years and over
- A formal or informal carer for a patient with cognitive impairment
- Capable of giving informed consent
- No known cognitive impairment
- An individual who is a caregiver for a patient with the following characteristics:
- Female
- Aged over 70 years of age at the time of diagnosis of cancer
- Primary operable (TNM categories: T1, T2, T3, N0, N1, M0) invasive breast cancer.
- Formal diagnosis of cognitive impairment (ICD-10 categories: F00.0-F00.9, F01.0-F01.9, F02.0-F02.8, F03) or an MMSE score indicating severe cognitive impairment.
- Incapable of giving informed consent to their breast cancer treatment
- An individual who is involved in the treatment decision-making for a person with mild/moderate/severe cognitive impairment (as defined by clinician).
- An individual who is able to participate in an interview in English language

Exclusion Criteria

- An individual who is a not a formal or informal caregiver for a patient with primary operable breast cancer and has a diagnosis of cognitive impairment.
- A carer who themselves has a severe cognitive impairment and is unable to give informed consent to take part in the study.
- An individual who is unable to take part in an interview conducted in English language.

Data Collection

Semi-structured interviews

The qualitative interviews will be undertaken by the PhD researcher to establish how caregivers make decisions about the patients' breast cancer treatment in-depth. Key questions will be grouped into themes and asked in the same order to all interviewees. The interviewer will pause, prompt and probe inductively on key responses and record reflective notes of the interview throughout the process. All interviews will be transcribed and analysed by the PhD researcher for this study.

Conduct of interviews

The interviews will last for approximately 45-60 minutes and will be guided by Kvale's (215) seven stages of an interview investigation (215). This will include using a range of probing, follow-up and direct questions (Table 1)

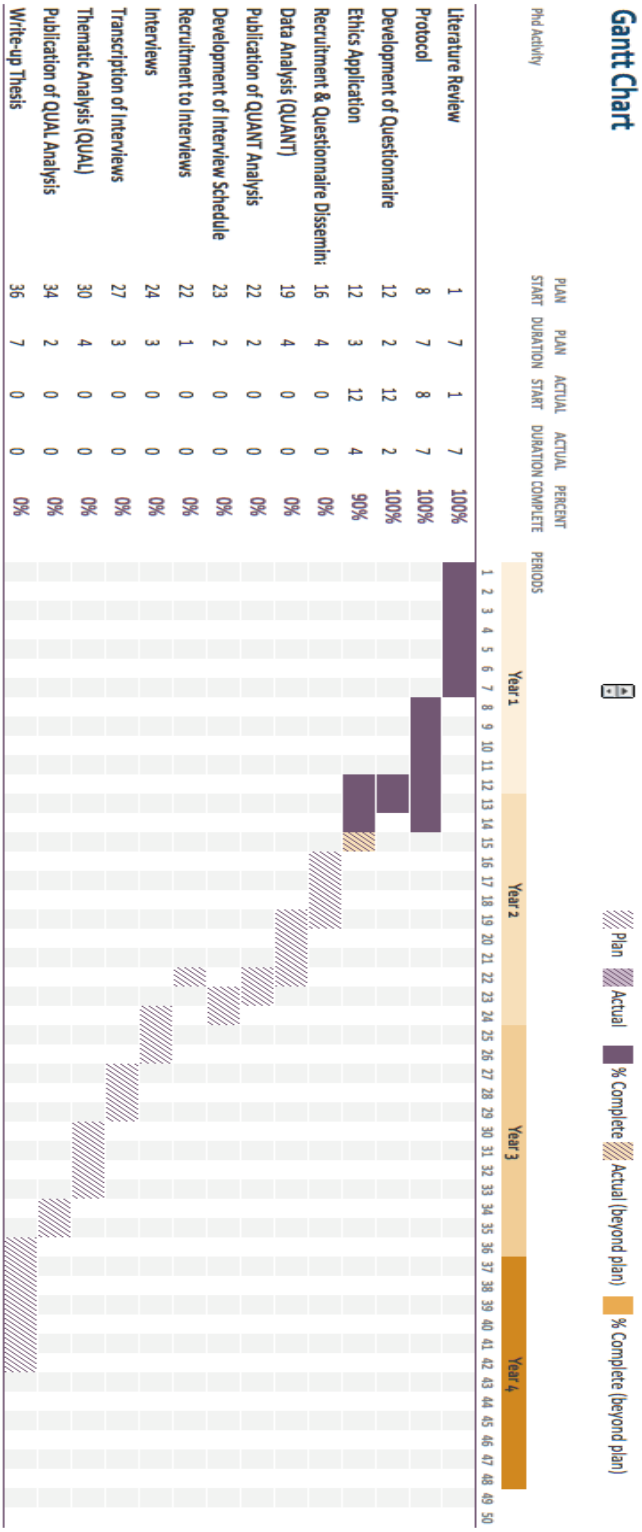
Table 1: Example Interview Questions

Type of Interview Question	Example
Introducing question	"Can you tell me about how you first came to be involved in the decision making for another person?"
Follow-up questions	"Had you been involved in any treatment decisions for another person before?"
Probing questions	"Could you give me some examples of decision-making aids or resources you considered while making the decision?"
Specifying questions	"How did you feel throughout the decision-making process?'
Direct questions	"Do you think that you made the right decision?"
Indirect questions	"How do you think your [relative/spouse] would have made that decision? Do you believe your [relative/spouse] would have made the same choice if they could decide for themselves?"
Structuring questions	"I would now like to introduce another topic…"
Interpreting questions	"Can you explain what you meant back when we discussed how you felt throughout the decision-making process"

Source: Table created using 'types of interview questions' (215)

It is important to establish a relaxed rapport with participants, and so the interviews will be undertaken in a setting most convenient to the interviewee. It is anticipated that this will either be in the carers' own home or a pre-booked interview room. Refreshments will be made available and travel expenses will be reimbursed for any participants who travel to attend the interview. If the participant is unable to attend a face-to-face interview, then the interview will be conducted over the telephone. With the interviewee's permission, the interview will be digitally recorded and transcribed using number identifiers in place of names. If a participant becomes upset or distressed by any of the questions discussed, the interview will be paused for a break and resumed when/if the caregiver feels able to continue.

Gantt Chart


Gantt Chart
Phd Activity
PLAN START
PLAN DURATION
ACTUAL START
ACTUAL DURATION
PERCENT COMPLETE
PERIODS
Year 1
Year 2
Year 3
Year 4
Plan
Actual
% Complete
Actual (beyond plan)
% Complete (beyond plan)
Literature Review 1 7 1 7 100%
Protocol 8 7 8 7 100%
Development of Questionnaire 12 2 12 2 100%
Ethics Application 12 3 12 4 90%
Recruitment & Questionnaire Dissemin 16 4 0 0 0%
Data Analysis (QUANT) 19 4 0 0 0%
Publication of QUANT Analysis 22 2 0 0 0%
Development of Interview Schedule 23 2 0 0 0%
Recruitment to Interviews 22 1 0 0 0%
Interviews 24 3 0 0 0%
Transcription of Interviews 27 3 0 0 0%
Thematic Analysis (QUAL) 30 4 0 0 0%
Publication of QUAL Analysis 34 2 0 0 0%
Write-up Thesis 36 7 0 0 0%

Ethical Considerations

Research involving vulnerable people

Before making contact with the caregiver to participate in the interview, the PhD researcher will check with the Bridging the Age Gap team for recent information about the circumstances of the individual that they care for. If the person they care for is still being followed-up on the trial and there is evidence that the person has been seen in the last 2 months, the recruiting centre will be contacted to ensure the person is still living. If a study withdrawal or death has been completed, the caregiver will be withdrawn from the study.

The content and line of questioning may involve recollection of sensitive issues that could potentially cause upset and distress. Caregivers may be vulnerable to psychological and emotional distress in different degrees at different points in their lives due to the circumstances in which they found themselves at a particular time. People who have relatives and friends with poor health may feel their participation would result in access to better treatment or support for themselves or others. The main emphasis of this study is to empower caregivers to make decisions and that this process will be in some way meaningful for them. The following steps will be taken to mitigate any foreseeable risk to caregivers during their participation in this study:

- A carer support group based in Sheffield has been approached to pilot the questionnaire and give feedback on its content.
- Compliance with legal requirements set out by the ethics committee.
- Avoid use of any biased language that gives rise to unreasonable generalisations that may result in the stigmatisation of participants.
- Agree on a mutual location for the interview stage, where both the researcher and participant feel least vulnerable.
- If a participant becomes visibly upset or uncomfortable with any questions asked, the interview will be placed on hold and resumed after a break, rescheduled for an alternate date or cancelled if the interviewee prefers.
- Where participants ask for further advice such as access to services or support, the researcher will direct them to their local NHS provider, GP or a carer charity

Confidentiality

Names and addresses of potential participants will be accessed by the local research team and PhD researcher. The PhD researcher will obtain relevant site-specific approval and a research passport in order to undertake this role on site. Sites that agree to take part will post information packs to caregivers asking for permission to access their details and take part in the study. Questionnaires can be returned anonymously, and participants can remain anonymous unless they express interest in participating in Phase 2. The PhD researcher will then contact only those that have provided their details to take part in an interview.

Consent

Interest will be expressed by responding to the invitation letter, completing a consent form and completion of the questionnaire. Full written consent to participate in the

interview and consent to audio recording will be obtained by signing a postal consent form. No further attempts will be made to contact individuals that do not respond to the invite letter or refuse consent after considering the study. Individuals are free to withdraw from the study at any time.

Ethics

Research Ethics Committee approval and R&D site specific approval will be obtained before the start of the research study.

Staff

The PhD researcher for this study will have Good Clinical Practice (GCP) training and possess an honorary research contract for undertaking this research within the NHS. The PhD researcher will adhere to the ethical principles outlined in the *Declaration of Helsinki* (333) and the *University of Sheffield Research Ethics Policy.*

Data Protection

All data collected as part of this study will be in accordance with the Data Protection Act, 1998. Any information pertaining to the identity of study participants will not be released. If a participant decides to withdraw consent for their data to be used in the study, it will therefore be confidentially destroyed and not included in the final analysis.

Data Management

Electronic copies of study information will be stored on a password protected hard drive that will only be accessed by the PhD researcher. Any hard copies of study documents and data will be stored in a secure room with a locked cabinet facility. Assigning participant ID numbers will protect the personal identity of all participants.

Archiving

At the end of the study, audio files, questionnaires and transcripts will be stored at the University of Sheffield Medical School for a minimum of 15 years. After this time, it will be confidentially destroyed.

Follow-up

Participants will be asked for permission to contact them in the future for any follow-up work generated from the results of the study. This could include asking their opinions on decision aids and other materials created as a result of the study findings. If participants ask for more information regarding local services and support, the PhD researcher will direct them towards their local health care provider who can sign post them to the appropriate services.

Funding

Postage, printing and transcription costs will be supported by the *Bridging the Age Gap* NIHR programme grant funded study budget.

Complaints

If participants have any concerns or complaints about any aspect of this study, details will be provided to contact the PhD researcher, supervisor of the researcher and details to make a formal complaint to the University of Sheffield Ethics Committee.

Dissemination and communication of findings

The PhD researcher will submit the results from this study to journals and present findings at scientific meetings and conferences. Results from the study will be made available to the participant if they wish.

Potential impact of this study

The study may change guidelines for making proxy decisions for people with cognitive impairments and facilitate the groundwork for developing proxy decision aids. The results from this study could potentially have implications for policy practice and generate future research questions.

12.2. Appendix 2: Quantitative Questionnaire

Making proxy treatment decisions for older women with dementia and breast cancer

The following questionnaire will ask you some questions about how you made a treatment decision on behalf of someone that you currently provide care for, or have provided care for in the past. This may be because they were not able to make this decision for themselves or without some help.

Please read through each question carefully and take as much time as you need to give your answer. The questionnaire from start to finish should take around 15 minutes to complete. There is no right or wrong answer to each question, and your answers will be kept confidential.

Words marked with an asterix (*) are defined in the glossary on the final page.

If you have any problems with completing the questionnaire, or would like help with completing it, please contact the PhD researcher:

(Charlene Martin. Telephone: 0114 2159013. E-mail: c.l.martin@sheffield.ac.uk).

Thank you for your time and participation.

Section 1: Demographics

This first set of questions will ask for some details about you:

1. What is your age?

Please write your age below:

2. What is your gender?

Please tick one of the boxes:

☐ Male
☐ Female

3. What is your ethnic group?

Please tick one of the boxes:

White

☐ English/Welsh/Scottish/ Northern Irish/British
☐ Irish
☐ Gypsy or Irish Traveller
☐ Any other White background (please specify):

_____

Mixed / Multiple Ethnic Groups

☐ White and Black Caribbean
☐ White and Black African
☐ White and Asian
☐ Any other mixed / multiple ethnic background (please specify):

_____

Black / African / Caribbean / Black British

☐ African
☐ Caribbean
☐ Any other Black / African / Caribbean background (please specify):

_____

Asian / Asian British

☐ Indian
☐ Pakistani
☐ Bangladeshi
☐ Any other Asian ethnic ethnic background (please specify):

_____

Other ethnic group

☐ Arab
☐ Any other ethnic group (please specify):

_____

4. Where do you live?

Please write below:

_____ City / town

_____ Postcode

5. What is your main occupation?

Please write below:

Section 2: Caregiver Relationship

This section will ask some questions about your relationship to the person that you care/cared for and have made a proxy treatment decision for:

6. What is your relationship to the person that you care for?

Please tick one of the boxes:

☐ Partner
☐ Daughter/Son
☐ Sister/Brother
☐ Nephew or Niece
☐ Unrelated
☐ Friend/Neighbour
☐ Other (please specify): _____

7. How long have you been a carer for this person?

Please write below:

_____ Years
_____ Months

8. Do you live with the person that you care for?

Please tick one of the boxes:

☐ Yes
☐ No

9. How many hours a week do you spend caring for this person?

Please tick one of the boxes:

☐ 10 or less
☐ 11-20
☐ 21-30
☐ 31-40
☐ 41-50
☐ All the time

10. Are you a full-time or part-time carer for this person?

Please tick one of the boxes:

☐ Full-time
☐ Part-time

11. Do you provide informal* or formal* care for this person?

Please tick one of the boxes:

☐ Informal (unpaid)
☐ Formal (paid)

12. Do you receive any additional financial support (such as benefits) for providing care for this person?

Please tick one of the boxes:

☐ Yes
☐ No

13. Are you responsible for the care or decision-making of anyone else?

Please tick one of the boxes:

☐ Yes
☐ No

If yes, who? _____

14. Do you have lasting power of attorney* for the person that you care for? (a legal document to say that you have permission to make decisions on another persons' behalf should they ever lose the ability to make their own decisions)

Please tick one of the boxes:

☐ Yes
☐ No

15. a. Did the person you care for make any advance decisions* about their future care? (By advance decision, we mean making future care decisions while the person still has the capacity to decide for themselves)

Please tick one of the boxes:

☐ Yes
☐ No

15. b. If yes, what was decided in advance?

Please give details:

Section 3: Information Needs

This section will ask you about the information you received prior and during the time that you made a proxy decision:

16. Did you have any awareness of breast cancer prior to this person's diagnosis?

Please tick one of the boxes:

☐ Yes
☐ No

17. Did you have any knowledge of the types of breast cancer treatments available?

Please tick one of the boxes:

☐ Yes
☐ No

18. Did the hospital provide any additional information to help you make a decision?

Please tick one of the boxes:

☐ Yes
☐ No

19. Were you satisfied with the information you received at the hospital?

Please circle on the scale:

1	2	3	4	5
Strongly Dissatisfied	Dissatisfied	Neither Satisfied or Dissatisfied	Satisfied	Very Satisfied

20. Did the doctor answer all of your questions before deciding on treatment?

Please tick one of the boxes:

☐ Yes
☐ No

21. Did you make use of the following resources to help you make a decision?

Please tick the boxes that apply:

- ☐ Internet
- ☐ GP
- ☐ Friend
- ☐ Family
- ☐ Charity/Support Service
- ☐ Leaflets
- ☐ Other (please specify) _____

22. Which source of information was the most useful in helping you make a decision?

Please tick the boxes that apply:

- ☐ Internet
- ☐ GP
- ☐ Friend
- ☐ Family
- ☐ Charity/Support Service
- ☐ Leaflets
- ☐ Other (please specify) _____

Section 4: Making the Decision

This section will ask you about how you made a proxy decision for someone that you care for. This will involve recalling some of the information sources you used and how long you weighed up the pros and cons of treatment options.

23. Can you remember which treatments were offered to the patient that you care for?

Please tick the boxes that apply:

☐ Tablets (Hormone tablets such as Tamoxifen, Letrozole, Arimidex or Exemestane)
☐ Surgery (Wide Local Excision, Mastectomy)
☐ Chemotherapy
☐ Radiotherapy
☐ Unsure
☐ No

24. Did the consultant recommend a particular type of treatment?

Please tick the boxes that apply:

☐ Tablets (Hormone tablets such as Tamoxifen, Letrozole, Arimidex or Exemestane)
☐ Surgery (Wide Local Excision, Mastectomy)
☐ Chemotherapy
☐ Radiotherapy
☐ Unsure
☐ No

25. Did the consultant or breast care nurses go through the pros and cons of each treatment?

Please tick one of the boxes:

☐ Yes
☐ No

26. How long did you spend making the decision?

Please give details and delete as appropriate:

____ Days/Weeks/Months

27. Did you have enough time to think about the decision before you made it?

Please tick one of the boxes

☐ Yes
☐ No

28. Who was responsible for making the final decision?

Please tick the boxes that apply:

☐ Myself
☐ Clinician
☐ Patient made an advance decision
☐ Someone else (please specify) _____

29. Do you feel you had enough access to support and information while making the decision?

Please tick one of the boxes

☐ Yes
☐ No

30. Were any of the following factors important to you when you were making the decision?

Please tick the boxes that apply:

☐ Aftercare
☐ Quality of Life
☐ What the person you care for would have wanted
☐ Other (please specify) _____

Section 5: Types of Proxy Decision Making

Below are 3 examples of a proxy decision. Please read through these definitions carefully and answer the following questions.
Advance Decision: When a person makes their treatment wishes known in advance
Substituted Judgment: When another person makes a decision based on what the person would have chosen for themselves
Best Interests: When another person makes a decision based on what they think is important for the patient

31. Which type of proxy decision matches the type of decision you made?

Please tick one of the boxes:

☐ Advance Decision
☐ Substituted Judgment
☐ Best Interests
☐ Unsure
☐ Other (please specify) _____

32. If you could make the same decision again, what type of proxy decision would you chose?

Please tick one of the boxes:

☐ Advance Decision
☐ Substituted Judgment
☐ Best Interests
☐ Unsure
☐ Other (please specify) _____

33. Which type of proxy decision do you think is the best one to use when making a decision for another person?

Please tick one of the boxes:

☐ Advance Decision
☐ Substituted Judgment
☐ Best Interests
☐ Unsure
☐ Other (please specify) _____

Section 6: After making a decision

This section will ask you some questions about your thoughts after making a proxy decision

34. I felt happy with the decision I made

Please circle on the scale:

1	2	3	4	5
Strongly Disagree	Disagree	Neither	Agree	Strongly Agree

35.a. If you could decide again, would you make the same decision?

Please tick one of the boxes:

☐ Yes
☐ No

35.b. If you answered "no", please explain what you would have changed

36. Did you find the process of making a decision stressful?

Please circle on the scale:

1	2	3	4	5
Strongly Disagree	Disagree	Neither	Agree	Strongly Agree

37. Did you seek any support after making the decision?

Please tick one of the boxes:

☐ Yes
☐ No
☐ If yes, who/where did you seek support? _____

Section 7: Final Thoughts

38. Do you have any thoughts on proxy decision making that has not been covered in this questionnaire?

Please share your thoughts:

Section 8: Follow-up

Please indicate if you would like to be involved in any future research as part of this study:

Would you be interested in taking part in future research involving testing decision-making aids to help caregivers make treatment decisions?

Please tick one of the boxes:

☐ Yes
☐ No

Would you like to receive information about the results of this study?

Please tick one of the boxes:

☐ Yes
☐ No

Would you be interested in taking part in a follow-on interview to discuss in more detail some of the topics explored within this questionnaire?

Please tick one of the boxes:

☐ Yes
☐ No

If you answered yes to any of the above questions, please leave your contact details here:

Name:
Telephone Number:
Address:
Email:

Thank you for completing this questionnaire

Glossary

Below are definitions for some of the terms used throughout this questionnaire:

Term	Definition
Advance Decision	An advance decision is when a person makes a decision about his/her treatment and care while they have capacity to decide. An example of an advance decision may be the refusal of life-sustaining treatment (such as a do not resuscitate order). This is called 'Advance Care Planning.'
Best Interest Decision	A best interest decision involves another person basing a decision on an assessment of a person's best interests. This involves weighing up the risks and benefits of treatment available and deciding which would benefit the patient most.
Formal Care	Formal care is where care is provided by a paid caregiver (for example, a nurse in a residential care home)
Informal Care	Informal care is where the care provided is unpaid (such as a family member)
Power of Attorney	Power of Attorney is when a person legally appoints another individual to make a decision on their behalf.
Proxy Decision Making	A proxy decision is when someone makes a decision on behalf of another person.
Substituted Judgment	Substituted judgement involves making a decision for someone else based on what he/she would want if they could decide for themselves. An example of this is gathering information about a person's preferences, values, attitudes and beliefs before making a decision.

12.3. Appendix 3: Ethics Approval Letter

NHS
Health Research Authority
Yorkshire & The Humber - Sheffield Research Ethics Committee
Jarrow Business Centre
Viking Business Park
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 428 3561

25 February 2016

Ms Charlene Martin
PhD Student
University of Sheffield
EU27, Medical School
Beech Hill Road
S10 2RX

Dear Ms Martin

Study title:	**Proxy decision making for older women with cognitive impairments and breast cancer**
REC reference:	**15/YH/0292**
Protocol number:	**STH18914**
IRAS project ID:	**167829**

Thank you for your letter of 28 January 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Assistant, Miss Kerry Dunbar, nrescommittee.yorkandhumber-sheffield@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk 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 management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the 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).

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).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Response to Provisional Opinion]		28 January 2016
Interview schedules or topic guides for participants [Interview Guide]	1	26 January 2016
Letters of invitation to participant [Invite Letter]	1	06 May 2015
Non-validated questionnaire [Decision Making Questionnaire]	1	06 May 2015
Other [Karen Collins (Supervisor) CV]		11 June 2015
Other [Interview Consent Form]	1	26 January 2016
Participant consent form [Participant Consent Form]	1	06 May 2015
Participant information sheet (PIS) [Participant Information Sheet]	2	26 January 2016
REC Application Form [REC_Form_04062015]		04 June 2015
Research protocol or project proposal [Study Protocol]	2	26 January 2016
Summary CV for Chief Investigator (CI) [Student CV (CI)]	1	06 May 2015
Summary CV for supervisor (student research) [Ms Lynda Wyld]		20 October 2012
Summary CV for supervisor (student research) [Dr Karen Collins]		

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 HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/YH/0292	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

[redacted]

Professor Basil Sharrack
Chair

Email: nrescommittee.yorkandhumber-sheffield@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Jemima Clarke, Sheffield Teaching Hospitals NHS Foundation Trust*

12.4. Appendix 4: Systematic Review Search Strategy

(("dementia"[MeSH Terms] AND "decision making"[MeSH Terms]) AND ("neoplasms"[MeSH Terms] OR cancer[Text Word])) AND ("caregivers"[MeSH Terms] OR carer[Text Word]).

12.5. Appendix 5: Cover Letter

[ADDRESS]

Ms. Charlene Martin
PhD Student
Department of Oncology
University of Sheffield
EU27, Medical School
Beech Hill Road
Sheffield, S10 2JF

Telephone: +44 (0) 114 2713611

Email: c.l.martin@sheffield.ac.uk

[DATE]

Dear [NAME]

We are writing to invite you to take part in a study that is interested in how carers make treatment decisions for older women who have been diagnosed with breast cancer. You have been invited to take part in this study as you have previously assented a friend or relative to the Bridging the Age Gap in Breast Cancer Study and may have been involved in making a treatment decision. We hope that the results from this study may help doctors and nurses in clinics provide better support to carers faced with making these decisions in the future.

Included in this pack is a participant information sheet (which outlines the study and explains how to take part), two copies of the consent form, a decision-making questionnaire, and a self-addressed envelope.

Please read through the participant information sheet carefully and take some time to consider whether you would like to take part. If you decide to take part, please sign both copies of the consent form (one copy is for you to keep) and return a copy of the consent form and completed decision-making questionnaire in the envelope provided. If you would like to take part in an interview, you can indicate this by leaving your details on page 14 of the Decision-Making Questionnaire, and we will contact you in the near future to make arrangements.

There is no obligation to complete the questionnaire or participate in the interview, and this will not affect the standard of care that you or your relative receive in any way.

Thank you for taking the time to consider this research study. If you have any further questions or would like to know more about any aspect of this study, please do not hesitate to get in touch.

Kind regards

Charlene Martin
PhD Student

12.6. Appendix 6: Patient Information Sheet

Participant Information Sheet

(07 November 2016, Version 3)

Title of study:

Proxy decision making for older women with cognitive impairments and breast cancer

Invitation to take part:

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve for you. Please take time to read through the following information carefully and discuss it with others if you wish. Take some time to consider if you would like to take part and ask the researcher if there is anything unclear or you would like more information.

What is the purpose of this study?

The purpose of this study is to understand how relatives and carers make medical treatment decisions on behalf of their relatives/friends who are no longer able to make decisions for themselves as a result of a loss of intellectual capacity (memory loss/dementia). Breast cancer is a very common disease in older women and consequently may occur coincidentally in older women who have also developed some problems with their memory (dementia). Women with breast cancer may be asked to make decisions about how they would prefer to be treated as there are often options for example about whether to have surgery or to have just hormone tablets. For most older women there is plenty of information and support to help them make this decision for themselves, often in discussion with their doctors, nurses, family and friends. For older women with dementia, they may not be able to weigh up the pros and cons of the different options for themselves and in this case the doctors and relatives/friends and carers may meet up to try and decide what may be in her best interest and what she would have wanted had she been able to decide for herself.

This is a difficult situation for a relative or carer to be in and may put them under a lot of pressure trying to imagine what their loved one would have wished and some may find it stressful, worrying or difficult, especially when the decision may have significant implications for their loved one.

This study wants to find out how carers go about making these decisions, what factors they take into account, what information sources they use and also how it has impacted on them psychologically. We hope that it may help doctors and nurses in clinics to provide better to support to carers faced with this difficult situation in the future.

Why have I been invited to participate?

You have been invited to take part in this study because you may have been involved in the decision making for someone who has recently received treatment for their breast cancer but who has some problems with their ability to make decisions for themselves. Your participation in this research is entirely voluntary and it is your choice should you wish to join this study.

Do I have to take part?

It is entirely your decision where or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

After you consent to the study, the researcher will ask you to complete a questionnaire and take part in a face-to-face interview.

- Questionnaires: The two questionnaires will take between 10-30 minutes to complete and will involve answering some questions about making a proxy treatment decision (deciding on behalf of someone else).
- Interview: The interview will last for approximately 45-60 minutes and will involve answering some questions about how you make proxy decisions in more detail.

Where will my interview be held?

If you express interest in participating in the interview, the researcher will contact you within 3 months to check if you are still happy to take part and ask you to complete a consent form. The interview can be undertaken either face-to-face or over the telephone. If you agree to a face-to-face interview, this can be held either at your home or in a pre-booked interview room in your town or city. Refreshments will be made available during the interview and travel expenses will be reimbursed. Interviews will take place in early 2017.

Will my interview be recorded and how will the recording be used and stored?

The audio recordings of your interview made during this research will be used only for analysis and for illustration in conference presentations. No other use will be made of them without your written permission, and no one outside the project will be allowed access to the original recordings. The recordings will be anonymised, and only anonymous quotes used, never the actual audio recording.

What are the possible disadvantages and risks of taking part?

There are no specific risks associated with taking part in the study, but you may be inconvenienced in terms of the time taken to fill in the questionnaire and take part in an interview.

What are the possible benefits of taking part?

The information you give will not have any direct benefit on the standard of care for the person you made a treatment decision for, but it will help to improve clinical practice for decision making for older people who are unable to make their own decisions.

Will my taking part in this study be kept confidential?

Yes. All information that is collected during the course of the study will be kept strictly confidential. As a general principle, the researcher has a responsibility to report to the relevant authorities any actions or planned actions which they believe is likely to result in serious and immediate harm to others. Any information collected will be securely stored at the Medical School, University of

Sheffield on paper and electronically, under the provisions of the 1998 Data Protection Act.
Your name will not be passed to anyone outside the research team who is not involved in the study. Any information collected will have your name removed so that you cannot be recognised by it. You will be allocated a study number which will be used to identify you on the questionnaire. Only the researcher will be able to identify you from this number.
In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely stored for a minimum of 15 years. Arrangements for confidential destruction will then be made.

What will happen to the results of the research study?
The results of this study will be presented at conferences and published in scientific journals, and will be made available to you if you wish. You will not be identifiable in any of the presented or published results.

Who is organising and funding the research?
The research is being conducted by the University of Sheffield and the National Institute for Health Research.

Who has reviewed the study?
This study will be reviewed by a Research Ethics Committee to safeguard your welfare, dignity, rights and wellbeing. The University Research Ethics Committee will review this study.

What will happen if I don't want to continue with the study?
You are free to withdraw from the study at any time and do not need to give a reason. If you decide to withdraw from the study, you have two options:

- Withdrawal from further data collection, but we will still use the data collected up to your withdrawal
- Complete withdrawal from the study with any information you have given destroyed if you wish.

What if something goes wrong?
If you have any concerns or complaints about any aspect of this study, please contact the PhD researcher for this study:
Ms Charlene Martin (PhD Student), Department of Oncology & Metabolism, EU27, Medical School, Beech Hill Road, Sheffield S10 2RX. Telephone: 0114 2159013.
Alternatively, you can contact the PhD supervisor of the project:
Ms Lynda Wyld (Senior Lecturer and Consultant Breast Surgeon), E Floor, Royal Hallamshire Hospital, Sheffield S10 2JF. Telephone: 0114 2159066.
If you remain unhappy and wish to complain formally, you can do this by contacting the University of Sheffield Complaints Service.

Please retain this information leaflet for future reference and thank you for taking the time to consider this research study.

12.7. Appendix 7: Consent Forms

Participant Consent Form

Title of Research Project: **Proxy decision making for older women with cognitive impairments and breast cancer**

Name of Researcher: Charlene Martin

Participant ID Number for this project: _ _ _ / _ _ _

	Please initial each box
1. I confirm that I have read and understand the information sheet dated 07/11/2016 explaining the above research project and I have had the opportunity to ask questions about the project.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without there being any negative consequences. In addition, should I not wish to answer any particular question or questions, I am free to decline.	☐
3. I understand that my responses will be kept strictly confidential. I give permission for members of the research team to have access to my anonymized responses. I understand that my name will not be linked with the research materials, and I will not be identified or identifiable in the report or reports that result from the research.	☐
4. I agree for the data collected from me to be used in future research	☐
5. I agree to take part in the above research project.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person confirming consent	Date	Signature

Participant Interview Consent Form

Title of Research Project: **Proxy decision making for older women with cognitive impairments and breast cancer**

Name of Researcher: Charlene Martin

Participant ID Number for this project: _ _ _ / _ _ _

	Please initial each box
1. I confirm that I have read and understand the information sheet dated 07/11/2016 (Version 3) explaining the above research project and I have had the opportunity to ask questions about the project.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without there being any negative consequences. In addition, should I not wish to answer any particular question or questions, I am free to decline.	☐
3. I understand that my responses will be kept strictly confidential. I give permission for members of the research team to have access to my anonymized responses. I understand that my name will not be linked with the research materials, and I will not be identified or identifiable in the report or reports that result from the research.	☐
4. I agree to take part in a research interview.	☐
5. I give permission for the interview to be audio-recorded.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person confirming consent	Date	Signature

12.8. Appendix 8: Topic Guide

Interview Guide

Topic 1: Introduction

- Can you tell me a little bit about yourself and your role as a carer?
    - How long have you been a caregiver for?
    - Do you enjoy caregiving?
        - What do you enjoy the most about being a caregiver?
    - Are there any particular aspects of providing care that you find difficult?
    - How many individuals do you currently care for and make decisions for?
    - What are your thoughts on making proxy decisions?
        - Are you aware any guidelines for making best interest decisions?
        - Do you refer back to any guidelines when making decisions?
        - Do you find these helpful?

Topic 2: Caregiver relationship

- Could you tell me a little bit about your relationship to the person you made a proxy treatment decision for?
    - Prior to making the breast cancer decision, how long had you known the person that you care for?
        - Did you know this person prior to them losing capacity?
    - Could you tell me how long you have spent caring for this person?
        - Could you describe the care you provide – what does this involve?
    - At what point did you first become involved in making decisions for this person?
        - Could you give me some examples of decisions you have made in the past for this person? *[for example, such as include financial decisions]*
    - Is there anyone else who is involved in making decisions for this person?
        - If yes – who else is involved?
        - Do you sometimes make decisions collaboratively?

Topic 3: During screening/before diagnosis

- Can you remember how the breast cancer was discovered?

        - Were there any symptoms or signs?
        - Was the cancer discovered during a routine breast screening?
        - Did the person see their GP first?
    - Did you attend any breast care related appointments with the person you care for?
        - If yes – which appointments *[For example, GP, Screening, Results appointments?]*
        - If yes – did you access any information before attending the appointments? If so, what information did you access?
        - If yes – did you ask any questions at the appointments?
        - Had had you attended any breast related clinic appointments in the past and did you know what to expect?
    - Before the screening visit, did you have any awareness about breast cancer and what the screening involves? Did you know what screening involves?

Topic 4: Receiving the results

- Before the results appointment, did you have any awareness about breast cancer and the types of treatment that might be available?
    - If yes –what information and treatments were you aware of?
- Can you remember how long it took between attending the screening appointment and receiving the results?
- Who attended the results appointment – did any you or other family members, friends or advocates attend?
    - If you attended the results appointment, can you remember who told you the results? Was it a breast nurse or a consultant?
    - Did you find the results easy to understand? Was there any terminology that you were unsure of?
    - Did the consultant or breast nurse provide you with any information at the results appointment?
    - If yes – what sort of information did you receive? Was the information in a format that was easy to understand?
    - Were you happy with the level of information you received?
        - If no – why not?

Part 5: Making the decision

- Can you recall any of the treatment options that were discussed at the results appointment?
    - If yes – can you recall which treatments were discussed?

- Did the consultant or breast nurse specialist talk to you about the pros and cons of each type of treatments?
  - If yes – were any decision aids used to demonstrate this (such as a web tool or a leaflet)
- Did the consultant or breast nurse specialist recommend a particular type of treatment?
  - If yes – can you remember which treatment?
- When was it decided that you would be responsible for making the decision about treatment?
- Did you talk to anyone else about making the decision? Such as other family members?
- How much time did you take to think about the different types of treatments?
  - Did you feel that you were given enough time to make an informed decision?
- Which treatment did you decide upon?
  - And what was the defining factor that made you choose that particular treatment?
- Did you make this decision based on the recommendation given by the consultant or breast nurses?
- Can you describe how did you felt during this time?
  - Did you access any support services?
  - Was it a stressful or a straight-forward decision?

Part 6: Treatment and after effects

- What did the treatment involve for the person you care for?
  - Did it involve having an operation or taking tablets?
  - If tablets – are/were you involved in administering tablets to the person you care for?
  - If surgery – were/are you involved in the post-operative care for the person you care for?
- Did the person cope well with the treatment?
  - Were any side effects experienced?
    - If yes – what side effects? Were any of these severe or difficult to deal with?
  - Did you anticipate/expect any of these side effects?
  - Has this affected the level of care that you provide for this person?
  - How did this affect you?

- Did the person you care for have any additional treatment for their breast cancer? Did the treatment pathway change from that which you originally chose?
- How has the person continued coped after starting the treatment?
  - Do you think their quality of life has changed?

Part 7: After making the decision

- Are you happy with the treatment decision you made for the person you care for?
- Do you think that the person would have made the same decision?
  - If no - what do you think that people might have chosen for themselves?
- If you were to make the same decision again, would you choose the same treatment?
- How has the experience of making a decision about breast cancer treatment affected you?
- Would you feel comfortable making another treatment decision for another person with breast cancer?

- Would you make the same treatment decision for yourself?

12.9. Appendix 9: Framework Matrix

Patient contextual information

Interview	Age		Dementia	
	Age and treatment options	Priorities for older patients	Awareness of breast screening/monitoring	Impact of symptoms on discussions and treatment
CG1 (Surgery)	Initial thoughts – domiciliary/hospice/comfort care "simply because of her age" (line 157) Prior to discussion – "I didn't even contemplate surgery, I just thought they wouldn't do it at her age" (line 285) After discussion – surgeon reassured, "age is no barrier" (line 161)	Mother has mobility issues – chair bound. "someone who's younger may be diagnosed […] and have a totally different outlook on life" (line 248) "mum is at a time of life where that's not top of her agenda" (line 210)		Unaware? "she took it in her stride, didn't bat an eyelid […] she never mentioned it, it doesn't bother her, and it hasn't done ever since it happened" (line 224)
CG2 (Surgery)	Age a concern – "it wasn't losing a breast; it was her going through general anaesthetic at her age" (line 111-112)	Mother has mobility issues – uses a Zimmer frame and wheelchair. Arthritis, rheumatism, cataracts, diabetic. Taking Warfarin (line 349-356)	Knew someone that had breast cancer, but "it was all quite new really" (line 87)	Sprung back from treatment but had an infection in wound. Recovered from it well. Patient remembers to take her adjuvant tablets herself.
CG3 (PET)	Mother diagnosed in her 90s. "it's different if somebody's 30 isn't it? [..] I just thought that was it" (line 175-176)	Mother has mobility issues.	Patient frightened: "mum didn't understand what was going on […] like taking a child for an injection but worse" (line 141-143)	Forgets treatment: "now and then she'll go […] I've got a lump […] and then we go through that again" (line 313-315) "she hasn't a care in the world because she forgets […] she can't remember she's got breast cancer" (line (307-308)

CG4 (Surgery)				
CG5 (Surgery)	"he (surgeon) didn't want to put mum through radio or chemo because in an earlier age he would do that, but it was unfair to try and prolong life for 20 years if breast cancer returns when mum is 90" (line 72-74)	Mother has a pacemaker, hearing loss, visual impairments (line 12-15)		Forgetful: "she'd come out and say oh it went fine, and she hadn't a clue what had happened" (line 27-28)
CG6 (Surgery)	"they did say chemotherapy wasn't really an option, they didn't think at her age and her condition she would be able to cope with that" (line 153-154)	Parkinson's disease.	Biopsy daunting, but "she didn't flinch at all, she just went with the flow" (line 116-118)	Verbal: "I didn't leave her […] mum can't really speak for herself and explain how she's feeling" (line 240) Forgetful: "she didn't understand what was going on. I don't think she even noticed her breasts had been removed" (line 330-331)
CG7 (Surgery)	"especially at mam's age because we ruled out chemotherapy because of mam's age so there were only one or two treatment options available after that" (line 419-420)	Minor blood pressure problem. "unless you're very body conscious, the best one is to get rid (line 418)	Beyond remit of breast screening programme ending, "you get this perfect storm coming" (line 181)	Forgetful: "mam will talk through things and she will immediately forget what she's said" (line 75)
CG8 (PET)		On calcium tablets, unable to live independently.	"my auntie wouldn't have thought of [..] self-diagnosis of breast cancer" (line 191-192) "GP service would have been your only hope" (line 193)	"my aunt's mental state was such that she wouldn't have been bothered" (line 195)

Caregiver Contextual Information

Interview	Carer-Patient Relationship		Caring Duties	
	Caregiver and family involvement	Living arrangements	Support	Outlook on caregiver role
CG1 (Surgery)	Breast patient widowed. Son is caregiver.	Lives in sheltered accommodation.	"virtually organise everything, have done for a number of years" (line 4) Finances, shopping, hospital appointments.	"uncomfortable" discussions, "might have been easier if I'd have had a sister […] I've just got on with it" (line 305-308)
CG2 (Surgery)	Breast patient widowed. Daughter is caregiver.	Lives independently	Emotional support: "I can go sometimes, and I can see she's quite down or she's not feeling well and boost her up" (line 51) Shopping, finances, cleaning.	"don't consider myself a carer; just a daughter really" (line 6)
CG3 (PET)	Breast patient widowed. Daughter is caregiver. No siblings to help. "everybody else has gone" (line 56)	Lives in residential care. Moved following issues with multiple carers going into patient's home and lack of continuity, "instead of helping me it was actually hindering" (line 40-41) "horrible decision [..] why am I here and why can't I come home?" (line 15)	"I was just repaying what she'd done for me" (line 61-62) Despite moving into care, still supports her mum, talks "new set of worries" (line 81) Prior to move into home, carer had given up work to care for mother. Shopping, bathing, cleaning.	"very emotional […] very tiring […] frustration […] a horrible spectrum of feelings: guilt, resentment" (line 380-382) "you haven't got a life, that's when you feel guilty" (line 382)
CG4 (Surgery)	Patient cared for by husband (retired GP)	Lives together with husband independently in apartment		

CG5 (Surgery)	Breast patient widowed. Daughter is caregiver.	Lives independently but has carers go in for half an hour, 3 x a week. Telephone call twice a day.	Pre-empting problems, helps over the phone: "the photos on my phone are bizarre. I've got a collection of remotes, the alarm panel." (line 470-476)	
CG6 (Surgery)	Breast patient widowed. Daughter is caregiver.	Lives in residential care. "could no longer meet her needs [..] it wasn't an easy decision, but it had to be done" (line 34)	"it's my duty to be doing this" (line 68) "I never wanted to say it was a burden […] but it was difficult" (line 39-40)	"I wouldn't say I enjoyed it, but I never begrudged it. I never saw it as a burden" (line 44)
CG7 (Surgery)	Breast patient widowed. Son is caregiver.	Lives independently		"I just deal with it in a bloke's manner […] no wishy-washy stuff […] we get it sorted" (line 344-345)
CG8 (PET)	Breast patient widowed. Nephew is caregiver. No other family close-by to help.	Moved patient to residential care after caregiver received their own cancer diagnosis: "I began to get worried […] that I wouldn't be able to provide that sort of back up" (line 307)	"it was sort of like payback time" (line 303) Prior to move into a care home, nephew would do grocery shopping, take aunt to GP.	

Decision-making theme 1: Clinical interactions

Interview	Clinical Interactions	
	Professional advice from clinicians	Clinician awareness of dementia diagnosis/dementia friendly
CG1 (Surgery)	"So, they did tell me about other treatment but said that [surgery] was the best way" (line 178)	
CG2 (Surgery)	"listening to the surgeon and nurses […] reassuring that women of my mother's age and older had gone through this operation and it's been a success" (line 117-118)	
CG3 (PET)	"It was taken out of my hands wasn't it, because I was talked around. Which I had no problem with" (line 129)	
CG4 (Surgery)		
CG5 (Surgery)	Inconsistent advice. Decided against radiotherapy but told by another consultant the decision would go to MDT. "threw us off keel" (line 313-317)	"if you're there they talk to me, not to her, and then she just disengages from the conversation" (line 39-41) Text reminders not appropriate for patient (line 221) Self-management group not possible for patient, carer would have to access: "mum's not on the internet and wouldn't know how to use a computer" (line 210)
CG6 (Surgery)	Advised against chemotherapy and radiotherapy. Accessed mother's Parkinson's nurse for advice mostly (line 170)	Asked if information tailored: "no nothing, we didn't have anything like that […] no it was all just general" (line 111) "they didn't say anything about dementia" (line 126)

CG7 **(Surgery)**	"I was worried because obviously I'm not a doctor […] did such a good job of synthesizing or rationalising the treatment options. They literally put it into bloke's language which was these are your options" (line 365-367) "they're experts, you've got to trust them, haven't you?" (line 368)	No specific dementia advice.
CG8 **(PET)**	"she was very trusting of the medical staff and myself, and in a way I'm sort of trusting in the medical staff […] they're there to help you" (line 344-345)	

Decision-making theme 2: Accessing information and support

Interview	Accessing information and support	
	Advance care planning and decision-making guidelines	Seeking additional information
CG1 (Surgery)	Having LPA health and welfare meant "I was able to come up with the care package that was deemed sufficient" (line 56-57) Knowledge of later life planning from job.	Felt there was enough information. Given range of information (line 193)
CG2 (Surgery)	"I just kind of always tried to do things for mum's best interest. It was as easy as that"	Given information, felt this was enough. Described keeping to own support system. Did not access any other services (line 123)
CG3 (PET)	No AD.	"I wasn't offered any information sheets […] just told we think this is the best thing and then mum was put on the medication and that was it" (line 133-135) Did not access any other support services.
CG4 (Surgery)	Knowledge of making best interest decisions from role as a GP.	Did not access further information. Happy with level of information received at breast clinic (line 146)
CG5 (Surgery)	Clinical assumptions about patient capacity to give consent: "some jump to a conclusion and just think she's incapable of making a decision […] perhaps they're rushing to get it through" (line 47-51)	Having a decision aid or booklet to write down and refer to would have been helpful – to use when discussing with family after the appointment. "Sometimes you just forget and sometimes you don't write, if you're making notes you don't write it down quickly enough" (line 301-303)
CG6 (Surgery)	No AD for treatment. "If I'd had some little clue that's what my mum wanted […] but there was no way, she didn't know" (line 328-329)	Searched online for info and to do own research. "you're scared aren't you […] you look for the worst-case scenario [..] I didn't want to lose my mum, so I was looking at statistics and things like that, whereas the leaflets you get don't tell you that, it's just basics" (line 138-144) Highlighted information was not tailored towards people living with dementia. Joined a Facebook group to talk to other women in similar position (line 206)

CG7 **(Surgery)**	No AD.	Did own research. “I went away and analysed it, checked it all out that it was as it should be” (line 375) Lack of information given on probabilities and longevity of life post-operation.
CG8 **(PET)**	No LPA. “I was put down as the contact and so as if I had POA which I hadn’t, and I didn’t” (line 369)	Received enough information in the clinic. Happy with explanations of treatment given.

Decision-making theme 3: Decision-making involvement

Interview	Decision-making involvement	
	Caregiver role in making the treatment decision	Involving the patient in the treatment decision
CG1 (Surgery)	"everything was dealt with through myself [..] the doctor was happy me making the decisions and speaking to my mum (line 222-223) "it was explained to her, but she probably didn't fully understand the complications, maybe" (line 228)	Felt decision reflected what the patient would have wanted: "mum wouldn't have wanted the upheaval of more medication, more hospital visits, going to the GP; she would have wanted […] a higher percentage of working, so yes I do, I do think she would" (line 237)
CG2 (Surgery)	Patient relies on carer to hear, as partly deaf. "the nurse wouldn't let me participate in the conversation and I found that very, very, bad" (line 279) "you just feel, are you making the right decision? So, I found it hard" (line 188-190)	Felt decision reflected what the patient would have wanted: "Yes I think she would, because she wasn't hesitating" (line 176)
CG3 (PET)	Patient relies on carer: "I'll still offer, although she's got the dementia, choices, or I'll tell her things […] and I'll go well the decision is yours. She'll go, no dear I'll just do what's best" (line 361-363) "it's difficult, and you try and remember what you think your parent would have wanted if they had full capacity. That's all you can do is think that you're doing the best for them" (line 19)	Tries to involve patient, but "she goes I'll do what you think's best" (line 360)
CG4 (Surgery)	"I've been making decisions all my life in the medical world, so it wasn't a problem, no. I didn't find any difficulty" (line 216-217)	Mostly the caregiver and her auntie (patient sister) involved in the decision.
CG5 (Surgery)	Made decision together with mum. Spoke to sister who also reassured them both in the decision. Issues over extent of involvement of MDT (line 316)	Patient was involved in the decision.
CG6 (Surgery)	"the most stressful thing about it was having it on your head that you weren't making the right decision and it's a big decision to make and just thinking, oh what if I've made the wrong decision?" (line 198-203)	

CG7 **(Surgery)**	Family involvement in facilitating but not making the decision: "as a family we've been facilitators to help mam make a decision. It's not us imposing our decision on man, so from that perspective it was fairly easy because we've just done what mam wanted to do" "as a family we looked at the different options and the family said various things and then the final decision was mam's"	Patient still has the final decision: "I see my role as facilitator, mam will talk through things and she will immediately forget what she's said […] the final decision was mam's, because it was going to be supporting mam in her decision" "she took a decision and we asked her several times. We didn't overrule any of mam's decisions"
CG8 **(PET)**	Patient relies on carer: "she'd sort of use this OK, sort of shrug and turn to me like that as if what do you think?" (line 339-340)	"they spoke to her […] now we're thinking of doing this, how do you feel about that?" (line 338)

Decision-making theme 4: treatment influence

Interview	Factors influencing choice of treatment	
	Reasons for choice of PET	Reasons for choice of surgery
CG1 (Surgery)	NA	Clinician giving successful example: "surgeon turned around and said this is what we're going to do, we're going to operate, we're going to do a mastectomy, I was gobsmacked" (line 159) Prolonging life: "to get her to be able to live as long as possible […] put an end to it as much as possible and prolong her lifespan" (line 251-252)
CG2 (Surgery)	NA	Clinician giving successful example: "listening to the surgeon, reassuring that women of my mother's age and older had gone through this operation and it's been a success" (line 118)
CG3 (PET)	Age: "because of her age they basically more of less said we wouldn't consider surgery" (line 123). Clinician recommendation. Carer preference: "I had no problem with that because I'd thought straightaway there was no way she was going to have surgery" (line 128-129) Patient understanding: "She might not understand what the tablet actually does for her, but to my mother it's just a tablet isn't it?" (line 226-227)	NA
CG4 (Surgery)	NA	To avoid surgery later: "we decided that she should have surgery, because if she had to have surgery in the future when she wasn't perhaps as well…" (line 90-91) Patient and caregiver decision: "the consultant left it up to us really […] I think we made our decision there and then, but we were given a choice" (line 157-158)

CG5 (Surgery)	NA	Patient understanding: “mum’s understanding of it was if it’s cancer and it’s a lump you’ve got to get rid of it” (line 142-143)
CG6 (Surgery)	NA	Patient ability to cope – radiotherapy would have worn mother out, so wanted to avoid this. “the double mastectomy made more sense to us, the safer option in the long run” (line 192-193)
CG7 (Surgery)	NA	Patient understanding: “with mam’s oncoming dementia, that influenced the kind of treatment we were leaning towards which was get rid, because it’s the least management option after that” Patient preference: “mum said no she’d prefer just to have the cancer out”
CG8 (PET)	Clinician recommendation. “they wanted to suggest, the therapeutic measures rather than surgical. I’m inclined to agree with that because she was approaching 90 at the time […] the surgical treatment probably would shorten your life inasmuch as you’ve had a greater risk” (line 119-121)	NA

12.10. Appendix 10: Example Interview Transcript

Interview type: Face-to-face
Setting: Caregiver's home, Liverpool
Duration: 00:49:03
Date: 24.07.2017

CM: I just wanted to start off by asking you a little bit about yourself and your role as a carer for your mum.

CG3: Right, well I'm aged 65. And although I gave up work at 58 to look after my mum, who at the time would have been 90, I think, effectively I have been caring for her… if I tell you there's just been my mum and I since I was 10.

CM: Oh really?

CG3: And she had a disease in her leg, which caused spontaneous breaks. So, at the age of eight I was looking after her. So, it's been a very long kind of - I'm getting emotional.

[note: paused recording to check if caregiver was OK to continue]

CG3: But it's not just been caring for her at the end with the dementia; there's been a long history. And as I say then I cared for her for seven years when I gave up work. And it was only towards, she had a fall and I realised I just couldn't go on any longer. Because my brother died 25 years ago, so it was only me and there was no close relatives that could help, it was as easy as that. So at the age of 95 we had to make the horrible decision of putting her in a care home. Which she still asks every day when we go, why am I here and why I can't come home? So that's the kind of brief resume.

CM: What are your thoughts in general on making proxy decisions? A proxy decision is when you make a decision on behalf of someone else…

CG3: It's difficult, and you try and remember what you think your parent would have wanted if they had full capacity. That's all you can do is think that you're doing the best for them.

CM: And I guess because you've known your mum before she lost capacity as well, you've kind of got…

CG3: We were very close, yeah. So it's funny I was given proxy for the first time for the election. Now something like that which is clear cut, who do you vote for, you know, A or B? And she knew. I mean she's still got the capacity that yeah who she wanted to vote for. So that wasn't difficult. Because that was just an A or a B and I went along and ticked the box. For medical issues, which I think is what you're researching, it's harder isn't it? And you can only hope you are after consulting with medical people that you're doing the right thing.

CM: Did you have any awareness of the different guidelines there are for making decisions?

CG3: Not really. No, I just kind of always tried to do things for mum's best interest. It was as easy as that. Sometimes very difficult; the worst one for me was making the decision for her to go into a home.

And basically I was told that if she didn't go into a home I would be ill. So I had to really then think of myself first, but really that was the worst thing.

CM: Was she living on her own before that?

CG3: Oh yeah, yeah she'd been living on her own, bearing in mind she'd also been on crutches for 30 years. So she'd been living on her own since, for 50 years, yeah. I mean the last was it 10 or 15 years, more than 15 years, she had carers coming in, we were very lucky we had a regular carer who came every breakfast and every teatime, you know, but then at the very end when she needed four carers that was too confusing. Because by this time she needed two carers for every visit, and of course they couldn't send the same people. So for somebody with dementia and had got eight different people every day and all she wanted was me, because that's somebody she knew, that was, instead of helping me it was actually hindering.

CM: So she didn't have that continuity of seeing the same people?

CG3: That's right. She was all right with her usual carer in the morning, great with her, she knew, you wouldn't have known there was anything wrong. But when literally eight people came in the day and they were all different and then the next day it was another eight people and that was all different. I can understand that even for somebody that can be very confusing if you've, for anybody can't it, if they don't know who's turning up. And if you've got dementia it must be really worrying, because all they like is a bit of continuity.

CM: Was that confusing with different people coming all the time…

CG3: Yeah.

CM: So just thinking about your role as a carer, are there any things that you enjoy in respect to caring for your mum?

CG3: Oh, that's a hard one isn't it? Because towards the end it was difficult I have to admit. I still like, although it's upsetting, I still enjoy seeing her. And when it wasn't as bad I used to like taking her out. We used to go and see all her relative who unfortunately have all passed away. That's another sad thing that when you reach 90-odd, you know, everybody else has gone. So it was nice taking her out, going to the park. And we still try and take her to the park and things like that to, just a basic thing, you're going for an ice cream. You know, she forgets she's had the ice cream and then says can I have another one? So, yeah, but I suppose the small things, with dementia as it deteriorates you look for smaller things all the time. But yeah at the beginning it didn't bother me because it was well that was just looking after my mum. Whether I was doing the washing, the shopping, it was tiring, but I was just repaying what she'd done for me.

CM: And so, in general, what are the types of things that you do for your mum? For example, on a general day?

CG3: Well as she's in a care home it's not as intense. So do you want a before and an after?

CM: Yes please.

CG3: Right, well, a before was literally, it was the housework, the shopping, making sure she'd drunk enough, eating enough, changing beds, housework, just keeping on like things like that. When I was

able to, as I said, I would take her out in the car to try and stimulate her, taking her to the hairdressers, sorting out appointments for the chiropodist, hospital appointments. I would try and take her to the hospital. These were the days when she was more mobile. And then it got to more, oh, I used to give her a bath as well, that was that. But then towards the end it got very more personal care. And there was more accidents and falls and so it just go more and more, you know, that was the demanding part of it. And to get the phone calls at maybe nine o'clock at night from the carers saying can you come and help us? I think you're supposed to be helping me. So although people say to you when somebody goes into a home they think that's the end of it, you know, your responsibilities have dropped, somebody said this to me once and it is so true, you change, what is it? Your worries, they're a different kind of a worry, because you're still checking up on the home. Is it all right? You know, mum was in one for three months and we didn't like it and we realised things weren't being done.

[Brief interruption]

CG3: Somebody said to me, you change your worries for another set of worries, and it's true. I'm forever kind of checking up, her hand care, her nail care. I have to check up on the chart, has she had a bath, why she hasn't had a bath, yeah, because I don't want things to slip so to speak. You still keep a check on the clothes, which mysteriously go missing, even though they're labelled and everything. So it's always, every visit, you just don't walk in and visit your mother, what have you, there's always this, I've got to do this, I've got to do that, do her nails need cutting? Yes they give her her food, yes they might take her to the toilet and they put her to bed, but there's still all these little things that you have to keep on top of, because she's your mum. You don't want her with huge fingernails with jam and marmalade all underneath the nails which, because that's all she can do is pick up the bread and butter and it all gets in her nails. I understand they haven't got the time, because I'm not the only person, you see all the, and it's always the women, the women are there cutting their nails and sometimes putting the nail varnish on. So they're the things you do now. And I still have to chase up appointments for hospitals or for my mum she has to wear surgical shoes, so I have to make sure they're all right. That's it really.

CM: Is the care home responsible for checking her to see if things are OK in terms of her health?

CG3: Well, yes, I was just thinking, because she's got the breast cancer, the care nurse comes out every, is it three months she comes? So she kind of checks her on that on a regular basis. Mum has had two chest infections, and they were absolutely, you know, they were on the phone to me straightaway. The doctor was there. So I couldn't fault them from that point of view. And I think she just got a knock on her leg, the next minute district nurse was called. And they did keep me informed of every little kind of thing that happens, so I think yeah they're quite good.

CM: So was it the district nurse that picked up on her breast cancer?

CG3: No, that was when I was bathing her at home, and I noticed and I thought to myself there's something wrong here, you know, so I, oh, I can't remember how we got, or did I get the GP in? I must have got the GP in mustn't I? Because the next stage it was the referral to the hospital and they did a biopsy there and then on the day.

CM: And up until that point had you had any awareness of breast cancer and the different treatments?

CG3: Well my aunt had had it, going back donkeys' years ago and she had a mastectomy. And she was on tamoxifen and that was as I say donkeys' years ago. So kind of in the family I'd had somebody that I knew and I think like all women you know to be aware of it aren't you? And then a colleague I know now she had her breast removed and – just trying to think is there anybody? I've known other people who've had lumpectomies and things like that, so yeah.

CM: Did you have any awareness of any other types of treatments apart from surgery and tamoxifen?

CG3: Only at the time of tamoxifen, that was the only drug I knew, and it wasn't until they, my mum's been on different hormonal drugs isn't it? Have I been made aware of the different drugs that there are now; albeit that she's now on tamoxifen because she had another two which worked for about a year and then after the year obviously the body got used to it and then she got moved on to another one, and this is her third one, the tamoxifen.

CM: So at the appointment where you found out that she had breast cancer and you were talking through the different types of options of treatments, can you remember which treatments they offered and any information that they gave you on that?

CG3: In all fairness because of her age they basically more or less said we wouldn't consider surgery. Because a) of her age and she was 90, probably nearly 91, and she'd already got the dementia, and they said we don't think it would be right to put somebody through that – which I don't think they would at 90. So really although it was kind of yes we can go down that line but we don't think it's worth it, they then said it was a slow, it wasn't an aggressive cancer. And they more or less just said we think we can treat it with drugs. So really I was kind of, part of it was taken out of my hands wasn't it, because I was talked around. Which I had no problem with that because I'd thought straightaway, in my own head, there was no way she was going to have surgery.

CM: Did they give you enough opportunities to ask different questions and look at different information booklets and things like that?

CG3: I wasn't offered any information sheets, I think I was just told we will, we think this is the best thing, we will discuss it with, I don't know whether I saw a consultant and she said we will discuss it. And then mum was put on the medication and that was it. And I had no qualms about it to be honest with you. I felt there was enough information bearing in mind her age, it was slow growing, she had the dementia, I thought there was enough information.

CM: Were you happy with what you received from the consultants at the hospital?

CG3: Oh yes I thought they were very good. As I say everything was done on the day, which I wasn't expecting, I just thought we were going to go along for an examination. She had a biopsy and something else was done, what was the other thing? Well it was difficult because mum didn't understand what was going on, except she was, I mean it was like taking a child for an injection but worse. And she couldn't understand, but she was in pain while they took the biopsy. And of course she was frightened and it was, it was very difficult. I was holding her hand, she was gripping it hard while she was taking

the biopsy. And I was like that, just, I can imagine, not that I've got children, how you must feel when you take your own child, because you think to yourself, I'd rather have it than you, yeah. And then I go to bed thinking ooh, and you're like that yourself feeling your own breast going ooh. Oh no.

CM: So it didn't take long between receiving the results then and deciding on treatment?

CG3: No, I'd more or less made my mind up in the consulting room straightaway. And I told my mum, we did discuss it albeit she can't remember. But even now in the home she'll sometimes say to me, I've got something to tell you later, and I said what is it? I've got a lump in my breast. And I go yes mum, that's why so-and-so comes. Oh, all right then. So she still must feel it and she goes oh, all right, yes. And that's five years now.

CM: That's interesting. And so yeah it sounds like it was quite a quick process then.

CG3: Yeah.

CM: Everything went quite quickly?

CG3: It did, it did, from seeing the GP and the letter it all happened very quickly.

CM: Did you talk to any family or friends about the decision at the time and how you felt about everything?

CG3: Not really because there's nobody to talk to because there was only me. I might have discussed it with my husband in all fairness. But really when I say discussed, just kind of said to him, this is what they're probably doing and kept him informed. We didn't debate it over, yeah.

CM: And did you access any other support services at that time?

CG3: No, I didn't. I feel quite neglectful now. I know when we got the initial letter from the hospital explaining what kind of, it was ductal carcinoma grade 2 blah, blah, but I did go on the web and looked all that up and saw how it affected and etc. and everything. So I suppose from that point of view. But I didn't feel that, mum was never in pain with the cancer, so I never felt that I needed any support. It was kind of, I suppose I sound very black and white don't I? But it was yes, OK we've got it, yes we can have the treatment. And there was always on the back of my mind, well she's 90-odd, you know. And it's proved right, I don't think at the moment she's going to die of the cancer it might be something else, because it's been five, six years.

CM: And she's doing really well?

CG3: Yeah.

CM: It's good going to reach 90 as well.

CG3: Exactly, so she was 90 when she got it, which is, it's different if somebody's 30 isn't it? Or even 50, 60, but at 90 you think to yourself, well, I just thought that was it, it was very kind of. I wasn't upset, which I was quite surprised at myself, because I think I just knew straightaway from the beginning. So now I'm talking about it I realise that I didn't get upset. I don't know why. I just kind of took it as here's another thing.

CM: Well you seem to me to be quite a strong person -

CG3: Yeah I've been told that before and everything. As I said when, from the age of 10 you have to be.

CM: Before your mum lost capacity, had you ever talked about advance care planning and what she might want to do in the future?

CG3: Well you see she always said to me, don't put me in a home. And you feel so guilty. So we didn't ever talk about - like some people might do - euthanasia and stuff like that. It was, she said just don't ever put me in a home will you? And I think like a lot of people she thought she might pass away nice and tidily for want of a better word, you know, and we won't have to face that problem. Then towards the end where she was at home when things were really bad one day and she said I'll have to go in a home won't I? So I said well it's something you'll have to think about, you know. But we could never ever get her for respite to kind of get a taster of it, do you see what I mean? And one time when I did need it and the social worker came along and said come on let's see if we can get you in. No! And she was adamant, adamant she wouldn't go. So even then it was, don't put me in a home and that's the hardest thing I've got to live with.

CM: Is respite where they go for a little bit somewhere to…?

CG3: Yeah like a week's break, holiday for want of a better word, so it would have given me a break. And she said no. No, she wouldn't. On another thing, to kind of put you in the picture, mum had a very unusual childhood we should say. She was only about seven when she was diagnosed with what they thought was a TB hip. And it wasn't, she'd had a perforated appendix, peritonitis. And you're talking 1927, no antibiotics. Anyway she survived but it destroyed the hip joint. And of course in 1927 they sent her off to what they thought for TB, sunshine home!

CM: Oh right.

CG3: Hayling Island, because she was in **[REDACTED]**, you see, my mum. So they put you out in the weather, rubber sheeting, snow, wind, rain, everything and you didn't see your parents. And she's only told me a couple of years before she had the dementia that she was obviously with people who were mentally unstable. Now can you imagine that as a seven-year-old?

CM: Oh it must have been quite terrifying.

CG3: That must have been awful. And I think from that is why she always said don't put me in a home. Because a home must have, they say with dementia you regress back to your childhood and that must have been at the back of her mind.

CM: Her perception of it must have been… thinking it would be like that…

CG3: Yeah. And she'll still say to me, get me out of here. And that doesn't help. So it is difficult making decisions, very, very difficult. And I think women, I mean I don't know if you're interviewing any men, but I do think women have a tendency to feel guilty.

CM: In the sense that it's your mum and…

CG3: Yeah. And have I made the right decision? You're always asking that. Other people say to you, yes you've made the right decision. But you're always asking yourself have I done the right thing? And then you talk yourself round. Eventually you go yeah, yeah, yeah. And then another day you might have a bad day and you go have I done the right thing? Yes I think I've done the right thing.

CM: So you're still weighing up the pros and cons sometimes.

CG3: Yeah, yeah.

CM: That's interesting though. Just going back to the treatment side of it, what would you say was the defining factor that made you choose endocrine therapy?

CG3: I just didn't want her to have surgery. And I was quite relieved when they said we wouldn't do it because of her age and because of the dementia. So as I said I was quite relived, I just thought well mum can understand that. That's another thing, she can understand just taking a tablet, you know, it's quite easy isn't it? She might not understand what the table actually does for her, but to my mother it's just a tablet isn't it?

CM: If your mum could have decided that for herself, do you think she would she have chosen that option as well?

CG3: Yes I think so.

CM: So she's on tablets… Are you involved in giving her the tablets?

CG3: No, the home do that - I mean just trying to think. When she was at home, she used to have one, she's always had it first thing in the morning, that was it, so the carer always used to give it to her anyway. Because she had blister packs so it was all, all the tablets were out, so she used to give it to her. I would always check that it had gone and it wasn't on the carpet, that's another thing. If you get a different carer that is something you have to watch out. Oh I gave her the tablet and they're there on the trolley or they're on the carpet and things like that.

CM: Oh right.

CG3: But the care home are very good, I've watched them and they give them the tablet and they wait and they watch and see that the tablet is taken, it is swallowed and it's not on the floor or anything stupid like that. Instead of maybe here's your tablet and they walk away and give it to somebody else. I've noticed that they are quite good in that respect, but they're very good.

CM: Do you know if your mum's had any side effects from the treatment?

CG3: She doesn't appear to have had any side effects. I mean the only reason she was changed was because it started to grow again, obviously increased in size, and so that was why the medication was changed. But no she doesn't seem to have any side effects. In fact I wasn't, I can't remember if I looked on the web what the side effects were. But she's a tough cookie my mum. I mean to go to 96, 30 years on crutches.

CM: Yeah, that's amazing.

CG3: And they still say yes she's got the cancer, she's got this bone disease, but she's got no heart problems or anything. Everybody goes does she have any blood pressure tablets, and I go no. And every time you take her blood pressure it's more normal than mine.

CM: She sounds very resilient and…

CG3: Oh, we keep thinking she'll just fossilise to be honest with you.

CM: Oh that's brilliant though. Would you say that having breast cancer, and the treatment, has affected the level of care that your mum receives?

CG3: They're very good at the home because they do, shall we say, I suppose visually check her to see if there's anything different. One time they did ring me and they thought the nipple had changed colour. So they told me and I said right I'll ring the breast care nurse. And whoosh she came out straightaway. And she just said no, everything's all right. So what one carer might have thought was unusual it actually wasn't it was all right. But it was better to be like that than just ignore it wasn't it, I felt. Because that's the one thing I do notice, that because I'm not, shall we say washing my mother, you know, when the care nurse comes and she says how is she? I go, well I honestly don't know because I haven't seen her undressed, you know, the carers now do that. So that's the one thing that I realise I have to depend on other people.

CM: Because you're relying on, I guess, the carer noticing something as well?

CG3: Yeah.

CM: So at the hospital, the breast care nurses, do they answer straightaway if you have a question?

CG3: Yeah. I won't say her name in case, but she's wonderful, because as I said she rang me up the other day and she said, there was a concern that was it and I rang her and left a message, and she came back straightaway and she said do you want me to come out? So I said well I'll monitor my mum for you. Mum was saying she was in pain, for the first time, and it was only because we were out, I was in the hospital with her, that was it, on another different issue, and she kept grabbing her breast and going ooh and saying she was in pain. And she's never done that. So whether it was just a one-off thing, because she never did it then, I asked the home to monitor her and she never did it, so whether it was just a one day where she was getting, she said it was like a shooting pain. But the care nurse said I'll come out. And I said well I'll monitor. And she never seemed to mention it again. But no I think they've been very good.

CM: So you said that she changed her medication. Was it twice?

CG3: Yeah.

CM: So your mum went on a different one. And was that process easy in terms of it being explained to you, why they were changing it?

CG3: Yeah, basically because as I said it was re-growing, so she then changed the drug. And that seemed to happen quite quickly, the medication came through straightaway from the kind of communication level, it happened very quickly. GP came out to the nursing home and then the nursing home, I think I asked, I might have asked actually, has the new medication arrived? And yeah it all happened quite quickly.

CM: And how were you feeling at that point in time?

CG3: OK. I mean I realise, I used to work, I was only trained as a medical secretary, but I kind of can appreciate this is what happens, you know, so I wasn't that anxious about it by any means. So it was just like OK how many drugs did we have before?

CM: OK. So one of my other questions was whether the quality of life of your mum had changed or not?

CG3: I don't think it's changed because of the breast cancer; it's changed because of the dementia. And she does know it funnily enough. Because that's the thing with dementia, it's, you can have fleeting moments. I always remember somebody saying to me, it's like doing, remember doing dot to dot when you were a kid and you joined all the numbers up didn't you? And with dementia it's like they might go one to five, miss out a couple of numbers and then maybe do 10 to 11 and then miss out another, and that's exactly what it's like. Sometimes you can have, because she'll say to me, I know there's something wrong with me, but I don't know what, nobody's telling me what it is. And it's the dementia isn't it? And even if I did tell her, which I have done once, she forgets about it. And getting back to the cancer, that was I thought brilliant in one respect because I did tell her after we'd been to the hospital. What was all that about? I said well they have said you've got cancer of the breast. Have I? So yes OK. What are they going to do about it? You're going to have some tablets. OK fine. And then the next day. Where did we go yesterday? We went to the hospital, you've got breast cancer. Have I? Now I think that's marvellous because you and I would be petrified wouldn't we? We'd be worrying about the future, you'd be am I on the right tablets, blah, blah, blah. She hasn't a care in the world because she forgets, which I think is great. So in that respect I think the dementia is great that she can't remember she's got breast cancer, if that makes sense.

CM: That's interesting.

CG3: There's a benefit in that aspect of having the dementia.

CM: So I suppose you're not that anxious about it if you're not aware of it…

CG3: Yeah. And now and again she'll just go, as I said, she'll go, I want to talk to you, I've got a lump. Yeah dear that's why the nurse comes. Does she? She comes every three months. Oh OK. And then we go through that again.

CM: So thinking back on the whole process and the past five years, would you have made the same decision, looking back in hindsight?

CG3: Yeah, because it was more or less as I said presented to me in a, it wasn't kind of said, this is what we will do, but it was more or less presented that this really is the only option because of mum's age. And I was fine.

CM: And how would you feel about making that decision for someone else in another situation?

CG3: Oh, other than my mother? Hmm, difficult one. You mean treatment for cancer in general? Ooh yeah, yeah I suppose that would be only, if it was my husband you mean? Or even if I had children, for children wouldn't it? Well I think yet again with children you just, like my mum, even though I've not got children, you'd go along with what you think would be in their best interest wouldn't you? If it was for my husband, are you asking me that then he's got no, I'm doing it by proxy again?

CM: Yeah… another proxy decision.

CG3: That's difficult. Actually I've not thought about that. Because with a mother/daughter relationship that's a bit, I don't know, I just think that's different than a husband. I don't know is the answer, that's a difficult one. You've really kind of set me to think that one. All I could say is, thinking about it, I mean funnily enough my husband's cousin has got cancer. And he's undergoing treatment for bowel cancer.

And his wife is feeling very kind of, not left out because she's informed of all the decisions and everything, but I think he's kind of saying to her, when he gets angry, you're not the one with the disease! And I think that's hard. And I keep saying to him, the disease affects the whole family doesn't it?

CM: Yeah, it's not just that one person.

CG3: It's not just that one person. So if he didn't have his faculties I think I would just try and do my best. I would probably do what I've done before, look things up and try and make, and then with advice of the medical field, but hopefully not be bombarded – which I don't think the medical field do nowadays to be honest with you. I think that's more a thing of the past isn't it? They do take into consideration what you want.

CM: Yeah, because I guess it's not that paternalistic in a sense nowadays.

CG3: No.

CM: I guess there's this emphasis on shared decision making and -

CG3: That's right.

CM: - being collaborative

CG3: Yeah. So, oh I'll have to tell him when he comes what I've decided. Well I'll ask him what he'll do for me; that's another thing.

CM: Has the experience made you think about those kind of things, like what you might want for yourself in the future if you were in that position or someone else?

CG3: I hadn't thought about, well you see it's like everybody else you put it off thinking about what might happen, but I mean joking apart because we haven't got children we had already bought our funeral plan. So I hadn't thought about being ill what's going to happen, but I've thought about what music I want. Because when you haven't got a family that's what you've got to realise that you don't want anybody else bothered with making a decision on something like that. And I do realise I've got to make power of attorney, things like that. So now you've thrown the spanners in the work, I've got to worry about that now.

CM: Have you got power of attorney for your mum?

CG3: Yes we got that put in situ quite a long time ago to be honest with you. And she understood that, and she still says, which God love her, she goes I'll do what you think's best. And she's always said that to me so I kind of, it gives me a bit of comfort, because she'll still say, I'll still offer, although she's got the dementia, choices or I'll tell her things, you know, and I'll go well the decision is yours. And she'll go no dear I'll just do what's best, what you say, like that – which makes me sound as if I'm an ogre.

CM: No, no..

CG3: But she says, she will say that, you'll know best, you'll know best, like that. And it is role reversal I think isn't it? So that's why I find it difficult when you ask about a husband because it's a different context altogether isn't it?

CM: Are you responsible for other decisions for your mum like maybe financial decisions and things like that?

CG3: That was one of the hardest decisions in my life; I had to sell the family home. And that was horrendous. I didn't know which was worse, both of them were horrible, mum going into the home and then having to make the decision, which I let it go for as long as I possibly could, but I had to sell the family home. And once that had gone, I'd lived there for 60 years, that was awful, because you felt as if you were not only losing your mother, but you were losing the memories.

CM: So I think that's pretty much all my questions -

CG3: Is it?

CM: Just my last one, was how has the whole experience of making the treatment decision for your mum affected you?

CG3: Very emotional as you can tell. It's very tiring. There's no easy way I'll be honest with you. I used to get, frustration as well, somebody else is going through it. You also get resentment. You get a horrible spectrum of feelings: guilt, resentment. Yes you want to do it, but then when it gets really, really bad and your life, you haven't got a life, that's when you feel guilty and resentful. And the one thing that used to bug me was when I had a friend, who hasn't got a good relationship with her mother at all, and she used to say to me oh I know. When people condescendingly say to you, I know. And you think to yourself, you don't bloody know! I mean it's probably like, because I know you're here to discuss cancer, but it must be like people saying to people who have got cancer, oh I know. And you don't know because you haven't got cancer, have you?

CM: It's a very personal experience.

CG3: It's a very personal experience, yeah. So it's a very difficult one. I recently put in an email to a person I know who's likewise going through the same thing with her mother, just a bit behind if you know what I mean in the pathway. And I said there's no easy way, and there isn't. But there's no easy way with cancer either is there?

CM: It's very difficult…

CG3: And everybody approaches it, from what I can see, completely different isn't it? And it depends on the person who's affected, isn't it? Some people are stronger than others. This relative of my husband's, I mean he's coping remarkably well, but he had such an easy-going nature. And that's what the partner can't come to terms with, because he's being argumentative, he's being nasty. And I said to her, I said, it's because of yes the cancer, but the chemo he's undergoing. I mean he's totally cheesed off isn't he?

CM: The side effects from that must be quite difficult as well.

CG3: Yeah and all he wants to do is feel 'normal'. What is normal? We all say that isn't it? So I suppose it does depend on the person, what treatment they're getting and it's a very broad spectrum really isn't it?

CM: I think it's like in terms of your mum, she's doing really well, and I think that's…

CG3: She's doing as well as she can do for 97. Got dementia, no immobile, God love her. Went into hospital walking, came out of hospital not walking. And breast cancer, so.

CM: Aw yeah, I do hope she's going to reach 100.

CG3: She keeps saying, I keep saying to her, you might reach 100. I don't want that telegram, she said I don't want a telegram and I don't want a cake.

CM: Oh no, you'll have to. That's amazing. I keep saying that to my gran, you're going to make it to 100.

CG3: And how old's your gran?

CM: She's 86, so she's got quite a while to go.

CG3: She's got quite a while to go. My mum had this theory, my grandmother lived into her 90s and she used to say to me, well I'd like to reach the age your grandmother lived and no longer. And I laughed and I said so what you going to do, drop dead the next day? And she said yes. And that was it. But then when you do see them deteriorate with the dementia there's part of you which you think you do wish that they might pass away just peacefully and not see the deterioration go any further because you just don't want to lose your mum. So that's probably why I wasn't worried about the cancer, if you see what I mean. Because the cancer to me wasn't as threatening as the dementia. And you might think that's a strange thing to say, because you can control the cancer, can't you?

CM: But with dementia there's no known cure as well…

CG3: No. No and I'm lucky, from what people tell me, she's not aggressive, she recognises us, we can talk about some things. You know, I still quote, I try and tell her what's happening, like it was Wimbledon, told her about President Trump, you know, there are elections going on. Are there? I said there's a man and there's a woman. Who are they? So I told her. And then I went in and told her who'd won. And there was this pause and she goes he's going to cause trouble. And I thought couldn't say any more than that could you?

CM: I think she's right.

CG3: Oh, deary me, so there you go. Has that helped you?

CM: Yeah, perfect, thank you very much for your time.

CG3: Not at all.

END OF INTERVIEW

Reference List

1. World Health Organisation. Global Health and Aging. 2011.
2. ONS. National life tables, UK: 2015 to 2017. 2018.
3. ONS. 2011 Census: Population Estimates for the United Kingdom, 27 March 2011: ONS; 2012 [updated 31 March 2014. Available from: http://www.ons.gov.uk/ons/dcp171778_292378.pdf.
4. ONS. Living Longer: How our population is changing and why it matters 2018 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/livinglongerhowourpopulationischangingandwhyitmatters/2018-08-13.
5. Swift H, Steeden B. Exploring representations of old age and ageing.; 2020.
6. Fiske ST, Cuddy AJ, Glick P, Xu J. A model of (often mixed) stereotype content: competence and warmth respectively follow from perceived status and competition. J Pers Soc Psychol. 2002;82(6):878-902.
7. Jackson SH, Weale MR, Weale RA. Biological age--what is it and can it be measured? Arch Gerontol Geriatr. 2003;36(2):103-15.
8. Park DC, Yeo SG. Aging. Korean J Audiol. 2013;17(2):39-44.
9. Marzetti E, Leeuwenburgh C. Skeletal muscle apoptosis, sarcopenia and frailty at old age. Exp Gerontol. 2006;41(12):1234-8.
10. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer. 2005;41(5):779-85.
11. Patnaik JL, Byers T, DiGuiseppi C, Denberg TD, Dabelea D. The Influence of Comorbidities on Overall Survival Among Older Women Diagnosed With Breast Cancer. J Natl Cancer Inst. 2011;103(14):1101-11.
12. Morgan J, Richards P, Ward S, Francis M, Lawrence G, Collins K, et al. Case-mix analysis and variation in rates of non-surgical treatment of older women with operable breast cancer. Br J Surg. 2015;102(9):1056-63.
13. Morgan JL, Collins K, Robinson TG, Cheung KL, Audisio R, Reed MW, et al. Healthcare professionals' preferences for surgery or primary endocrine therapy to treat older women with operable breast cancer. Eur J Surg Oncol. 2015;41(9):1234-42.
14. Morgan JL, Walters SJ, Collins K, Robinson TG, Cheung KL, Audisio R, et al. What influences healthcare professionals' treatment preferences for older women with operable breast cancer? An application of the discrete choice experiment. Eur J Surg Oncol. 2017;43(7):1282-7.
15. Society BG. Comprehensive Geriatric Assessment Toolkit for Primary Care Practitioners. 2019.
16. NICE. Quality Standard [QS136]. 2016.

17. NHS England South. Safe, compassionate care for frail older people using an integrated care pathway; practical guidance for commissioners, providers and nursing, medical and allied health professional leaders. 2014.
18. Klepin H, Mohile S, Hurria A. Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw. 2009;7(2):226-36.
19. Gosney MA. Clinical assessment of elderly people with cancer. Lancet Oncol. 2005;6(10):790-7.
20. Owusu C, Berger NA. Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care. Clin Pract (Lond). 2014;11(6):749-62.
21. Wedding U, Höffken K. Care of breast cancer in the elderly woman--what does comprehensive geriatric assessment (CGA) help? Support Care Cancer. 2003;11(12):769-74.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
23. Kallogjeri D, Piccirillo JF, Spitznagel EL, Steyerberg EW. Comparison of Scoring Methods for ACE-27: Simpler Is Better. J Geriatr Oncol. 2012;3(3):238-45.
24. WHO. Active Ageing: A Policy Framework. World Health Organization; 2012 2012-08-27 21:37:45.
25. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014;30(3):421-42.
26. WHO. International Statistical Classification of Diseases and Related Health Problems (ICD-10). Geneva: World Health Organisation; 1992.
27. Holtzman DM, Morris JC, Goate AM. Alzheimer's disease: the challenge of the second century. Sci Transl Med. 2011;3(77):77sr1.
28. Starkstein S, Garau, L.M., Cao, A. Prevalence and Clinical Correlates of Disinhibition in Dementia. Cognitive & Behavioral Neurology. 2014;17(3):139-47.
29. Ritchie K, Kildea D. Is senile dementia "age-related" or "ageing-related"? — evidence from meta-analysis of dementia prevalence in the oldest old. The Lancet. 1995;346(8980):931-4.
30. WHO. Dementia: a public health priority. World Health Organization; 2014 2014-01-09 10:47:39.
31. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013;9(1):63-75.e2.
32. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112-7.
33. Society As. Dementia 2015: Aiming higher to transform lives. 2015.
34. Knapp M, Prince M, Albanese E, Banerjee S, Dhanasiri S, Fernandez J-L, et al. Dementia UK: The Full Report. London: Alzheimer's Society; 2007 2005-04-01.
35. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. The Lancet. 2013;382(9902):1405-12.
36. Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Ma L, Walker LP, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nat Genet. 2009;41(2):192-8.

37. Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and Area-Based Socioeconomic Factors Associated With Dementia Incidence in England: Evidence From a 12-Year Follow-up in the English Longitudinal Study of Ageing. JAMA Psychiatry. 2018;75(7):723-32.
38. Alzheimer's Society. Mapping the Dementia Gap 2012. Progress on improving diagnosis of dementia 2011-2012: Alzheimer's Society; 2012 [updated 01 March 2014. Details on diagnosis rates in England]. Available from: http://alzheimers.org.uk.
39. Society As. Helping you to assess cognition: A practical toolkit for clinicians 2015 [Available from: https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/alzheimers_society_cognitive_assessment_toolkit.pdf.
40. NICE. Dementia: Assessment, management and support for people living with dementia and their carers 2018 [Available from: https://www.nice.org.uk/guidance/ng97/chapter/Recommendations.
41. Society. As. What is mild cognitive impairment (MCI)? Factsheet 470LP. 2015.
42. Society As. The progression of Alzheimer's disease and other dementias.; 2015.
43. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, et al. Dementia UK: Update. 2nd Edition.; 2014.
44. Prestia A, Caroli A, van der Flier WM, Ossenkoppele R, Van Berckel B, Barkhof F, et al. Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. Neurology. 2013;80(11):1048-56.
45. Köhler S, Allardyce J, Verhey FRJ, McKeith IG, Matthews F, Brayne C, et al. Cognitive decline and dementia risk in older adults with psychotic symptoms: A prospective cohort study. American Journal of Geriatric Psychiatry. 2013;21(2):119-28.
46. Goate A, Hardy J. Twenty years of Alzheimer's disease-causing mutations. Journal of Neurochemistry. 2014;120(1):3-8.
47. Cohen SI, Linse S, Luheshi LM, Hellstrand E, White DA, Rajah L, et al. Proliferation of amyloid-beta42 aggregates occurs through a secondary nucleation mechanism. Proc Natl Acad Sci U S A. 2013;110(24):9758-63.
48. Jacques A, Jackson GA. Understanding dementia. 3rd ed. Jackson GA, editor. Edinburgh: Churchill Livingstone; 2000.
49. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet. 1997;349(9046):151-4.
50. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord. 1999;13(3):S115-23.
51. Gorelick PB. Risk Factors for Vascular Dementia and Alzheimer Disease. Stroke. 2004;35:2620-2.
52. Auning E, Rongve A, Fladby T, Booij J, Hortobagyi T, Siepel FJ, et al. Early and presenting symptoms of dementia with lewy bodies. Dement Geriatr Cogn Disord. 2011;32(3):202-8.
53. Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, et al. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. American Journal of Pathology. 1998;152(4):879-84.

54. Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004;55(2):164-73.
55. Borroni B, Grassi M, Costanzi C, Archetti S, Caimi L, Padovani A. APOE genotype and cholesterol levels in lewy body dementia and Alzheimer disease: investigating genotype-phenotype effect on disease risk. Am J Geriatr Psychiatry. 2006;14(12):1022-31.
56. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106-18.
57. Tateno M, Kobayashi S, Saito T. Imaging Improves Diagnosis of Dementia with Lewy Bodies. Psychiatry Investigation. 2009;6(4):233-40.
58. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry. 2003;74(9):1206-9.
59. Olszewska DA, Lonergan R, Fallon EM, Lynch T. Genetics of Frontotemporal Dementia. Curr Neurol Neurosci Rep. 2016;16(12):107.
60. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. J Am Geriatr Soc. 2002;50(8):1431-8.
61. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease Technology appraisal guidance [TA217] 2018 [Available from: https://www.nice.org.uk/guidance/ta217/chapter/3-The-technologies.
62. Roman GC, Salloway S, Black SE, Royall DR, Decarli C, Weiner MW, et al. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. Stroke. 2010;41(6):1213-21.
63. Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C. Galantamine treatment of vascular dementia: a randomized trial. Neurology. 2007;69(5):448-58.
64. Araki T, Wake R, Miyaoka T, Kawakami K, Nagahama M, Furuya M, et al. The effects of combine treatment of memantine and donepezil on Alzheimer's Disease patients and its relationship with cerebral blood flow in the prefrontal area. Int J Geriatr Psychiatry. 2014;[Epub ahead of print].
65. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord. 2007;24(1):20-7.
66. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. London: Department of Health; 2009.
67. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012;3:73.
68. Alzheimer's Society. Optimising treatment and care for people with behavioural and psychological symptoms of dementia. A best practice guide for health and social care professionals. London: Alzheimer's Society; 2011.
69. NICE. Dementia Quality Standards, QS1: NICE; 2010 [updated 01 April 2014. Available from: http://publications.nice.org.uk/dementia-quality-standard-qs1.
70. NICE. Dementia: assessment, management and
support for people living with dementia
and their carers 2018 [Available from: nice.org.uk/guidance/ng97.
71. Mental Capacity Act, (2005).

72. Care Act, (2014).
73. Society As. Making your home dementia friendly. London: Alzheimer's Society; 2017.
74. Livingston G, Leavey G, Manela M, Livingston D, Rait G, Sampson E, et al. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. BMJ. 2010;341:c4184.
75. NICE, SICE. Dementia: Supporting People with Dementia and their Carers in Health and Social Care. 2006 [updated 29 February 2014. Available from: www.nice.org.uk/CG42.
76. Alzheimer's Society. Assistive technology - devices to help with everyday living: Factsheet 437LP. In: Society As, editor. Alzheimer's Society: Alzheimer's Society; 2012.
77. UK AsR. Dementia in the family. The impact on carers.; 2015.
78. Levine C, Halper D, Peist A, Gould DA. Bridging troubled waters: family caregivers, transitions, and long-term care. Health Aff (Millwood). 2010;29(1):116-24.
79. Gitlin L, Wolff J. Family Involvement in Care Transitions of Older Adults: What Do We Know and Where Do We Go From Here? Annual Review of Gerontology & Geriatrics. 2011;31(1):31-64.
80. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20(6):649-55.
81. Merrilees J. The Impact of Dementia on Family Caregivers: What Is Research Teaching Us? Curr Neurol Neurosci Rep. 2016;16(10):88.
82. Springate BA, Tremont G. Dimensions of caregiver burden in dementia: impact of demographic, mood, and care recipient variables. Am J Geriatr Psychiatry. 2014;22(3):294-300.
83. Kasuya RT, Polgar-Bailey P, Takeuchi R. Caregiver burden and burnout. A guide for primary care physicians. Postgrad Med. 2000;108(7):119-23.
84. Stenberg U, Ruland CM, Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. Psychooncology. 2010;19(10):1013-25.
85. Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016. 2019.
86. Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H, et al. The treatment of early breast cancer in women over the age of 70. British Journal of Cancer. 2011;105(2):189-93.
87. Moller H, Flatt G, Moran A. High cancer mortality rates in the elderly in the UK. Cancer Epidemiology. 2011;35(5):6.
88. McPherson K, Steel CM, Dixon JM. Breast cancer--epidemiology, risk factors, and genetics. BMJ. 2000;321(7261):624-8.
89. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrida S, et al. Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopasual patients. Cancer. 2004;101(6):1302-10.
90. Parkin DM, Boyd L, Walker LC. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. British Journal of Cancer. 2011;105.
91. **Carley H**, K**ulkarni A**. Hereditary Breast Cancer Genetics and Risk Prediction Techniques. In: **Wyld** L, **Markopoulos** C, **Leidenius** M, **Senkus-Konefka** E, editors.

Breast Cancer Management for Surgeons: A European Multidisciplinary Textbook: Springer; 2017. p. 43-59.
92. NICE. Early and locally advanced breast cancer: diagnosis and management | Guidance | NICE. NICE; 2018.
93. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histolopathology. 1991;19(5).
94. Wishart GC, Bajdik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012;107(5):800-7.
95. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-74.
96. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;141(1):13-22.
97. Cronin M, Sangli, C., Liu, M-L., Pho, M., Dutta, D., Nguyen, A., Jeong, J., Wu, J., Langone, K.C., Watson, D. Analytical Validation of the Oncotype DX Genomic Diagnostic Test for Recurrence Prognosis and Therapeutic Response Prediction in Node-Negative, Estrogen Receptor–Positive Breast Cancer. American Association for Clinical Chemistry. 2007;53(6):1084-91.
98. Zhang Y, Schnabel CA, Schroeder BE, Jerevall PL, Jankowitz RC, Fornander T, et al. Breast cancer index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. Clin Cancer Res. 2013;19(15):4196-205.
99. Slodkowska EA, Ross JS. MammaPrint 70-gene signature: another milestone in personalized medical care for breast cancer patients. Expert Rev Mol Diagn. 2009;9(5):417-22.
100. Sanidas EE, Fitzal F. Oncoplastic Breast-Conserving Therapy. In: Wyld L, Markopoulos C, Leidenius M, Senkus-Konefka E, editors. Breast Cancer Management for Surgeons: A European Multidisciplinary Textbook: Springer; 2018.
101. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918-26.
102. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569-75.
103. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127-35.
104. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.

105. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-77.
106. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010;376(9735):91-102.
107. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365(9453):60-2.
108. (EBCTCG) EBCTCG. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.
109. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381(9869):805-16.
110. Lee SY, Seo JH. Current Strategies of Endocrine Therapy in Elderly Patients with Breast Cancer. Biomed Res Int. 2018;2018:6074808.
111. Harder H, Ballinger R, Langridge C, Ring A, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer: patients' perspectives on information giving and decision making. Psychooncology. 2013;22(12):2729-35.
112. Goldvaser H, Amir E. Role of Bisphosphonates in Breast Cancer Therapy. Curr Treat Options Oncol. 2019;20(4):26.
113. Fleisch H. The role of bisphosphonates in breast cancer: Development of bisphosphonates. Breast Cancer Research. 2001;4(30).
114. (EBCTCG) EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386(10001):1353-61.
115. NICE. Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates. 2017 [Available from: https://www.nice.org.uk/advice/es15/chapter/Key-points.
116. Pinto AC, Ades F, de Azambuja E, Piccart-Gebhart M. Trastuzumab for patients with HER2 positive breast cancer: delivery, duration and combination therapies. Breast. 2013;22 Suppl 2:S152-5.
117. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.
118. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
119. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800.

120. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncology. 2012;13(4):e148-60.
121. Hill DA, Horick NK, Isaacs C, Domchek SM, Tomlinson GE, Lowery JT, et al. Long-term risk of medical conditions associated with breast cancer treatment. Breast Cancer Res Treat. 2014;3 [Epub ahead of print].
122. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. Jama. 2001;285(7):885-92.
123. McKean LN, Newman EF, Adair P. Feeling like me again: a grounded theory of the role of breast reconstruction surgery in self-image. Eur J Cancer Care (Engl). 2013;22(4):493-502.
124. Osborn G, Jones M, Champ C, Gower-Thomas K, Vaughan-Williams E. Is primary endocrine therapy effective in treating the elderly, unfit patient with breast cancer? Ann R Coll Surg Engl. 2011;93(4):286-9.
125. Hooper SB, Hill AD, Kennedy S, Dijkstra B, Kelly LM, McDermott EW, et al. Tamoxifen as the primary treatment in elderly patients with breast cancer. Ir J Med Sci. 2002;171(1):28-30.
126. Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006(1):Cd004272.
127. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol. 2014;40(6):676-84.
128. Beach B, Bowell S, Mitchell J. Ageism in Breast Cancer. 2019.
129. Public Health England. Are women screened over the age of 70? : Public Health England; 2014 [updated 01 March 2014. Available from: http://www.cancerscreening.nhs.uk/breastscreen/over-70.html.
130. Moser K, Sellars S, Wheaton M, Cooke J, Duncan A, Maxwell A, et al. Extending the age range for breast screening in England: pilot study to assess the feasibility and acceptability of randomization. J Med Screen. 2011;18(2):96-102.
131. Collins K, Winslow M, Reed MW, Walters SJ, Robinson T, Madan J, et al. The views of older women towards mammographic screening: a qualitative and quantitative study. British Journal of Cancer. 1022010. p. 1461-7.
132. Burack RC, Gurney JG, McDaniel AM. Health status and mammography use among older women. J Gen Intern Med. 1998;13(6):366-72.
133. Raik BL, Miller FG, Fins JJ. Screening and cognitive impairment: ethics of forgoing mammography in older women. J Am Geriatr Soc. 2004;52(3):440-4.
134. Robb C, Boulware D, Overcash J, Extermann M. Patterns of care and survival in cancer patients with cognitive impairment. Critical Reviews in Oncology and Hematology. 2010;74(3):218-24.
135. Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Degner L, Stockton C, et al. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. British Journal of Cancer. 2014;110(3):573-83.

136. Richards P, Ward S, Morgan J, Lagord C, Reed M, Collins K, et al. The use of surgery in the treatment of ER+ early stage breast cancer in England: Variation by time, age and patient characteristics. Eur J Surg Oncol. 2016;42(4):489-96.
137. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: failure to operate for early breast cancer in older women. Eur J Surg Oncol. 2014;40(10):1230-6.
138. Enger SM, Thwin SS, Buist DS, Field T, Frost F, Geiger AM, et al. Breast cancer treatment of older women in integrated health care settings. J Clin Oncol. 2006;24(27):4377-83.
139. Land LH, Dalton SO, Jorgensen TL, Ewertz M. Comorbidity and survival after early breast cancer. A review. Crit Rev Oncol Hematol. 2012;81(2):196-205.
140. Hurria A, Leung D, Trainor K, Borgen P, Norton L, Hudis C. Factors influencing treatment patterns of breast cancer patients age 75 and older. Crit Rev Oncol Hematol. 2003;46(2):121-6.
141. NABCOP. National Audit of Breast Cancer in Older Patients. 2018.
142. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007(2):CD005002.
143. Barcenas CH, Niu J, Zhang N, Zhang Y, Buchholz TA, Elting LS, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol. 2014;32(19):2010-7.
144. Rosenstock AS, Lei X, Tripathy D, Hortobagyi GN, Giordano SH, Chavez-MacGregor M. Short-term mortality in older patients treated with adjuvant chemotherapy for early-stage breast cancer. Breast Cancer Res Treat. 2016;157(2):339-50.
145. study UostfesbcioaRftBtAG. Battisti, Nicolò.
Ring, Alistair.
Bradburn, Mike.
Wyld, Lynda.
. American Association for Cancer Research. 2020;80(4).
146. Biganzoli L, Aapro M. Elderly breast cancer patients: adjuvant chemotherapy and adjuvant endocrine therapy. Gynakol Geburtshilfliche Rundsch. 2005;45(3):137-42.
147. Torke AM, Schwartz PH, Holtz LR, Montz K, Sachs GA. Caregiver perspectives on cancer screening for persons with dementia: "why put them through it?". J Am Geriatr Soc. 2013;61(8):1309-14.
148. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Arch Intern Med. 2008;168(18):2033-40.
149. Fisher-Morris M, Gellatly A. The experience and expression of pain in Alzheimer patients. Age Ageing. 1997;26(6):497-500.
150. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer. 2013;108(11):2205-40.
151. Rafia R, Brennan A, Madan J, Collins K, Reed MW, Lawrence G, et al. Modeling the Cost-Effectiveness of Alternative Upper Age Limits for Breast Cancer Screening in England and Wales. Value Health. 2016;19(4):404-12.

152. Karuturi M, Wong ML, Hsu T, Kimmick GG, Lichtman SM, Holmes HM, et al. Understanding cognition in older patients with cancer. J Geriatr Oncol. 2016;7(4):258-69.
153. Gorin SS, Heck, J.E., Albert, S., Hershman, D. Treatment for Breast Cancer in Patients with Alzheimer's Disease. Journal of the American Geriatrics Society. 2005;53(11):1897-904.
154. Smith F, Grijseels MS, Ryan P, Tobiansky R. Assisting people with dementia with their medicines: experiences of family carers. Int J Pharm Pract. 2015;23(1):44-51.
155. Hurria A, Rosen C, Hudis C, Zuckerman E, Panageas KS, Lachs MS, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. J Am Geriatr Soc. 2006;54(6):925-31.
156. McWilliams L, Swarbrick C, Yorke J, Burgess L, Farrell C, Grunde G, et al. Bridging the divide: the adjustment and decision-making experiences of people with dementia living with a recent diagnosis of cancer and its impact on family carers. Ageing & Society. 2018;1-22.
157. Jones B. BresDex: helping women make breast cancer surgery choices. J Vis Commun Med. 2012;35(2):59-64.
158. Carreca I, Balducci L, Extermann M. Cancer in the older person. Cancer Treat Rev. 2005;31(5):380-402.
159. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. Eur J Cancer. 2007;43(15):2161-9.
160. McKoy JM, Burhenn PS, Browner IS, Loeser KL, Tulas KM, Oden MR, et al. Assessing Cognitive Function and Capacity in Older Adults With Cancer. Journal of the National Comprehensive Cancer Network. 2014;12(1):138-44.
161. Extermann M, Hurria A. Comprehensive Geriatric Assessment for Older Patients With Cancer. Journal of Clinical Oncology. 2007;25(14):1824-31.
162. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.
163. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.
164. Jauhari Y, Gannon MR, Dodwell D, Horgan K, Tsang C, Clements K, et al. Addressing frailty in patients with breast cancer: A review of the literature. Eur J Surg Oncol. 2020;46(1):24-32.
165. Hobbs GS, Landrum MB, Arora NK, Ganz PA, van Ryn M, Weeks JC, et al. The role of families in decisions regarding cancer treatments. Cancer. 2015;121(7):1079-87.
166. Mental Capacity Act Code of Practice. In: Affairs DfC, editor. London: The Stationary Office; 2005.
167. Barbas NR, Wilde EA. Competency Issues in Dementia: Medical Decision Making, Driving, and Independent Living. Journal of Geriatric Psychiatry and Neurology. 2001;14(4):199-212.
168. BMA. Advance decisions and proxy decision-making in medical treatment and research. London: British Medical Association; 2007.

169. Feinberg LF, Whitlatch CJ. Decision-making for persons with cognitive impairment and their family caregivers. Am J Alzheimers Dis Other Demen. 2002;17(4):237-44.
170. Beauchamp T, Childress J. Principles of Biomedical Ethics. 5th Edition ed. Oxford: Oxford University Press; 2001.
171. Buchanan A, Brock D. Deciding For Others: The Ethics of Surrogate Decision Making. Cambridge: Cambridge University Press; 1990.
172. Ahalt C, Walter LC, Yourman L, Eng C, Perez-Stable EJ, Smith AK. "Knowing is better": preferences of diverse older adults for discussing prognosis. J Gen Intern Med. 2012;27(5):568-75.
173. GMC. Consent: patients and doctors making decisions together. General Medical Council; 2008.
174. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ. 2010;340.
175. Singer PA, Martin, D.K., Lavery, J.V., Thiel, E.C., Kelner, M., Mendelssohn, D.C. Reconceptualizing Advance Care Planning From the Patient's Perceptive. Arch Intern Med. 1998;158:879-84.
176. Seckler AB, Meier DE, Mulvihill M, Paris BE. Substituted judgment: how accurate are proxy predictions? Ann Intern Med. 1991;115(2):92-8.
177. Office of the Public Guardian. OPG602 Making decisions: A guide for family, friends and unpaid carers. The Mental Capacity Implementation Programme; 2009.
178. Moore CD, Sparr J, Sherman S, Avery L. Surrogate decision-making: judgment standard preferences of older adults. Soc Work Health Care. 2003;37(2):1-16.
179. Torke AM, Alexander GC, Lantos J. Substituted Judgment: The Limitations of Autonomy in Surrogate Decision Making. Journal of General Internal Medicine. 2008;23(9):1514-7.
180. Office of the Public Guardian. Making decisions: The Independent Mental Capacity Advocate (IMCA) Service. The Mental Capacity Implementation Programme; 2007.
181. Hope T, Slowther A, Eccles J. Best interests, dementia and the Mental Capacity Act (2005). J Med Ethics. 2009;35(12):733-8.
182. Hirschman KB, Kapo, J.M., Karlawish, J.H.T. Why Doesn't a Family Member of a Person With Advanced Dementia Use a Substituted Judgment When Making a Decision for That Person? 2006;14(8):659–67.
183. Crotty M. The foundations of social research: Meaning and perspective in the research process. London: Sage; 1998.
184. King N, Horrocks C. Interviews in Qualitative Research. London: Sage; 2010.
185. Kuhn TS. The structure of scientific revolutions. 2nd Edition ed: University of Chicago Press; 1970.
186. Guba E. The Paradigm Dialog: Sage; 1990.
187. Creswell JW. Research design : qualitative, quantitative, and mixed methods approaches. 3rd Edition ed. USA: Thousand Oaks : Sage Publications, c2009; 2009.
188. Teddlie C, Tashakkori A. Major issues and controversies in the use of mixed methods in the social and behavioural sciences. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in social and behavioural research. Thousand Oaks, CA: Sage; 2003. p. 3-50.

189. Bryman A. Social Research Methods. USA: Oxford University Press; 2016.
190. Creswell JW, Plano Clark VL. Designing and Conducting Mixed Methods Research. 2nd Edition. ed. USA: Sage; 2011.
191. Tashakkori A, Teddlie C. Introduction to Mixed Method and Mixed Model Studies in the Social and Behavioral Studies. In: Plano Clark V, Creswell J, editors. The Mixed Method Reader. USA: Sage; 2008.
192. Campbell D, Fiske D. Convergent and discriminant validation by the multitrait-multimethod metric. Psychological Bulletin. 1959;56(2).
193. Plano Clark VL, Creswell JW. Mixed Methods Reader. Thousand Oaks, CA: Sage; 2008.
194. Tashakkori A, Creswell J. The New Era of Mixed Methods. Journal of Mixed Methods Research. 2007;1(1):4.
195. Higgins JPT, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition ed: Wiley Blackwell; 2019.
196. Pluye P, Robert, E., Cargo, M., Bartlett, G., O'Cathain, A., Griffiths, F., Boardman, F., Gagnon, M.P., & Rousseau, M.C. Proposal: A mixed methods appraisal tool for systematic mixed studies
reviews 2011 [Available from: http://mixedmethodsappraisaltoolpublic.pbworks.com. Archived by WebCite® at http://www.webcitation.org/5tTRTc9yJ.
197. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
198. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
199. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg. 2010;126(6):2234-42.
200. Morgan JL, George J, Holmes G, Martin C, Reed MWR, Ward S, et al. Breast cancer surgery in older women: outcomes of the Bridging Age Gap in Breast Cancer study. Br J Surg. 2020.
201. UKCRN. Bridging the Age Gap in Breast Cancer: Improving Outcomes for Older Women 2014 [updated 25 October 2014. Available from: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=13847.
202. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53(282):457-81.
203. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41-55.
204. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics. 1996;52(1):249-64.
205. Steiner PM, Cook TD, Shadish WR. The importance of reliable covariate measurement in selection bias adjustments using propensity scores. Journal of Educational and Behavioral Statistics. 2011;36(2):213-36.
206. Westreich D, Lessler J, Funk MJ. Propensity score estimation: neural networks, support vector machines, decision trees (CART), and meta-classifiers as alternatives to logistic regression. J Clin Epidemiol. 2010;63(8):826-33.

207. Becker S, Ichino A. Estimation of average treatment effects based on propensity scores. The Stata Journal. 2002;2:358-77.
208. Fallowfield L. Questionnaire design. Arch Dis Child. 1995;72(1):76-9.
209. Andres L. Designing & Doing Survey Research. London: Sage; 2012.
210. Collins K. Advanced sampling designs in mixed research: current practices and emerging trends in the social and behavioural sciences. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in the social & behavioural research. 2nd Edition ed: Sage; 2010.
211. Sapsford R. Survey Research. 2nd Edition ed: Sage; 2007.
212. Fink A. The Survey Handbook. 2nd Edition ed: Sage; 2003.
213. Collins K, Stevens T, Ahmedzai S. Can consumer research panels become an integral part of the cancer research community? Clinical Effectiveness in Nursing. 2005;9(3-4):112-8.
214. Management. CfEB. Critical Appraisal Checklist for Surveys. 2014.
215. Kvale S. InterViews: An Introduction to Qualitative Research Interviewing. Thousand Oaks, CA: Sage; 1996.
216. McCracken G. The Long Interview. USA: Sage; 1988.
217. Musselwhite K, Cuff L, McGregor L, King KM. The telephone interview is an effective method of data collection in clinical nursing research: a discussion paper. Int J Nurs Stud. 2007;44(6):1064-70.
218. Fontana A, Frey J. Interviewing. The Art of Science. In: Denzin NK, Lincoln YS, editors. Collecting and Interpreting Qualitative Materials: Sage; 1998. p. 361-76.
219. Mason M. Sample Size and Saturation in PhD Studies Using Qualitative Interviews. Qualitative Social Research. 2010;11(8).
220. Miles M, Huberman M, Saldana J. Qualitative Data Analysis. A Methods Sourcebook. 3rd Edition ed. USA: Sage; 2014.
221. Elo S, Kyngäs H. The qualitative content analysis process. J Adv Nurs. 2008;62(1):107-15.
222. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
223. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman and Burgess, editor. Analysing Qualitative Data. London: Routledge; 1994. p. 1753-194.
224. Ritchie J, Lewis J. Qualitative research practice: a guide for social science students and researchers. London: Sage; 2003.
225. Lincoln YS, Guba EG. Naturalistic Inquiry. USA: Thousand Oaks: Sage; 1985.
226. Tobin GA, Begley CM. Methodological rigour within a qualitative framework. J Adv Nurs. 2004;48(4):388-96.
227. Spencer L, Ritchie J, Lewis J, Dillon L. Quality in Qualitative Evaluation: A framework for assessing research evidence. London; 2003.
228. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. Qual Health Res. 2006;16(3):377-94.
229. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ. 2010;341.
230. O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. J Health Serv Res Policy. 2008;13(2):92-8.

231. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. In: Association WM, editor.: World Medical Association; 2008.
232. ONS. Living longer: How our population is changing and why it matters 2018 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/livinglongerhowourpopulationischangingandwhyitmatters/2018-08-13.
233. National Collaborating Centre for Mental Health. Dementia. A NICE SCIE Guideline on Supporting People with Dementia and Their Carers in Health and Social Care. London: The British Psychological Society and Gaskell; 2007.
234. McWilliams L, Farrell C, Grande G, Keady J, Swarbrick C, Yorke J. A systematic review of the prevalence of comorbid cancer and dementia and its implications for cancer-related care. Aging Ment Health. 2017:1-18.
235. Hopkinson JB, Milton R, King A, Edwards D. People with dementia: what is known about their experience of cancer treatment and cancer treatment outcomes? A systematic review. Psychooncology. 2016;25(10):1137-46.
236. Stern C, Jordan Z, McArthur A. Developing the review question and inclusion criteria. Am J Nurs. 2014;114(4):53-6.
237. United Nations (UN) DoESA. World Population Ageing 2015. 2015.
238. Pluye P, Hong QN. Combining the power of stories and the power of numbers: mixed methods research and mixed studies reviews. Annu Rev Public Health. 2014;35:29-45.
239. Gale N, Heath G, Cameron E, Rashid S, Redwood S. using the Framework Method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013;13(117).
240. Harrison Dening K, King M, Jones L, Vickestaff V, Sampson EL. Advance Care Planning in Dementia: Do Family Carers Know the Treatment Preferences of People with Early Dementia? PLoS One. 2016;11(7):e0159056.
241. Smyth KA. Current practices and perspectives on breast cancer screening and treatment in older women with dementia. Journal of the American Geriatrics Society. 2009;57(2):272-4.
242. Courtier N, Milton R, King A, Tope R, Morgan S, Hopkinson J. Cancer and dementia: an exploratory study of the experience of cancer treatment in people with dementia. Psychooncology. 2016;25(9):1079-84.
243. McWilliams L, Farrell C, Keady J, Swarbrick C, Burgess L, Grande G, et al. Cancer-related information needs and treatment decision-making experiences of people with dementia in England: a multiple perspective qualitative study. BMJ Open. 2018;8(4):e020250.
244. Witham G, Haigh C, Mitchell D, Beddow A. Carer Experience Supporting Someone With Dementia and Cancer: A Narrative Approach. Qual Health Res. 2018;28(5):813-23.
245. Bartlett H, Martin W. Ethical issues in dementia care research. In: Wilkinson H, editor. The perspectives of people with dementia: Research Methods and Motivations. London: Jessica Kingsley Publishers; 2002. p. 47-62.

246. Kimmick G, Fleming ST, Sabatino SA, Wu XC, Hwang W, Wilson JF, et al. Comorbidity burden and guideline-concordant care for breast cancer. J Am Geriatr Soc. 2014;62(3):482-8.
247. Libert Y, Dubruille S, Borghgraef C, Etienne AM, Merckaert I, Paesmans M, et al. Vulnerabilities in Older Patients when Cancer Treatment is Initiated: Does a Cognitive Impairment Impact the Two-Year Survival? PLoS One. 2016;11(8):e0159734.
248. Goodwin JS, Samet JM, Hunt WC. Determinants of survival in older cancer patients. J Natl Cancer Inst. 1996;88(15):1031-8.
249. Kukull WA, Brenner DE, Speck CE, Nochlin D, Bowen J, McCormick W, et al. Causes of death associated with Alzheimer disease: variation by level of cognitive impairment before death. J Am Geriatr Soc. 1994;42(7):723-6.
250. Morgan J, Ward S, Francis M, Collins K, Robinson TG, Reed M, et al. The effect of dementia on the treatment of older women with breast cancer. Future Oncology. 2015;11(4):13-.
251. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998;351(9106):857-61.
252. Tei M, Wakasugi M, Kishi K, Tanemura M, Akamatsu H. Incidence and risk factors of postoperative delirium in elderly patients who underwent laparoscopic surgery for colorectal cancer. Int J Colorectal Dis. 2016;31(1):67-73.
253. Plas M, Rotteveel E, Izaks GJ, Spikman JM, van der Wal-Huisman H, van Etten B, et al. Cognitive decline after major oncological surgery in the elderly. Eur J Cancer. 2017;86:394-402.
254. Severn A. Anaesthesia and the preparation and management of elderly patients undergoing surgery. Eur J Cancer. 2007;43(15):2231-4.
255. Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol. 2010;28(29):4434-40.
256. Sanoff HK, Deal AM, Krishnamurthy J, Torrice C, Dillon P, Sorrentino J, et al. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. J Natl Cancer Inst. 2014;106(4):dju057.
257. Morgan J, Wyld L, Collins KA, Reed MW. Surgery versus primary endocrine therapy for elderly women with operable primary breast cancer (70 years plus). Cochrane Database of Systematic Reviews. 2014.
258. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3):189–98.
259. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J. 1965;14:61-5.
260. Read JA, Crockett N, Volker DH, MacLennan P, Choy ST, Beale P, et al. Nutritional assessment in cancer: comparing the Mini-Nutritional Assessment (MNA) with the scored Patient-Generated Subjective Global Assessment (PGSGA). Nutr Cancer. 2005;53(1):51-6.
261. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.

262. Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet. 2014;114(7):1088-98.
263. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7th ed: Wiley-Blackwell; 2009 November 2009, Wiley-Blackwell. 336 p.
264. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. Am J Epidemiol. 2014;179(2):226-35.
265. Therneau TM, Grambsch P, M. Modelling Survival Data: Extending the Cox Model: Springer; 2000.
266. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. J Clin Oncol. 2007;25(32):5121-7.
267. Gu J, Groot G, Boden C, Busch A, Holtslander L, Lim H. Review of Factors Influencing Women's Choice of Mastectomy Versus Breast Conserving Therapy in Early Stage Breast Cancer: A Systematic Review. Clin Breast Cancer. 2018;18(4):e539-e54.
268. Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Nygård JF. Survival is Better After Breast Conserving Therapy than Mastectomy for Early Stage Breast Cancer: A Registry-Based Follow-up Study of Norwegian Women Primary Operated Between 1998 and 2008. Ann Surg Oncol. 2015;22(12):3836-45.
269. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine E, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003;21(12):2268-75.
270. Reed MW, Wyld L, Ellis P, Bliss J, Leonard R, Groups AaETM. Breast cancer in older women: trials and tribulations. Clin Oncol (R Coll Radiol). 2009;21(2):99-102.
271. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. IARC Sci Publ. 1980(32):5-338.
272. The Mental Capacity Act 2005 Code of Practice, (2007).
273. Smebye KL, Kirkevold M, Engedal K. How do persons with dementia participate in decision making related to health and daily care? a multi-case study. BMC Health Serv Res. 2012;12:241.
274. Tyrrell J, Genin N, Myslinski M. Freedom of choice and decision-making in health and social care: Views of older patients with early-stage dementia and their carers. Dementia. 2006;5.
275. Horton-Deutsch S, Twigg P, Evans R. Health care decision-making of persons with dementia. Dementia. 2007;6.
276. Miller LM, Whitlatch CJ, Lyons KS. Shared decision-making in dementia: A review of patient and family carer involvement. Dementia (London). 2016;15(5):1141-57.
277. Martin C, Shrestha A, Burton M, Collins K, Wyld L. How are caregivers involved in treatment decision making for older people with dementia and a new diagnosis of cancer? Psychooncology. 2019;28(6):1197-206.
278. Kedia SK, Chavan PP, Boop SE, Yu X. Health Care Utilization Among Elderly Medicare Beneficiaries With Coexisting Dementia and Cancer. Gerontol Geriatr Med. 2017;3:2333721416689042.
279. Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study

identifying MDT perceptions and barriers to decision making. Ann Oncol. 2013;24(5):1211-9.
280. Buist DS, Chubak J, Prout M, Yood MU, Bosco JL, Thwin SS, et al. Referral, receipt, and completion of chemotherapy in patients with early-stage breast cancer older than 65 years and at high risk of breast cancer recurrence. J Clin Oncol. 2009;27(27):4508-14.
281. Hinsliff-Smith K, Feakes R, Whitworth G, Seymour J, Moghaddam N, Dening T, et al. What do we know about the application of the Mental Capacity Act (2005) in healthcare practice regarding decision-making for frail and older people? A systematic literature review. Health Soc Care Community. 2017;25(2):295-308.
282. Kim Y, Schulz R. Family caregivers' strains: comparative analysis of cancer caregiving with dementia, diabetes, and frail elderly caregiving. J Aging Health. 2008;20(5):483-503.
283. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Increasing response rates to postal questionnaires: systematic review. BMJ. 2002;324(7347):1183.
284. Morgan JL, Collins K, Reed MW, Mamdani J, Cousins S, Ingram S, et al. Bridging the age gap in breast cancer interim analysis of the impact of comorbidity, dementia and frailty on rates of surgery in older women. European Journal of Surgical Oncology (EJSO). 2014;40(11):39-40.
285. Surr CA, Kelley R, Griffiths AW, Ashley L, Cowdell F, Henry A, et al. Enabling people with dementia to access and receive cancer treatment and care: The crucial role of supportive networks. Journal of Geriatric Oncology. 2020.
286. Witham G, Beddow A, Haigh C. Reflections on access: too vulnerable to research? Journal of Research in Nursing. 2013;20(1):28-37.
287. Hubbard G, Illingworth N, Rowa-dewar N, Forbat L, Kearney N. Treatment decision- making in cancer care: the role of the carer. Journal of Clinical Nursing. 2010;19(13-14):2023-31.
288. Robinson L, Dickinson C, Bamford C, Clark A, Hughes J, Exley C. A qualitative study: professionals' experiences of advance care planning in dementia and palliative care, 'a good idea in theory but ...'. Palliat Med. 2013;27(5):401-8.
289. Baillargeon J, Kuo YF, Lin YL, Raji MA, Singh A, Goodwin JS. Effect of mental disorders on diagnosis, treatment, and survival of older adults with colon cancer. J Am Geriatr Soc. 2011;59(7):1268-73.
290. Goldzweig G, Merims S, Ganon R, Peretz T, Baider L. Coping and distress among spouse caregivers to older patients with cancer: An intricate path. Journal of Geriatric Oncology. 2012;3:376-85.
291. Dodgson JE. Reflexivity in Qualitative Research. J Hum Lact. 2019;35(2):220-2.
292. Berger R. Now I see it, now I don't: researcher's position and reflexivity in qualitative research. Qualitative Research. 2015;15(2).
293. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Methods to increase response rates to postal questionnaires. Cochrane Database Syst Rev. 2007(2):MR000008.
294. ONS. Life expectancy at birth and at age 65 for local areas in England and Wales, 2009-11 2013 [updated 31 March 2014. 20]. Available from: http://www.ons.gov.uk/ons/dcp171778_320078.pdf.

295. Malik MK, Tartter PI, Belfer R. Undertreated Breast Cancer in the Elderly. Journal of Cancer Epidemiology. 2013;2013.
296. Cornwell J. The care of frail older people with complex needs: time for a revolution.: The King's Fund.; 2012.
297. Bandeen-Roche K, Xue QL, Ferrucci L, Walston J, Guralnik JM, Chaves P, et al. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci. 2006;61(3):262-6.
298. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
299. British Geriatrics Society. Comprehensive Assessment of the Frail Older Patient 2014 [updated 19 October 2014. Available from: http://www.bgs.org.uk/index.php/topresources/publicationfind/goodpractice/195-gpgcgassessment.
300. SIOG. Practice Guideline. Comprehensive Geriatric Assessment (CGA) in oncological patients 2011 [updated 17 October 2014. Available from: http://www.siog.org/images/SIOG_documents/cga_practice_guideline_wildiers_jul2011.pdf.
301. Kenis C, Decoster L, Van Puyvelde K, De Greve J, Conings G, Milisen K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol. 2014;32(1):19-26.
302. APPG. Age is just a number. All-Party Parliamentary Group on Breast Cancer; 2013 10 October 2014.
303. Alzheimer's Society. Dementia 2012: A national challenge. London: Alzheimer's Society; 2012.
304. Department of Health. Improving care for people with dementia policy: Department of Health; 2014 [updated 10 February 201410 February 2014]. Available from: https://www.gov.uk/government/policies/improving-care-for-people-with-dementia.
305. Dementia Action Alliance. Benefits of Timely Dementia Diagnosis. A Report for Consideration in Primary Care.; 2013.
306. Prince M, Bryce R, Ferri C. World Alzheimer Report 2011: The benefits of early diagnosis and intervention. 2011 September 2011.
307. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis. 2010;19(4):1401-8.
308. Miyoshi K. What is 'early onset dementia'? Psychogeriatrics. 2009;9(2):67-72.
309. Garand L, Dew MA, Eazor LR, DeKosky ST, Reynolds CF, 3rd. Caregiving burden and psychiatric morbidity in spouses of persons with mild cognitive impairment. Int J Geriatr Psychiatry. 2005;20(6):512-22.
310. Cancer Research UK. Figure 1.1: Breast Cancer (C50): 2009-2011 2014 [Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/#source1.
311. Forbes LJL, Simon AE, Warburton F, Boniface D, Brain KE, Dessaix A, et al. Differences in cancer awareness and beliefs between Australia, Canada, Denmark, Norway, Sweden and the UK (the International Cancer Benchmarking Partnership): do

they contribute to differences in cancer survival? British Journal of Cancer. 2013;108(2):292-300.
312. Linsell L, Burgess CC, Ramirez AJ. Breast cancer awareness among older women. Br J Cancer. 2008;99(8):1221-5.
313. Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women > or =65 years. British Journal of Cancer. 2007;96(8):1197-203.
314. Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. Br J Cancer. 1999;79(5-6):858-64.
315. NICE. Breast cancer quality standard. 2011 [updated 10 October 2014. Available from: https://www.nice.org.uk/guidance/qs12.
316. Breast Cancer Care. Improving outcomes and experiences for older women with breast cancer: A policy briefing by Breast Cancer Care. 2011.
317. Jatoi I. The effect of local therapy on breast cancer mortality: is there an age-interaction? Indian J Surg Oncol. 2014;5(1):5-9.
318. Wyld L, Garg DK, Kumar ID, Brown H, Reed MW. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. Br J Cancer. 2004;90(8):1486-91.
319. Wyld L, Reed M, Robinson T. Surgery for Older Adults with Cancer. In: Bellizzi K, Gosney M, editors. Cancer and Aging Handbook: Research and Practice. First ed: Wiley-Blackwell; 2012.
320. NICE. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients 2012 [updated 22 Nov 2014. Available from: http://www.nice.org.uk/guidance/cg151/resources/guidance-neutropenic-sepsis-prevention-and-management-of-neutropenic-sepsis-in-cancer-patients-pdf.
321. NICE. CG80 Early and locally advanced breast cancer: NICE guideline. In: Excellence NIfHaC, editor.: NICE; 2009.
322. Creswell JW. Qualitative Inquiry and Research Design: Choosing among five approaches. 2nd Edition ed. Thousand Oaks: Sage Publications; 2007.
323. Pope C, Maysa N. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ; 1995.
324. Frankfort-Nachmias C, Nachmias D. Research methods in the social sciences. 7th ed. New York: Worth Publishers; 2008.
325. Pope C, van Royen P, Baker R. Qualitative methods in research on healthcare quality. Qual Saf Health Care. 2002;11(2):148-52.
326. Johnson RB, Onwuegbuzie AJ. Mixed Methods Research: A Research Paradigm Whose Time Has Come. Educational Researcher. 2004;33(7):14-26

327. Forthofer M. Status of mixed methods in the health sciences. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in social & behavioral research. Thousand Oaks: Sage; 2003. p. 527-40.
328. O'Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. BMC Health Services Research. 2007;7(1):85.

329. Creswell J, Klassen A, Plano Clark V, Clegg Smith K. Best Practices for Mixed Methods Research in Health Sciences. 2011.
330. Bryman A. Barriers to Integrating Quantitative and Qualitative Research. Journal of Mixed Methods Research. 2007;1(8):8-22.
331. Aiken LR. Rating scales & checklists: Evaluating behavior, personality, and attitude. New York: John Wiley & Sons; 1996.
332. Patton MQ. Qualitative evaluation methods. Beverly Hills, CA: Sage; 2002.
333. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. In: Association WM, editor.: World Medical Association; 2008.