Improving Health-Related Quality of Life in Metastatic Breast Cancer:

Taking stock of achievements and delivering better measurement.

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The candidate confirms that the work submitted is their own and that appropriate credit has been given where reference has been made to the work of others.

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Abstract

Breast cancer is the most commonly diagnosed cancer worldwide and, the prevalence of those living with metastatic breast cancer (MBC) is also increasing. Metastatic patients face challenges associated with disease symptoms, receiving multiple systemic treatments, and the uncertainty of having a life-limiting disease with an unknown trajectory. The aim of this thesis was to better understand and assess the quality-of-life (QOL) related issues women living with, and being treated for, MBC experience. The objective was to develop an international tool to measure QOL of these patients, following the guidelines of European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life group.

A systematic review identified physical symptoms (e.g. gastrointestinal issues) as the most commonly reported problems. Psychosocial issues were less common, particularly within studies of investigational medicinal products. Review findings were integrated into a mixed-methods study designed to generate and assess QOL issues in MBC. Qualitative and quantitative data were simultaneously collected via semi-structured interviews and a survey. 187 patients and 41 Healthcare professionals were recruited from eight different countries. A core set of 44-issues was identified which included both physical symptoms (e.g. hair loss) and psychosocial problems (e.g. fear/uncertainty). An iterative approach was adopted to operationalise the issues into items, and consisted of a review of a pre-existing items from EORTC Item Library and expert consensus. A provisional 44-item questionnaire was created that assessed 40 core issues.

A qualitative review of Breast Cancer Now's online forum was conducted. Physical symptoms (e.g. fatigue) were most common, followed by psychological experiences (e.g. anxiety/fear), supporting previous findings of the systematic review and interview study. The triangulation analysis also provided complementary data for the issues included in the provisional questionnaire. Ultimately, this thesis concludes that better measurement of QOL in MBC patients will lead to better supportive treatments and patient-centred care.

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BCN – Breast cancer now

CTIMP - Clinical Trial of an Investigational Medicinal Product

EORTC – European Organisation for Research and Treatment of Cancer

EORTC QLG – European Organisation for Research and Treatment of Cancer Quality of Life Group

ESMO - European Society for Medical Oncology

FDA – Food and Drug Administration

HCP – Healthcare Professional

HRQOL – Health-Related Quality of Life

LCC – Leeds Cancer Centre

MBC – Metastatic Breast Cancer

NHS – National Health Service

PPE – Personal Protective Equipment

QOL – Quality of Life

RCT - Randomised Control Trials

REC – Research Ethics Committee

UOL – University of Leeds

Chapter 1. Introduction

Cancer impacts the lives of thousands people in the UK and around the world. Its impact can be seen either first-hand, as a secondary experience via a family member or close friend or on a tertiary level, through friends or social groups. It is now thought that 1 in 2 people in the UK will be diagnosed with cancer in their lifetime, with rising incidence rates associated with an increasing and aging population [1]. Breast cancer is the commonest cancer in UK, with 55,920 cases diagnosed each year 2016-18. Women account for the vast majority of all cases, the incidence of male breast cancer is low, accounting for approximately 1% of cases [2]. Survival rates for breast cancer patients are high, with 76% of patients alive 10 years post diagnosis, many of whom are living with metastatic or advanced disease. As a result of these characteristics, cancer is increasingly conceptualised as a chronic, or long-term, disease [3].

Higher rates of survival in this patient group are linked to the available treatment options, which traditionally include surgery, radiotherapy, hormonotherapy and chemotherapy, and more recently targeted therapies and immunotherapy [4]. The treatment of breast cancer is complex and requires the consideration of several factors including, but not limited to, the molecular subtypes and menopausal status of the patient [5]. Treatments have significant short and long-term toxicities associated with them, both of which can have a substantial impact on the lives of patients [6]. As a result, the importance of assessing patients' Health-Related Quality of Life (HRQOL) has been recognised within the clinical care pathway, and has since been established as study endpoints in clinical trials of new treatments [7].

Despite the success of treating early breast cancer and the increasing survival rates over the past decades, it remains that approximately 20% of patients will go on to develop metastatic disease, which unlike early breast cancer, is treatable but incurable [8]. These patients face the challenge of enduring the symptoms of their disease, receiving multiple cycles of systemic treatment, and living with the uncertainty associated with being diagnosed with a long term and life-threatening disease with an unknown prognosis [9].

The perceptions and knowledge of metastatic breast cancer (MBC) have been shown to be significantly lower than that of early breast cancer with metastatic patients reporting feeling forgotten and neglected at both a societal and clinical level [10]. For instance, the national breast cancer awareness campaign runs for an entire month, however, just one day is dedicated to MBC. In the UK, charities such as Breast Cancer Now champion these patients via multimedia campaigns designed to educate, support and improve the lives of these patients and ensuring no one is left behind [11]. Work of a similar nature is

also being conducted internationally by the Advanced Breast Cancer Global Alliance whose Global Charter aims to drive change in the care of patients with advanced breast cancer [12].

The terminology used to define this patient group is varied and its use often depends on the target audience of the publication, for example a clinical trial publication, a patient information leaflet or day to day language. By definition, breast cancer patients whose cancer has spread to another region of the body are referred to as metastatic breast cancer patients [13], yet multiple terms exist to describe this group. For example, MBC patients are also be referred to as having stage IV, advanced and/or secondary breast cancer. The term advanced is commonly used to describe this patient group however offers a less robust definition as it can also be applied to those with stage III or locally advanced cancer. International differences in the terminology are also seen, with the use of secondary breast cancer adopted within the UK and predominately used when communicating with or to the patient/general population [14]. For clarity, the terminology used throughout this thesis will be metastatic breast cancer.

This thesis studied the lived experiences of patients with MBC and aimed to improve the measurement of Quality of Life (QOL) in this patient group via the development of an internationally validated measure that can be used in multinational clinical trials as well as psychosocial interventions. The remainder of the chapter provides an introduction to MBC, its treatments, and the physical symptoms and QOL issues faced by this patient group. The aims and objectives of this thesis are then presented.

1.1 Metastatic Breast Cancer

Metastatic breast cancer is breast cancer that has spread from its primary location in the breast to another part of the body [13]. Metastasis is a complex process that ultimately permits malignant cells to establish secondary tumours at distant sites, including the bones, lungs, brain, or liver [15]. The most common site for the cancer to spread is to the bones, which accounts for around three quarters of cases [16]. Around 15-30% may develop brain metastasis, which of all the sites, has the lowest survival rates [17, 18]. The location of metastasis is associated the overall prognosis and treatment response [15], patients with bone metastasis have been shown to have the best survival rates [18]. The spread of cancer cells away from the original tumour site is achieved via several methods, including traveling through the blood stream or lymphatic system. This process has been likened to the ‘seed and soil’ hypothesis [19]. The cancer cells that have spread remain as breast cancer cells and are treated as such. By this, metastasis to the bones does not become bone cancer, it remains to be breast cancer.

When the patients first diagnosis of breast cancer is metastatic, it is referred to as being de novo metastatic breast cancer. In these instances, by the time the breast cancer is first detected, it has already spread to another region of the body [20]. For those diagnosed with metastatic disease, whether its de novo or not, systemic drug therapies are the main treatment options and include, chemotherapy, hormone therapy, targeted therapy, immunotherapy or a combination of these. The type of treatment is depended on several factors, mainly the molecular subtype of breast cancer (see 1.1.3 below).

1.1.1 Incidence rates

Breast cancer is now the most commonly diagnosed cancer, accounting for around 12% of all new cancer cases, and is the leading cause of cancer related death amongst females. Globally, the mortality and incidence rates increased annually across a 27 year period, with significant increases in mortality rates seen in the younger (under 50) and older (70 and over) age profiles [21]. Global incidence rates are higher in 'transitioned' countries such as those in North America, Australia and Northern Europe however, incidence rates are being shown to be increasing rapidly in countries across South America and Africa, highlighting why breast cancer has now superseded Lung cancer to become the leading cancer incidence in 2020 [22]. Mortality rates are highest for women living in 'transitioning' countries, such as those in Western Africa and the Caribbean, with the higher rates largely attributed to later presentation of disease at time of diagnosis [23].

There were 685,000 breast cancer deaths worldwide in 2020, many of whom had metastatic disease [22]. Of those diagnosed with breast cancer, 20-30% will develop metastatic disease and 10-15% have metastatic disease at presentation [5, 8]. Overall survival after a MBC diagnosis remains relatively low, between 2-3 years, with a five-year survival rate of around 25% [24, 25]. Despite significant advancements in the treatment and care given to patients, MBC remains a treatable, yet incurable, disease [26].

1.1.2 Molecular Types of MBC

1.1.2.1 Hormone receptor positive (ER+ & PR+)

The most common molecular subtype in breast cancer is known as the hormone receptor positive subtype. Cancer cells are referred to as hormone positive if they express the oestrogen receptor (ER) and/or the progesterone receptor (PR). Tumour growth is stimulated when these hormones bind to their respective receptors in the cell. This

subtype accounts for approximately 65% of all breast cancers diagnosed and has a range of treatment options available that target the hormone receptors [27]. In the past 10 years, combinations of hormonal treatments, fulvestrant or letrozole, with targeted agents, such as albociclib, ribociclib, and abemaciclib have improved outcomes for these patients [5, 28].

1.1.2.2 HER2 - *human epidermal growth factor receptor 2* (*HER2*)

The second most common subtype is 'Human epidermal growth factor receptor 2' (*HER2*). HER2 is overexpressed in around 15-20% of breast cancers which is somewhat lower when compared to the prevalence of the hormone receptor positive subtype [29]. When HER2 is overexpressed it is referred to as being HER2-positve, meaning higher levels of the HER2 protein receptor. These receptors are found on the cancer cells and are important for the growth of the tumour. Studies have identified its overexpression to be associated with a more aggressive disease and poor disease-free survival [30]. However, the development and use of new monoclonal antibody treatments that block the HER2 receptors (pertuzumab & trastuzumab), led to significant improvements in overall survival when combined with chemotherapy agents, such as and docetaxel [31]. Breast cancers that do not overexpress HER2 are referred to as HER2-negative and their treatment is dependent on the remaining molecular pathology.

1.1.2.3 Triple negative

Triple-negative breast cancer (TNBC) is the least common subtype of breast cancer. A tumour is classified as TNBC when the negative expression of hormone receptors, oestrogen (ER) and progesterone (PR), as well as the human epidermal growth factor receptor-2 (HER2) are detected [32]. TNBC accounts for 10–20% of all breast cancers and is subtype associated with high mortality and poor prognosis [33]. This is due to its molecular phenotype, as TNBC is not sensitive to hormone or targeted therapy, and for most patients, chemotherapy remains the main treatment option for this subgroup [5, 34]. However, immunotherapy has emerged as an option in the first-line setting for those with Programmed death-ligand1 (PD-L1) ≥1% in immune cells [35]. Atezolizumab plus nab-paclitaxel is an option for first-line treatment for PD-L1-postive TNBC either presenting with de novo MBC or at least 12 months since (neo)adjuvant chemotherapy [5].

1.1.3 Treatments

A range of treatment options are available for metastatic breast cancer, which can be broadly grouped into three categories: chemotherapy, hormonal/endocrine therapy and targeted/biological therapies [36]. Patients may receive other treatments aimed at ameliorating symptoms and side effects, such as anti-emetics to alleviate nausea and radiotherapy to relieve pain. Bone-modifying agents, such as bisphosphonates can also be given to patients with MBC and bone metastases to help reduce the risk of fractures. The process of selecting the optimal treatment is a complex, multidimensional process, involving the careful consideration of the cancer subtype, patient status and co-morbidities, previous treatments and patient preferences. Shared decision making is recommended to engage with patients and establish the goals of treatment [5].

Recent years have seen the number of treatment options available to patients grow, and new treatment combinations being established in clinical practice. The introduction of cyclin-dependent kinase (CDK)4/6 inhibitors combined with endocrine therapy as the standard of care for ER-positive/HER2-negative patients is an example of such progress [37, 38]. Further to this, atezolizumab, was the first immunotherapy for PD-L1-positive TNBC to substantially improve outcomes and is another example of how treatment advancements have paved the way for better disease control, enabling patients to receive multiple lines of treatment [5, 39]. However, unlike patients with early breast cancer, the treatment for MBC is no longer with curative intent. Instead, treatment objectives aim to prolong survival, control symptoms and maintain Quality of Life (QOL). The majority of patients receive sequential treatments for many years [25].

1.1.3.1 Chemotherapy

Chemotherapy for MBC is used to control the disease, prolong survival, prevent or reduce disease related symptoms and improve the individuals QOL but unfortunately cannot cure the disease. The mechanism behind these cytotoxic agents is the destruction of the cancer cells via the disruption or termination of the cell division process, as uncontrolled cell growth is a key characteristic of malignant cells. The use of chemotherapy is of particular importance in those patients that are refractive to hormonal treatments, as they can induce a rapid tumour response. Current practice recommends the sequential monotherapy as the preferred line of treatment in MBC, unless the patient presents in visceral crisis, rapid clinical progression or in need of rapid symptom control, whereby combination chemotherapy is used [5].

Cytotoxic agents are formed of multiple classes including taxanes, anthracyclines and anti-metabolites [40]. Taxanes are the most common class used in the treatment of MBC patients. Taxanes are microtubule inhibitors. Microtubules are involved in the cells ability to divide and replicate itself, therefore inhibiting these structures results in the death of the cell [40]. Examples of taxanes include docetaxel and paclitaxel [40]. Anthracyclines are another class of chemotherapy treatments which destroy cells by damaging the genetic structure of the cancer cells. Whilst this class of chemotherapy offers effective anti-cancer treatment, they carry significant side effects, mainly those impacting the heart [41]. Anthracyclines include, doxorubicin and epirubicin.

Antimetabolites, such as capecitabine and gemcitabine, attack cells at a specific stage of the cell cycle. Once they have been incorporated into the cell, they attack the cell and prevent it from being able to divide [42]. Other treatments available also include those that are platinum-based such as carboplatin and cisplatin.

Systemic side effects are common amongst those receiving chemotherapy as the mechanism utilised to destroy the cancer cells also impact non-malignant cells that share similar proliferation properties to those of the cancer cells. These include cells found within, hair follicles, nails, the mouth, bone marrow and digestive tract, resulting in hair loss, sore mouth and diarrhoea [43]. Nausea and vomiting, dry mouth/altered taste, irritated eyes, feeling ill and headaches are also common amongst those receiving chemotherapy-based treatments [43].

1.1.3.2 Hormonal Therapy

Hormone therapy (HT) is used in cases were cancer cells are hormone positive. HT works to stop or slow down the progression of the tumours by disrupting hormone levels in the body. This is achieved via hormone suppression or the disruption of the hormones ability to interact with the cancer cells [44]. There are several classes of drugs with distinct mechanisms of action.

Compounds that decrease endogenous oestrogen production include Gonadotropin-releasing hormone (GnRH) agonists, also known as luteinizing hormone-releasing hormone (LH-RH) agonists, and aromatase inhibitors (AI). GnRH and LH-RH agonists include treatments such as goserelin (Zoladex), These block ovarian function by interfering with signals from the pituitary gland that stimulate the ovaries to produce oestrogen, consequently reducing the growth of breast tumours [45]. They are used for treatment in premenopausal women to suppress the ovarian function often in combination with aromatase inhibitors.

Aromatase inhibitors suppress the levels of oestrogen by inhibiting or inactivating the enzyme ‘aromatase’, which is used by the body’s peripheral tissue to synthesise oestrogen [46]. AI’s are oral medications, that have two categories, steroidal and nonsteroidal. Non-steroidal AIs include, anastrozole and letrozole whose action temporarily inactivates aromatase. Exemestane is an orally active steroidal AI that permanently inactivates the enzyme and has been shown to demonstrate activity following AI resistance [44]. AI are used in post-menopausal women.

Mechanisms that directly antagonise oestrogen receptors are known as selective oestrogen receptor modulators (SERMs) and selective oestrogen receptor degraders (SERDs) [47]. These compounds are designed to compete with oestrogen by binding and altering the oestrogen receptors which in turn blocks and prevents the activation of the receptor [47]. Tamoxifen is an oral drug, and an example of a SERM used in the treatment of ER-positive metastatic breast cancer patients. Tamoxifen was originally developed at the University of Leeds, and was the first widely used hormonotherapy for breast cancer. Fulvestrant is another SERM, which has a higher affinity for ER compared to tamoxifen, and functions only as an oestrogen antagonist [44]. Fulvetsrant is administered as intra muscular injection on a monthly basis.

Hormone therapy is generally the first line for treatment for patients with hormone receptor (HR) positive disease, including those with visceral metastasis, providing they are free from visceral crisis [5]. The first line agent is dependent on a number of factors including type, duration and time since completing adjuvant HT. Recently published guidelines on the treatment of MBC propose only a small group of patients can be treated with HT alone. Instead, patients with HR-positive/HER2-negative breast cancer are treated with Targeted therapy + HT, as it has been shown to provide a substantial progression free survival benefit, significantly increases overall survival and either maintains or improves QOL [5].

The side effects and ongoing health related issues experienced as a result of HT have been shown across numerous clinical trials [48, 49]. Common side effects of Tamoxifen include hot flashes, night sweats, weight gain, mood swings. Oestrogen deprivation from AI’s is linked to the increase of menopausal symptoms such as sleep disturbances, vaginal dryness, decreased libido, fatigue and hot flushes [50], as well as dizziness, sweating, weight gain/loss as well as joint and bone problems, and mood disorders [51].

Menopausal status determines the choice of HT. Tamoxifen can be used in both pre- and post-menopausal women, whereas AI work only in post-menopausal women. Increasingly, a treatment strategy in pre-menopausal women is to induce ovarian

suppression (either temporary with GnRH agonists, or permanent with radiotherapy or surgically) and combine with AI [5].

1.1.3.3 Targeted Therapy

Targeted therapies (TT) for MBC are often used in combination with chemotherapy or hormonal therapies to improve their effectiveness. Targeted therapies can differentiate between the cancer and normal cells, leading to fewer side effects. The mechanism in which the TT works differs across the various agents, however all interfere with cancer cells ability to grow, divide, repair and/or communicate with other cells [52].

The type of TT received is depended on the cancer histology. Monoclonal antibodies, antibody-drug conjugate and tyrosine-kinase inhibitors are used in the treatment of HER2-postive cases. Monoclonal antibodies are synthetic versions of immune system proteins that are designed to attach to a specific target on the cancer cell to kill or prevent it from growing. They include treatments such as trastuzumab, pertuzumab and margetuximab [53-55]. Antibody-drug conjugates are a monoclonal antibody linked to a chemotherapy agent and includes treatments such as TDM-1 (Kadcyla) and trastuzumab deruxtecan [56]. Tyrosine- Kinase inhibitors block the signals, such as those telling the cell to grow, from being relayed. Tyrosine-kinase inhibitors include lapatinib and tucatinib.

In recent years, the treatment for HR-positive/HER2-negative cancer has seen the establishment of cyclin-dependent kinase (CDK)4/6 inhibitors combined with hormonal therapy (HT) as standard of care in MBC [5]. This combination has been shown to provide benefits in overall survival, as well as benefits in progression free survival all whilst maintaining a good toxicity profile [38, 57]. CDK4/6 inhibitors include palbociclib, ribociclib and abemaciclib which block the CDK proteins in the cell, stopping the cells dividing and thus slowing the growth of the cancer in HR-positive cases.

Alpelisib is a PI3K inhibitor which blocks the formation of the PI3K protein in cancer cells which impacts the cells ability to grow. The SOLAR-1 phase III clinical trial found progression free survival benefit in postmenopausal patients previously treated with an Aromatase inhibitor [58]. Another treatment available for the treatment of HR-positive/HER2-negative is everolimus. It is an mTOR inhibitor and works to block the protein in cells that helps them grow and divide. Further to this, it has been shown to reduce levels of growth factors involved in the development of new blood vessels such as vascular endothelial growth factor [59].

With the increased use of targeted therapies, there has been a wave of new and frequently occurring adverse events associated with this type of treatment. Such issues include, sore mouth and mouth ulcers, diarrhoea and neutropenia [60]. Vomiting, nausea, hair loss/thinning and fatigue are also common side effects [61]. For certain targeted therapies, such as alpelisib, patients were found to develop diabetes [62].

1.1.3.4 Immunotherapy

In the era of precise medicine, the development of treatments such as atezolizumab and pembrolizumab has resulted in new lines of treatments for tumours that were previously thought to have poor immunogenic properties, such as triple-negative breast cancer [63]. These treatments work by blocking antibodies against programmed death 1 (PD-1)/ PD-L1 resulting in effective local tumour control. Atezolizumab is a monoclonal antibody that attaches to PD-L1 and “blocks” its checkpoint function, which facilitated the attack of the cancer cells by the immune system [64].

Immunotherapy treatments are generally well tolerated, side effects can include fatigue, nausea, diarrhoea back pain, fatigue, hyponatremia, hypotension and migraine [65, 66] Immune-related side effects can be serious when more than one immunotherapy compound is used in combination, affecting multiple organs and requiring immediate active management [5].

1.1.3.5 Radiation Therapy

Radiotherapy is traditionally and most commonly used as a palliative treatment for pain associated with bone metastases. Whole brain radiotherapy was the only available palliative treatment for brain metastases until recent developments in targeted radiotherapy and neuro-surgery produced better results particularly when brain metastases are solitary and limited number.

As highlighted, the treatment of MBC is a complex process and require detailed plans to determine the most appropriate and effective mode of treatment. Treatment planning for MBC is an example of individualised/personalised medicine, taking into account tumour molecular profile, cancer spread, co-morbidities and patient preferences. To aid in this process, international guidelines are published and continuously updated by organisations such as the European Society for Medical Oncology and American Society of Clinical Oncology, on the recommended treatment plans [5, 67]. New drugs are being tested with new mechanisms of actions and new toxicities. Collecting data not only on the side-effects, as reported by clinicians, but also on their impact on patient experience

is essential to inform shared decision making and personalised approaches to treatments.

1.2 Quality of Life

The complexity and uncertainty of the MBC disease trajectory, combined with the sequential treatment regimens, has the potential to negatively impact all aspects of the patient's life. Throughout their illness journey, a wide spectrum of physical symptoms and side effects, and psychosocial issues, such as distress, anxiety or family, social or employment difficulties are experienced by the patient [9, 68]. In the initial phases of the illness trajectory, women experience a period of adjustment to being diagnosed with a treatable, but incurable disease. This includes feelings of stress, worry and the onset of physical symptoms [69]. Following this, patients are faced with the challenges associated with living with a progressive disease, such as the difficulties in coping with the demands of the continuous treatment regimens and relentless nature of the disease. In the final phases, patients begin the downward trend towards the end of their lives, categorised by the increased frequency of illness crisis, such as uncontrolled symptoms resulting in hospital admissions and/or referral to a specialist palliative care support pathway [9, 70]. Understanding such issues is vital in providing the best possible care to the patient and therefore makes assessing QOL in this patient group crucial.

Since the 1990's, improvements in survival for both recurrent and de novo MBC patients have been shown [71], and with patients now living longer, the acute symptoms and side effects of treatments are coupled with wider, long-term issues relating to living with a disease that is life-threatening but treatable and as such, MBC can now be defined as 'chronic' [3]. Issues span multiple domains, with MBC patients being found to have lower functional, social, physical and emotional well-being [69]. The consequences of the disease and treatments are reflected in the patient's Health Related Quality of Life (HRQOL), which has been recognised as an important endpoint in cancer treatment and trials [72].

Quality of life, or HRQOL, is a multi-dimensional concept, comprised of physical, psychosocial, emotional and functional dimensions, that captures the patient's subjective perceptions of their state of health [73, 74]. As QOL relies on the subjective perceptions of the patient, a self-reported method of assessment is required, one that can take on the views and insights provided directly by the patient [75].

The current body of literature indicates patients with MBC have worse QOL than other breast cancer groups [76, 77], yet receive less support than those with early breast

cancer [25]. This is highlighted within palliative care setting, which is tasked with improving QOL and ameliorating the physical and psychological burden placed on the patient [78], whereby, despite being in regular contact with cancer centres, the uptake of women accessing these specialist services remained to be low. As shown by the high number of patients reporting significant pain and worsening QOL [69].

The Decade report underlined the decline seen in overall QOL in MBC patients over the last 10 years by identifying that the needs of the MBC patient remain unmet, as well as highlighting the inconsistency in which HRQOL data was reported within the literature [25]. Further to this, patients report maintaining their QOL as being amongst one of their main concerns in regards to treatment outcomes. The “Here and Now” survey conducted by Cardoso and colleagues, QOL was identified by patients as the largest area of care in need of improvement [79]. Identifying the physical and psychological impact MBC and its treatment has on patients QOL should be a focus for healthcare providers as QOL is a leading concern in this setting [80].

1.3 Patient Reported Outcome Measures

With the push towards patient centred healthcare, the collection of data to better understand the needs and perceptions of patients has never been more critical [81]. Whilst clinician reported data, such as the reporting of adverse events in clinical trials, are highly valuable, assumptions of the overall impact on the patient cannot be made. Instead, to understand the effect on the individual, data must be provided directly by the patient [75].

Patient-reported outcome measures (PROMs) are measurement tools developed to quantifiably assess a patient’s subjective experience of their treatment and/or disease, without the need for interpretation by a healthcare professional [82]. PROMs are particularly useful in the measurement of outcomes that are not observable and thus can only be measured by the patient themselves, such as the impact of symptoms and side effects. They contribute unique data that would otherwise but unobtainable and are frequently used within the literature to assess the QOL of MBC patients in both clinical practice and research [83-85]. Within a clinical environment, the inclusion of PROMs in routine care has been shown to improve patient satisfaction, QOL and health related outcomes [86]. PROMs are increasingly included as study endpoints in clinical trials whereby comprehensive accounts of the global benefit of the new therapeutic treatments are required [87, 88]. QOL has been shown to support labelling claims of the new treatments being developed and tested [82].

Several organisations have led the way in the development of valid questionnaires to assess QOL within a cancer population. The European Organisation for Research and Treatment of Cancer (EORTC) and the Functional Assessment of Chronic Illness Therapy (FACIT) group are two examples of organisations pushing the boundaries in the development of questionnaires to transform the subjective concept that is QOL into a measurable concept [89, 90].

The current tools for assessing QOL in clinical research include generic cancer measures, that capture the wider 'cancer experience' and measures that are specific to a particular cancer site or treatment. Examples of generic measures include the EORTC Core Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy - General (FACT-G) [91, 92]. While general cancer-related PRO measures have been used in MBC research, the need for disease specific assessment methods was called for [93]. Disease specific measures now include the EORTC Breast Cancer module EORTC QLQ-BR45, previously the QLQ-BR23, and the Functional Assessment of Cancer Therapy – Breast (FACT-B) both of which are used in combination with their generic counterpart to assess HRQOL in breast cancer patients [94, 95]. Whilst these measures are specific to breast cancer, concerns have been raised over their appropriateness for use in the metastatic setting [93]. One MBC specific questionnaire was identified, metastatic breast cancer progression (MBC-P) questionnaire which looked to measure the importance of progression free survival in this patient group. This questionnaire however was not validated nor was it widely used within clinical research [96].

Breast-cancer specific PROMs were developed primarily for early-stage breast cancer, therefore translating them to patients with MBC can be challenging, as although both are breast cancer, they differ biologically, clinically and in the wider impact they have on the patient and their family [97]. Despite recent updates to the EORTC QLQ-BR23, it is thought that updated module (QLQ-BR45) may still not capture the full range of unique issues associated with living with advanced disease [98]. This raises concerns over the measures ability to detect change in the metastatic population and therefore lack the ability to accurately demonstrate variation between treatments when used in clinical trials. A MBC specific measure would reduce the heterogeneity in the questionnaires used to evaluate QOL in this sample, which has widely been a criticism of MBC research as it complicates the interpretability and comparability of the outcomes across studies [93].

The Global Status of Metastatic Breast Cancer report supports the need for a MBC-specific QOL instrument, that can be applied in both research and clinical practice [25]. The report recognises its development as an essential step towards improving our understanding of QOL in these patients, as well as to flag unmet needs, and better assess QOL in this group of patients. The development of such a measure is also endorsed by the European Society for Medical Oncology (ESMO) within the most recent guidelines [5]. To address the gap in the literature, the EORTC commissioned a work package, from which my PhD was funded, to develop a MBC-specific questionnaire. The EORTC Quality of life group employ a modular approach to assessment whereby the core questionnaire (EORTC QLQ-C30) is used in tandem with a disease-specific module (questionnaire) to assess the QOL of a particular cancer group. My thesis informed large parts of this development, including the literature reviews, collection and analysis of data and creation of the provisional MBC-specific module. The EORTC's published guidelines for module development were used to guide the research and consists of four phases.

- Phase I is focussed on the generation and identification of the relevant and important issue women living with MBC experience as a result of their treatment and/or diagnosis.
- Phase II consists of the item development stage. During Phase II, the issues previously identified in phase I are operationalised into full questionnaire items.
- Phase III pre-tests the items for clarity and establishes initial psychometric properties.
- Phase IV is the final stage of the EORTC's module development process which involves the large-scale international validation of the questionnaire.

My thesis focused on the first two phases of the development process. Whilst the guidelines provided a comprehensive overview of the developmental procedures, scope was available to expand and explore alternative methodologies within my PhD, such as a systematic review and analysis of an online forum posts.

1.4 Aims and objectives

The overall objective of this PhD was to better understand the quality-of-life related issues women living with, and being treated for, metastatic breast cancer experience. The thesis is driven by this, with the aim of delivering an international tool to address the gap in the literature that calls for a linguistically and culturally acceptable tool that better measures QOL in this patient group.

Research questions

- How is QOL currently being assessed in MBC patients in clinical trials and other studies?
- What issues do patients with MBC experience as a result of their disease and/or treatment?
- What issues are most relevant and important to patients?
- How can we better assess QOL in MBC?
- How does the data reported in online forums compare with the core issues included in the QOL questionnaire?

Hypothesis

- The heterogeneity and prolonged treatments of MBC will result in a range of treatment and disease related symptoms, as well as having a wider psychological and social impact on the patient's life.
- There will be a range of measurement tools used to assess QOL in MBC.

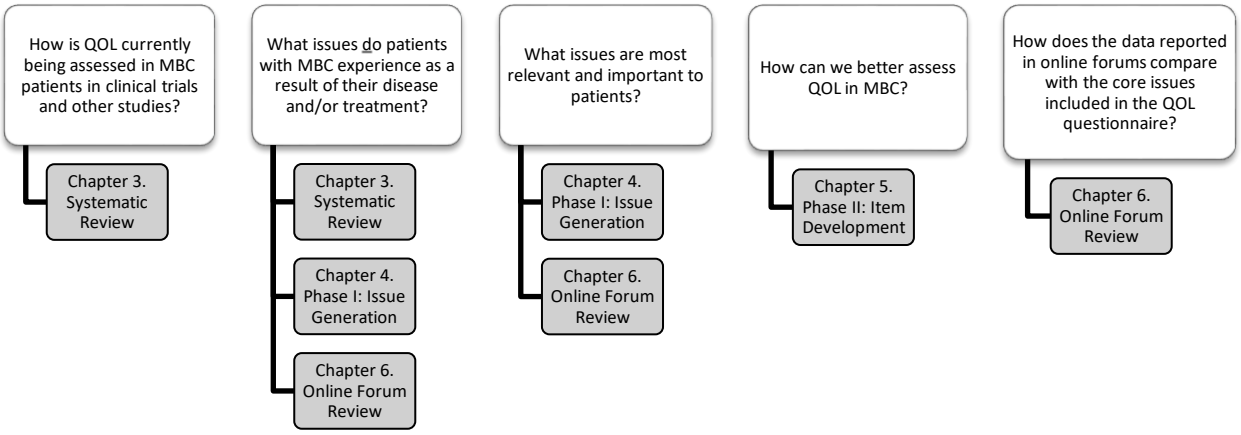


Figure 1. ***Overview of the research questions and the corresponding thesis chapters.***

1.5 Outline of the thesis

Chapter 2 – Methodology

This chapter details the methodological approaches and frameworks adopted throughout the thesis in order to answer the research aims and objectives. It outlines the position of this work within the EORTC development framework, and provides details on the methods selected at each phase of the development process. The chapter concludes with the ethical considerations surrounding this project, as well as the wider context in which this research was conducted.

Chapter 3 – Systematic review

Chapter 3 presents the systematic review of the literature to provide evidence of the current knowledge on QOL. A mixed methods review was conducted to capture the QOL related issues and measurement tools reported in Phase III Clinical Trials of Investigational Medicinal Products (CTIMPs) and Non-CTIMP studies (including observational & qualitative research).

Chapter 4 – Phase I: Issue Generation

Building upon the work completed in Chapter 3, this chapter presents the research activities conducted in Phase I of the development process. Patients and healthcare professionals completed a semi-structured interview and a questionnaire survey to generate data on the relevance and importance of the QOL related issues experienced.

Chapter 5 – Phase II: Item Development

Chapter 5 presents the methods and results of the second phase of development which aimed to operationalise the issues selected for inclusion in Phase I into fully formed questionnaire items. This work resulted in the development of a provisional questionnaire to be validated in the future international studies.

Chapter 6 – Online forum review

Chapter 6 outlines the qualitative review conducted to explore and compare the range of issues discussed within an online forum hosted by the UKs largest breast cancer charity (Breast Cancer Now). The results of this review were triangulated with the findings from Chapter 3 and 4 to compare the results from the different methodological approaches with the aim of providing complementary data in addition to the standard methods used when developing questionnaires.

Chapter 7 – Discussion

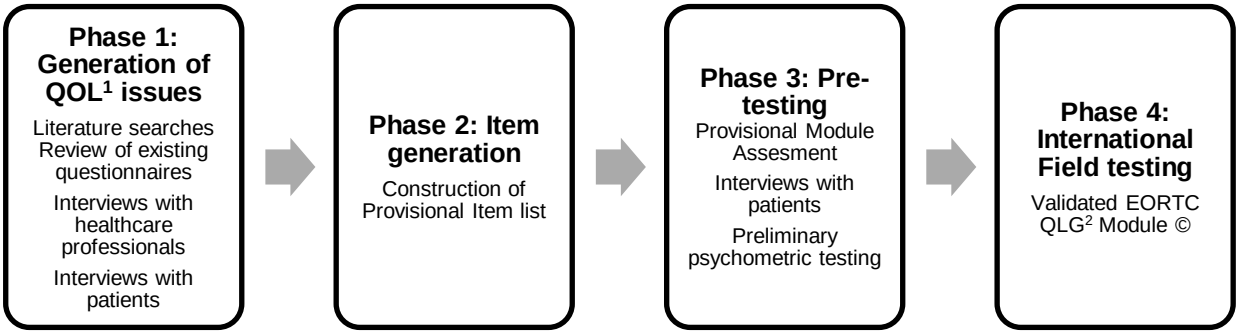
Chapter 7 discusses the key results of the research conducted within this thesis and their wider implications in both a clinical and research settings. A reflective account of the research journey is provided including the challenges and learnings associated with coordinating a multi-centred international project. Final conclusions of the thesis are presented.

Chapter 2. Methodology

Chapter 2 presents the methodological approaches utilised within the thesis to answer the research aims and objectives outlined in Chapter 1. It provides an overview of the wider framework from which the thesis was structured as well as details on the underlying concepts and rational from which the methods were selected. Detailed descriptions of the specific research methods are described within the individual chapters. Whilst this thesis was positioned within the wider European Organisation for Research and Treatment of Cancer (EORTC) Quality of life group project, I was able to develop and deliver additional components to explore and understand the impact of Metastatic Breast Cancer (MBC) on patients Quality of Life (QOL) and wellbeing. Here, I cover the different methods used within questionnaire development and the conceptual frameworks underpinning the research. Then an overview of the EORTC module development methods is presented. The final section of this chapter highlights the ethical considerations and research governance procedures followed.

2.1 Methodological framework

As discussed in Chapter 1, the structure of the thesis was largely determined by the EORTC's module development guidelines which outlined four key phases of developing an internationally validated questionnaire module [99]. This thesis focussed on Phases I+II. Within the thesis, a mixed methods approach was adopted. The methods were incorporated within each phase and used to address the research questions set out in Chapter 1.



[1]Quality of life, [2]European Organisation for Research and Treatment of Cancer Quality of life Group.

Figure 2. *EORTC module development framework v4*.

My role within this large scale, international research project was study coordinator. This included, but was not limited to, establishing the network of collaborators; Undertaking the research governance procedures in the UK, including the development of the research protocol and study materials and supporting the applications made by the collaborators; Managing research activities, for example recruitment, data collection and data analysis and the general management and running of the project. This proved to be a huge undertaking on my part as my PhD was largely dependent on the successful delivery of the project.

The complexity of delivering a research project of this nature was high. The use of a rigorous and methodologically sound framework from which to build and deliver high impact research was crucial. A strength of the methodological approach adopted in this project stemmed from the guidance provided by the EORTC module development framework [99]. The process of developing new, patient reported outcome measures are discussed throughout the remainder of this chapter.

2.2 Questionnaire development

Patient Reported Outcomes Measures (PROMs) were developed to assess health outcomes directly from the patient's perspective [100]. Their primary use was within clinical research as they provide a patient-centred method for assessing impact and effectiveness of treatments. Over recent years, the field of patient reported outcomes research has progressed, with the implementation of PROMs within routine clinical practice as well as in non-pharmaceutical trials [101]. The inclusion of PROMs in clinical research is now well established, with many regulatory institutes, including the Food and Drug Administration (FDA), supporting their inclusion in Clinical Trials of an Investigational Medicinal Product (CTIMPs) [82]. Quality of life is one example of a PROM that has been identified as an important endpoint in such trials.

PROMs data provides valuable information on the impact new treatments have on the patient beyond the adverse events recorded by the Healthcare Professionals (HCPs). A common concern, and/or criticism of the older QOL related PROMs used in cancer patients relates to lower levels of content validity. This is a result of the older measures being developed without the involvement of patients, rather, they were created by clinicians and other healthcare professionals only [91, 102].

The inclusion of patients in the development of PROMs has since been established as a critical part of the development process and is endorsed by the FDA who recognise the importance of the patient's voice. Measures that fail to include patients run the risk of

omitting relevant and important issues experienced by the patients, and thus limiting the validity of the measure [103]. To highlight this issue, a systematic review investigating studies of PROM development, identified that over a quarter of the included papers failed to involve patients at any stage of the development process [104]. Future studies should include patients within multiple stages to ensure the development of a valid measure.

Advances in this area have been seen over the years with updated methodologies and published guidelines now available to researchers developing PROMs in order to improve the quality of newly developed measures (EORTC and COSMIN checklist) [99, 105]. For measures developed without the involvement of patients, such as the EORTC QLQ-C30, work has been conducted to assess its content validity to ensure that despite the lack of patient involvement, it is in fact a valid measure for assessing QOL in cancer patients [102].

The inclusion of patients throughout the development process was carefully considered in this project to ensure the questionnaire was representative of the patient's needs and wants. Wiering et al., highlighted four stages in which patients can be involved (issue generation, issue evaluation, item review and item development) [104]. This current project involved patients in two of these stages, including 'issue generation' and 'issue evaluation'. In Phase I, women living with, and being treated for, MBC were interviewed to identify the QOL related issues experienced by this patient group. Further to this, patients assessed each of the core QOL related issues identified for their relevance and importance to them. The results of which facilitated the work completed in Phase II. Phase III of the project intended to involve patients across the 'item review and development' stages, whereby patients would review the items to ensure each were suitable in terms of their coverage as well as their level of comprehension. Item development is complex, and often completed by specialists as the process requires the individual core issues or domains to be operationalised, often from single words, to fully formed questionnaire items. This is particularly challenging when working internationally with multiple cultures and languages. It can be argued that patients are involved in the 'item development' stage as during Phase III, patients are given the opportunity to comment on the wording of the items before the questionnaire is finalised. The feedback provided at this phase can be used to modify and amend the items as and when required.

Currently, there is no single commonly agreed approach for the development and design of questionnaires [106]. Multiple methodological approaches are available within the literature, including the EORTC guidelines as well as the COSMIN checklist for assessing the methodological quality of PROMs [105]. Common themes between these

methods revolve around the concept of content validity, with the EORTC methodology focused on optimising content validity and the importance of the patients voice. Further to this, the EORTC methods require simultaneous development in several languages and cultures resulting in a questionnaire that is internationally valid. For the purpose of this thesis, the EORTC's module development guidelines were used as a framework to guide the research as it offers a robust and well-established methodology for developing QOL questionnaires within a cancer population.

The first version of the guidelines for module development were published in 1993 [107] and have since provided module developers with a framework to build high quality PROMs. The guidelines have been revised over the years to reflect the advances within the field, with the current guidelines in their Fifth Edition. The guidelines standardise the development process to ensure uniformity and high quality standards are maintained across all modules. Figure 3 provides an overview of the development process, as applied in my thesis, and the methods involved at each phase. It is important to note that within the module guidelines there was a scope for me to expand and explore additional methods and encompass these within my thesis. These expansions include a scoping review of the drug treatment Investigator Brochures (IBs) and the qualitative analysis of an online cancer forum.

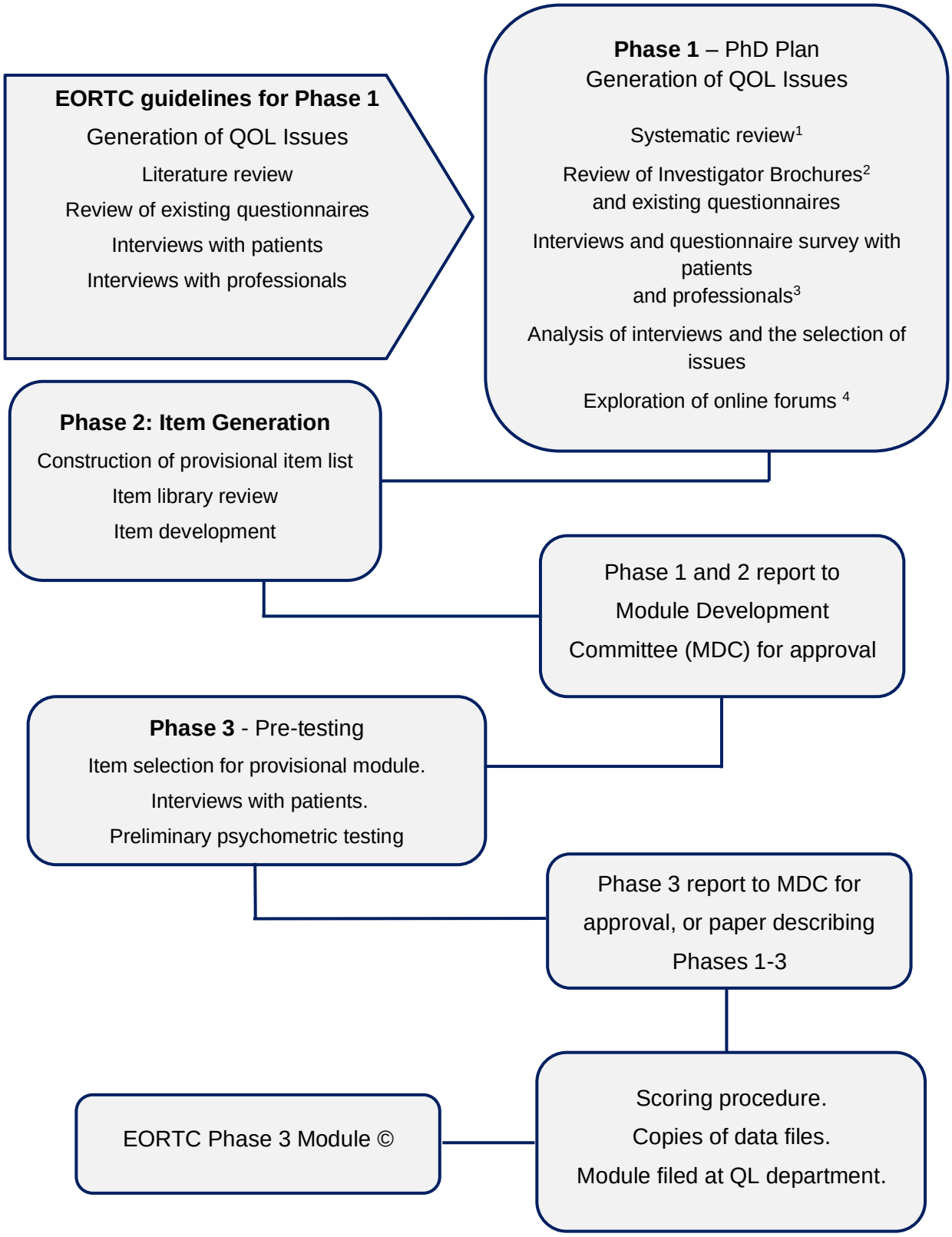


Figure 3. ***PhD plan for module development and EORTC development guidelines v4.***

[1]Systematic review of clinical trials, psychosocial, observational, and qualitative studies
[2]Review of the medical literature for therapies used to treat MBC
[3]Extended interviews exploring the QOL related issues associated with MBC
[4]Review of Breast Cancer Now online forums

2.2.1 Conceptual framework

The implementation of a conceptual framework is an integral step when developing a questionnaire, helping ensure the research covers the relevant domains and provides insight into the relationships between them [108]. In light of the clinical characteristics of MBC, it was theorised that a wide range of issues were likely to be experienced and reported by patients and therefore a relevant framework was needed to reflect this and facilitate the inclusion of the appropriate concepts. Further to this, it was expected that the range of issues would go beyond physical symptoms and side effects, and so the framework had to have been capable of capturing the breadth of the impact of MBC upon physical, psychological and social functioning.

Examples of established of theoretical frameworks which have the potential to encompass the symptoms of disease but also the psychological impact of a long-term condition are the Health Related Quality of Life (HRQOL) conceptual model and the Generic Choice Model for long term conditions (GCM) [109, 110]. The HRQOL conceptual model explores the relationships between biomedical factors, symptoms, functioning, general health perceptions and overall QOL and was revised in 2005, by Ferran et al., in an attempt to facilitate its application within health research by defining each of the included variables (Figure 4) [111]. The model explains HRQOL conceptually by linking traditional clinical variables, such as those from medical histories and physical examinations, to symptoms of disease, the impact of disease symptoms on functional status, and also takes into account the influence of the individual personality and the environment. Figure 4 highlights how the concepts are linked within the model. The arrows indicate the dominant associations, and whilst not categorised in the figure, reciprocal interactions are recognised to exist.

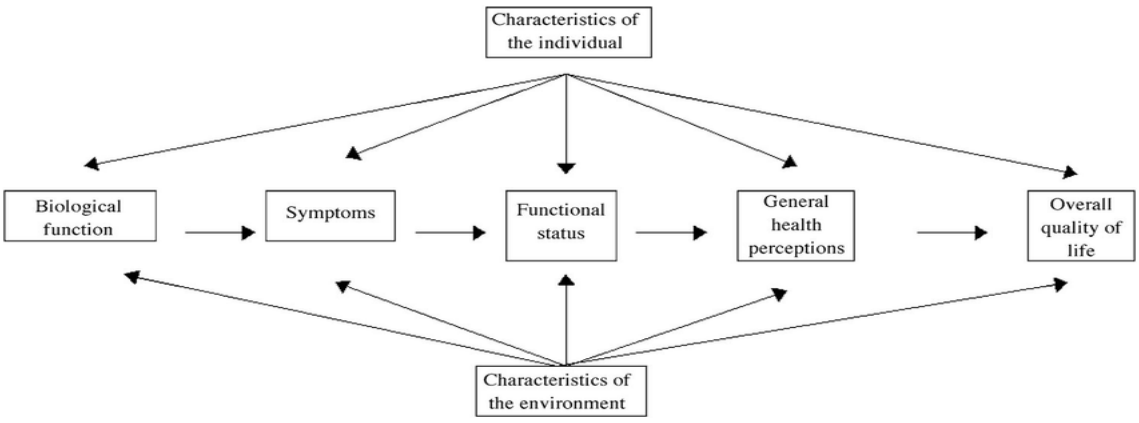


Figure 4. Revised Wilson and Cleary model *(1995) linking clinical variables with Health-Related Quality of Life: a conceptual model of patient outcomes*. Adapted by Ferrans et al. 2005.

The Generic Choice Model for long term conditions [109] was originally published in 2007. It was developed in conjunction with a number of patient organisations in an attempt to improve good clinical practice and reduce the inequalities patients living with long-term conditions experience. The GCM gave onus to the patient over their care by helping identify the specific needs and desired outcomes of treatments, which is of importance as clinical care progresses towards a more personalised approach. Whilst this model was proposed for patients with a chronic condition, its application within oncology has been demonstrated in previous research [3]. The application of this model within the metastatic breast setting was proposed due to the argument that with the expansion of new effective treatments, MBC could be considered a long-term condition. This was defined within a study conducted by Harley et al. (2015), who applied the model within a chronic cancer sample to explore patient experience when living with cancer as a long-term condition. The framework consisted of six domains, 1. Clinical services, 2. Self-care and self-management, 3. Needs for Independent Living, 4. Work, finances, and benefits, 5. Psychological experiences and 6. Support pathways.

Both models were considered for inclusion, however the GCM was selected as the primary conceptual model as it encompassed the core domains associated with MBC. The GCM was implemented throughout the thesis, and provided a framework from which the results of the chapters were mapped. Specifically, it was used in the categorisation the QOL related issues identified in the systematic review, the drug Investigator Brochure (IB) review and the online forum review. It was also utilised in the design and development of key instruments, including the 'issue list questionnaire' used in Phase I interviews, and the provisional QOL questionnaire developed in Phase II. The application of the conceptual model in this way facilitated the interconnectivity between each piece of work and ultimately, the ability to compare and contrast the different research findings. The model aided the development process as it enabled the conceptualisation of the issues included within the proposed questionnaire [108].

2.3 Phase I: Issue Generation

The objective of Phase I was to identify and assess the QOL related issues affecting women living with metastatic breast cancer. The phase consisted of two key tasks, each aimed at achieving the highest possible level of content validity in the final module. The first involved reviewing the literature to identify and generate an exhaustive list of potential issues. The second involved interviews with patients and health professionals to determine the issues' relevance and importance, followed by analysis and decisions for inclusion in the new module.

2.3.1 Literature review

Literature reviews provide a comprehensive summary of research previously conducted on a given topic and are often the starting point for all research as they allow for the collection, evaluation and identification of gaps within the area of research. Multiple forms of review exist, each with their associated strengths and limitations. The type of review conducted for any given research is dependent on several factors, including the time-frame in which the work needs to be completed, resources available to the researcher and level of comprehension required to answer the research question [112]. Common review types include narrative reviews, rapid reviews, scoping reviews and systematic reviews [112]. Narrative or scoping reviews usually have the shortest timeframe for completion and offer a broad overview of the literature. They are useful when looking to identify gaps within the research. Data produced as a result of such reviews can be limited in their generalisations in comparison to other reviews, such as rapid or systematic reviews.

Despite the name, rapid reviews are more extensive as they employ a more systematic approach to identifying the research. They are used to assess what is known about a particular issue and can offer more detailed analysis, contributing to data that may inform clinical practice [112]. Limitations exist over the level of comprehension they provide [14]. Systematic reviews are regarded as the gold standard for synthesising evidence in healthcare due to their rigorous and systematic methodology. They provide a more complete coverage of the literature and provide a robust platform and level of data from which to build research from [113].

In this thesis, two reviews were conducted to capture the relevant data needed to facilitate the development of a valid, and robust questionnaire. The reviews aimed to provide a comprehensive dataset of the range of issues and problems women living with, and being treated for metastatic breast cancer experience. The primary review was a systematic review and consisted of a systematic search of literature to capture the data required for the development of the new QOL questionnaire, as well as provide information to further our understanding of how QOL is assessed within this patient group. Systematic reviews are regarded as the gold standard for synthesising evidence from the literature as they result in a more complete exploration of the available data published within this area and thus allowed for the development of a comprehensive search strategy needed to answer the proposed research questions [113]. With regards to the EORTC module development guidelines, the completion of a systematic review was not a requirement, for example, a scoping or rapid review could have been

completed instead. However having considered the methodological strength of systematic reviews, it was decided that this method would provide a robust platform from which to answer the research questions outlined in Chapter 1.

In addition to the systematic review, a second review was completed as part of this thesis. The methodological requirements of this review were found to be best suited to that of a scoping review as the aim of this review was to provide a broad overview and complimentary data to support the primary review in a timely and efficient manner [114]. The scoping review was conducted to specifically explore and extract the most common adverse events documented within the investigator brochures of the current treatments used within the MBC setting. Whilst the use of scoping reviews is well practiced, the utilisation of this method to review drug investigator brochures was somewhat novel within the methodological approach to questionnaire development. For example, it is not currently standard procedure within the EORTC module development guidelines, yet offers a new method for extracting adverse event data from within the literature [99].

2.3.2 Qualitative methods

Qualitative methodologies are increasingly being utilised to further our understanding of various health-related topics. The qualitative method allows for the collection of rich data to examine the 'how' and 'why' behind a patient's behaviour, needs, and/or experience of a particular health related issue [115, 116]. Qualitative methods favour research that aims to explore, understand, and evaluate the thoughts, feelings and actions of patients in a humanistic, and patient-centre way [116]. Due to the wide range of applications of this methodology, recent years have seen an increased number of studies adopting this approach [117].

Multiple methods of collecting qualitative data exist, and includes interviews, focus groups and ethnographic observations. Observations allow for the study, and collection of data, from a range of phenomena and are used to facilitate the development of theories as well as to offer insight into how naturally occurring issues are experienced without intervention [118]. Within healthcare this may include the observation of staff to assess levels of procedural compliance [119]. When compared to other qualitative methods such as interviews and focus groups, observations are a less common method data collection.

Interviews are one of the most common methods of qualitative data collection within social and health research [120], repeatedly selected as they provide a rich source of data well suited for the exploration of personal experience. They are particularly

beneficial when conducting research investigating topics of a sensitive or difficult nature as they often take place on a one-to-one basis allowing the researcher to facilitate discussion as well as offer support to participant if needed. This is an advantage interviews have over other methods, such as focus groups. Focus groups are a method of collecting qualitative data from multiple people at the same time, making them an efficient way of collecting data. The data is often rich as participants can facilitate discussions that may otherwise not have been captured. Alternatively, this can also be seen as a drawback as discussions can become dominated by individuals [121].

Despite the advantages qualitative research has with regards to the data they produce, common criticisms of interviews are that they are time consuming and require specialist skills to conduct interviews correctly. However, in the current research landscape, societal changes towards engaging with new technologies has provided greater scope to conduct interviews remotely. The advancements and access to technology has facilitated the ability to conduct interviews remotely, which saves a great deal of time for both the participant and the researcher [122].

Semi-structured interviews were selected as the most appropriate method for collecting qualitative data in Phase I as they allow the collection of rich, open-ended, data from the participants [123]. Specifically, interviews provide participants with the freedom to discuss their experiences of living with and being treated for MBC, whilst also providing structure from which to guide discussions and stay within the remit of the study objectives. In the case of the Healthcare Professionals (HCPs), interviews provide the scope for the open discussion around their experiences of treating women with MBC and the exploration of the issues often discussed within their consultations. The inclusion of an interview guide provides structure to the interview and the use of probes and follow-up questions facilitate the exploration of the participants experiences, a critical process in the generation of new issues and in the development of PROMs.

A methodological benefit of conducting patient interviews in the earliest phase of the development process is due to the improvements shown in the content validity of the final questionnaire. Patients are able to report the issues that are directly relevant to them, these issues are subsequently included throughout the development process resulting in a questionnaire derived directly from the patient's experience. This strength is highlighted by Rothman et al (2009), who states 'patient interviews are the most important of four steps to ensure high content validity is achieved and demonstrated' and for this reason, qualitative interviews were included at the earliest phase of the module development process [124]. Further to this, qualitative interviews have been a

cornerstone of EORTC QLG module development for many years, with their inclusion endorsed by the FDA guidance [82]. Other methods, such as focus groups were considered, however due to the nature of the topic and the discussion of the aforementioned personal experiences, it was not deemed appropriate for this to take place in a group setting [117]. Therefore, semi-structured interviews were selected.

In recent years, the use of alternative sources of data for conducting health research has expanded. An example being the increasing use of online forum data to explore health-related topics. Within oncology, online forums are often hosted by charities and have been found to provide a rich set of real-world data that span multiple conditions, treatments, and other domains. This data can be analysed using qualitative methods. A limitation of this data is that depending on the type and location of the forum, it is difficult to define the included sample, however, guidance on completing research of this nature is available to navigate the challenges of conducting internet mediated research using online forums [125].

In addition to the two reviews, interviews and quantitative work completed as part of Phase I, a qualitative analysis of an online breast cancer forum was conducted. Following Smedley's guidance for conducting reviews of online forums, and the BPS guidelines for conducting internet mediated research of this nature, a content analysis was conducted to further identify the issues women living with MBC experience as a result of the disease and/or treatment [125]. This method was selected due to its availability as a rich source of qualitative data and its potential to generate new data, not previously seen in traditional methods such as in literature reviews or interviews/questionnaires. Previous literature have explored online forums and found them to be a valuable source of data, however its integration into the wider methodological approach in patient reported questionnaire development remains to be seen. The inclusion of this method aims explore this further and determine the value this method adds to the overall development of the questionnaire.

2.3.3 Quantitative methods

Quantitative methods of collecting data are well established within health-related research [126]. This approach uses statistical methods to draw inferences from data consisting of values and counts [127]. It is considered as an objective method of inquiry, and its deductive strategy and theoretical underpinnings allow for the exploration of numerical data to answer questions relating to 'what', 'how many' and 'how often' and

the generalisation of findings to the sample population [128]. Structured procedures such as randomised control trials, questionnaires and surveys are amongst the methods used.

Randomised Control Trials (RCTs) are used within healthcare research to evaluate the effect of new therapeutic agents, these are referred to as a Clinical Trial of an Investigational Medicinal Product (CTIMP). CTIMPs are often conducted to investigate the efficacy and safety of new treatments and/or new treatment combinations and to provide other data of interest, for example, the impact the treatment has on QOL. The scientific approach of RCTs provides great strength to the method, with RCTs considered to be the most rigorous way of determining causal relationships between the intervention (drug) and the outcome (overall survival/quality of life) [129].

Questionnaires are a quantitative method commonly used in health research to advance knowledge regarding cause-and-effect relationships between certain variables [130]. In a structured questionnaire, participants respond to prompts by selecting predetermined answers from scales including Likert scales or multiple-choice options. They allow for the collection of standardised data from large samples that when analysed can be generalised across the target population [131]. They are an efficient, effective, and inexpensive method of collecting data [132].

Limitations associated with the quantitative method relate to the data produced as a result. They require a large sample size to enable the statistical analysis and production of reliable results. The sample size is also related to the generalisability of the results, with smaller samples leading to poorer generalisability [133].

In addition to the use of semi-structured interviews to collect qualitative data, a quantitative, survey based approach to data collection was also utilised in Phase I of the development process. The inclusion of a quantitative method facilitated the collection of large quantities of numerical data relating to the perceived relevance and importance of a predefined list of issues shown to impact MBC patients, developed from the review findings. The quantitative data gave an objective account of the data from which empirical decisions could be made over which issues were deemed most relevant and important for inclusion in the final QOL questionnaire. This was of particular benefit when conducting large scale international research as it allowed the quantification of large amounts of subjective data, providing the order and structure needed to develop the new QOL questionnaire.

2.3.4 Mixed methods

Recent years have seen a rise in research adopting a mixed methods approach. Often research is dichotomised into being either quantitative or qualitative, however the mixed methods approach utilises both methods within the same study. Whilst the concept of mixing methodologies of conflicting ideologies has raised opposition among some, the pragmatic benefits seen, particularly within health research, has led to an increase in its use [134]. Further to this, the increase in its popularity is seen as the value of qualitative approaches have been more widely recognised within this area of research.

The underlying assumption of the mixed approach is its ability to address research questions in a more comprehensive way when compared to using either quantitative or qualitative methods alone [135]. This is often the case in health-related research where research questions tend to be broad and complex and consist of multiple dimensions. This combined strategy can therefore be used to offset the weaknesses and exploit the advantages associated with the individual methods, as well as enabling both exploration and statistical analysis in the same study, both crucial components in the development of a questionnaire [136].

Numerous reasons for selecting a mixed methods approach have been published within the literature, many of which cover the advantages highlighted above. However, Bryman (2006) identified 16 rationales as to why researchers would choose this methodological approach and in the case of this research, the rationales included ‘completeness’ and ‘instrument development’ [137].

Overall, this thesis aimed to establish a comprehensive account of QOL in MBC by answering the research questions outlined in Chapter 1. To achieve this aim, multiple methodological approaches were considered. In Phase I, a mixed methods approach was adopted. It was established that in order to best answer the research questions set out in this phase, it was necessary to draw upon the strengths of utilising both qualitative and quantitative methods. Increasingly, this methodological approach has become more prevalent within health research as its ability to offset the weaknesses and exploit the advantages associated with quantitative and qualitative methods has been shown [131]. In keeping with the aims of the study, this mixed approach facilitated both exploration and statistical analysis of the QOL related issues within the same study, a critical component in the development of a questionnaire [136].

The formulation of the mixed method approach to data collection in Phase I involved semi-structured interviews and administration of a quantitative based survey. The

methods were combined, whereby participants first completed the open-ended questioning aspect of the interview, followed by the completion of the survey. Whilst the quantitative questionnaire provided an objective assessment of the issues in terms of highlighting those of greatest relevance and importance in MBC, the integration of within the qualitative interviews provided scope to gather a more in-depth insight into the participants views and opinions on the subject [138]. Concept elicitation and the 'think aloud technique' were used throughout the interviews to bring together data and provide a comprehensive account of the issues experienced [137].

The quantitative data was the primary focus of analysis in Phase I, the qualitative data used to establish missing issues raised during the interviews however a full qualitative analysis was not possible due to limited access to interview data from the collaborating sites and the external time pressures of delivering a large international project during a pandemic. COIVID-19 placed huge demands on the project, particularly with the time delays in caused in the recruitment of patients across the collaborating countries. However, the lack of a formal qualitative analysis from the interview data, was compensated by the additional work carried out on the analysis of an online cancer forum. The analysis of the Phase I data was conducted by myself with support from my supervisory team. Preliminary findings were presented at biannual meetings with the EORTC QLG and feedback was provided and incorporated into the decision making process across the subsequent chapters.

2.3.5 Defining the patient sample

Sampling involves the selection of a portion of the finite population being studied. There are various methods of sampling participants to a research study, each with their strengths and weakness. The sample method chosen is often defined by a number of factors, including study design, research objectives or study setting. Two common forms of sampling include, probability and non-probability sampling. Probability sampling, also known as random sampling, refers to the selection of a sample based on randomisation, in that each subject within a population has a known nonzero chance of being selected allowing for a wider inference to be made of the whole population [139]. This is a more complex, time-consuming and expensive method when compared to non-probability sampling.

Non-probability sampling does not attempt to select a random sample from the population of interest, rather it uses subjective methods to decide which elements are included in the sample. This type of sampling can be divided into three primary

categories: (1) quota sampling, (2) purposive sampling, and (3) convenience sampling. [139]. Due to the heterogeneity of the clinical characteristics and illness trajectories associated with MBC, a purposive sampling technique was the most appropriate method for this study to ensure that a balanced and representative sample was collected, not only from the UK but also across the collaborating countries.

Purposive sampling is also referred to as judgmental sampling or expert sampling and the main objective is to produce a sample that can be considered “representative” of the target population. Despite the fact that the sample was recruited from a convenient sample, i.e. patients attending the breast cancer clinic, the development and implementation of a sampling matrix gave purpose and direction to the sampling strategy. Key demographic and clinical characteristics were outlined by a leading team of experts prior to recruitment to ensure a representative sample was obtained (age, treatment, time since diagnosis). Despite the advantages of being inexpensive and less time consuming, this method is a subjective approach, for example, expert opinions can differ and others may select different key characteristics to sample, however with a global network of leading experts in agreement, this sampling method was selected.

2.4 Phase II: Item Development

The objective of Phase II was to operationalise the core set of issues identified in Phase I into fully formed questionnaire items developed in line with existing EORTC questionnaires. An iterative approach to item development was adopted throughout this phase, whereby each issue was operationalised in a systematic manner, drawing on multiple sources to ensure the resulting items were expertly formed. As part of this approach, existing questionnaire items from the EORTC Item Library were reviewed and leading experts from around the world consulted in the decision making process. Consensus meetings enabled the utilisation of this expertise to guide the development process and the formation of the provisional questionnaire. On completion of Phase II, the provisional questionnaire is presented in a format consistent with the EORTC QLQ-C30.

Further to this, in the development of questionnaire items, several key factors and considerations have been highlighted within the literature. Examples include the style of the item, the language and phrasing of the item and the response style [132, 140-142]. The style in which items are developed and presented in questionnaires is vitality important as it determines how the responder interacts and completes the measure. The style choice can elicit different information from the responder and items should therefore

be developed and presented in line with the objectives of the questionnaire. For instance, a questionnaire assessing QOL in children or young adults will differ in style to those assessing QOL in adults, this includes the appropriate use of language and phrasing, as well as the items response options, for example, Likert-Scale or free text [132, 141].

The use of language and the direction of phrasing, be it positive or negative is a critical component of item development. The impact of poorly written items can affect the overall quality of the data produced. Common pitfalls that result in the development of poor items include, the assumption of a higher educational level and reading age, the use of unfamiliar terms, overly complex phrasing, and grammatical ambiguity, for example double negatives [143]. To address these potential limitations, careful consideration of the language used within the literature, including previous questionnaires and that used by patients within qualitative data should be taken when developing new items [132]. To facilitate the creation of acceptable items, the initial process is first carried out in collaboration with a specialist team at the EORTC before being presented and reviewed by patients for final approval.

Face validity refers to the subjective assessment of a questionnaire to determine the degree in which it relates to the concepts it claims to measure and is assessed by reviewing the items against the aims and objectives of the questionnaire [140, 142]. This form of validity stems from the items included within the questionnaire, with clear, unambiguous and relevant items providing the highest levels of face validity [144]. During Phase II, the original issue was at the forefront during item development to ensure each item captured the context of the original issue. Despite criticisms surrounding the strength of face validity, it offers a fundamental strength that binds the raw data obtained in Phase I and the items developed in Phase II. For without this, the original context may be lost during the development of the item. Items were developed in English, however, were reviewed at this stage for their translatability into other languages first by the collaborators and then by the EORTC QLG translation department where the full translation of the items is conducted.

As with the importance of using appropriate language when creating items, there is also an importance of the chosen response style. Various styles are available and include multiple choice, Likert Scale and free text questions [132]. The Likert scale was developed in 1932 and has since become a popular and fundamental way in which constructs are measured [145, 146]. Its use has been shown across multiple disciplines, such as psychology, sociology, politics and healthcare due to its proven reliability as a psychometric scale [147].

Within the context of this research, it was important that the new questionnaire followed the format of EORTC QLQ-C30 as the two are proposed to be used together. The benefit of using this format was that it maintained consistency across the questionnaires aiding the comprehension for patients. The response format selected was a 4-point Likert scale to assess each of the included items.

2.4.1 Consensus methods

Formal consensus methods have been used to solve problems within health and medicine research for numerous years and whilst expert consensus is not a surrogate for evidence-based data, it serves a valuable methodology for defining levels of agreement and decision-making [148, 149]. There are several methods sited within the literature, namely the Delphi method and the Nominal Group Technique (NGT). The Delphi method is a well-established approach to achieving consensus and is widely applied across diverse fields of research. The nominal group technique is a structured face-to-face meeting facilitating discussion and allows participants to voice their opinions [150]. Both have formal rules for collecting and analysing information and place an emphasis on the production of immediate solutions to problems. Despite the structured approach of the methods, each have been adapted for use across various studies [151].

Pragmatically speaking, a full-scale Delphi study was not feasible, due to restrictions in time and resources. The NGT approach was considered, however the overly structured nature of technique was not required for the aims at this stage of the questionnaire development. Therefore, a modified approach to obtaining consensus was adopted in this thesis. Applied outside of the constraints of structured protocols, this can be described as an informal approach to consensus using iterative input form a wider expert group of experts. The group consisted of academics and clinicians from across the globe, and included those with expertise and knowledge of questionnaire development, and/or experience in the treatment and care of MBC patients. Further to this, study collaborators and members of my supervisor team also formed part of the expert group. Due to the international nature of the project, virtual methods were used to collect the data, this included emails and virtual meetings.

The inclusion of a consensus methodology in Phase II, provided validation to the item selection process. By drawing on the experience and expertise of a wider group of individuals, the risk of bias in the selection process was reduced as it limited the reliance on my own experience in the decision making process [152]. Further to this, the inclusion of a diverse expert group facilitated the selection of the most appropriate items across

all of the different languages and cultures involved in this project. There is of course potential for bias when gathering expert consensus in this manner, however, the core issues were selected by patients, and the decisions made at this point related to the selection or development of items that best represented these core issues. The completion of Phase III mitigates the risk of bias further, as patients will consult on the questionnaire and provide feedback on whether or not the items are suitable. Procedural methods of the consensus exercise are detailed in Chapter 5.

2.5 Ethics

In any research it is important to remember that ethical considerations are an ongoing process that must be managed and maintained throughout the research study. Prior to the commencement of the study, potential ethical issues and their mitigations were reviewed, discussed and submitted as part of the ethical approval process. The key considerations are discussed below.

All aspects of the study were conducted in accordance with the MRC Good Research Practice guidelines, Good Clinical Practice (GCP) guidelines and the Data Protection Act (2018). Ethical approvals were sort and obtained from the Research Ethics Committee as well as local approvals from the Leeds Teaching Hospitals NHS Trust. As this was an international study, each site was responsible for submitting and obtaining the relevant approvals needed to conduct research within their country.

2.5.1 Ethical considerations

The University of Leeds was the sponsor of the project. The sponsor is the organisation that takes on the overall responsibility for the project and delegates specific tasks to any other individual or organisation that is willing and able to accept them. The chief investigator (CI) is the overall lead researcher for a research project, within international projects the CI is also referred to as Coordinating Investigator and are responsible for the overall conduct of a research project. Individuals responsible for the conduct of the research at each site or centre are referred to as Principal Investigators (PI). The data controller was the University of Leeds and was responsible for the management and oversight of the data.

2.5.1.1 Data handling and confidentiality

Each site was responsible for the recruitment of its own participants and therefore responsible for storing files containing personally identifiable information. Personal information was securely stored locally at each centre and was not used in research outputs or shared with collaborating sites. Before completed study materials were returned to the study coordination centre (University of Leeds), all sensitive information, such as names and addresses, were removed and pseudonymised using a unique study ID. Each site held their own link code document for the patients they recruited. This was to identify patients for quality assurance, and the correction of errors during the statistical analyses. This document was not shared between sites, including the sponsor, and was stored within a password-protected folder on the sites secure server.

The coordinating centre (University of Leeds) received only the pseudonymised data from the collaborating sites (UK and international sites) and included the participant's demographic and clinical information, study notes taken during the interview, transcripts from the interviews if recorded (UK only) and the completed issue list questionnaire. The EORTC Data Processing Agreement (DPA), outlining the obligations for all collaborators was in place for the duration of this project. Centres which required a DPA were assigned contracts stating the specific requirements expected from their site. Whilst this was not a necessity in the research protocol, it was a crucial step for the activation of certain sites. As study coordinator, I was responsible for the establishments of DPA contracts as and when they were required. This added a great deal of complexity in the management of data within this project, as it was important that each site adhered to the EORTC DPA to ensure data was processed in line with the regulations. The high standards set out in the EORTC DPA and study protocol for the sharing of data between sites was critical in ensuring the consistency, and quality, of the data was maintained throughout the project.

The EU General Data Protection Regulation (GDPR) was a legislation that came into force on the 25th May 2018, with the aim of improving the law surrounding data protection and data privacy. It means that special consideration was given to how participant data was used and stored, and that participants involved in the study were required, by the Health Research Authority (HRA), to receive a transparency statement on how their personal data was used in the present study.

Study documents and files, such as consent forms and questionnaires were stored in locked filing cabinets and/or electronically stored in password-protected folders on secure servers. Access to files was limited to members of the research team. Where

storage of sensitive data was required, for example, information necessary to send out information sheets, consent forms and reminders, all centres were required to securely store this data away from other study documents. To minimise the risk of breaching confidentiality, the collection of personal information was kept to a minimum and all research data was pseudonymised using a unique participant ID.

2.5.1.2 Informed consent

Informed consent was obtained by a researcher with the required permissions, trained in Good Clinical Practice (GCP) and who worked in line with EU confidentiality guidelines and codes of conduct. The voluntary nature of the study was be emphasised, and the participants were told of their right to refuse participation. For patients, it was also made clear that participation in the study will in no way affect their ongoing care.

Prospective participants received a comprehensive information sheet and were encouraged to ask any questions they had either in person or via telephone/email. They were offered the opportunity to take the information sheet away with them to further consider their decision, and arrangements were made for them to inform the researcher of their decision (and to potentially consent) at a later date. Patients willing to participate were asked to sign a consent form that detailed their involvement and how their data would be used. The Patient Information Sheet (PIS) was developed with the help of a Patient and Public Involvement and Engagement (PPIE) group to ensure that not only all of the relevant information was included but also that it was accessible to the lay person. For example, easy to read, and was ordered in a logical way i.e. patients did not want to read about GDPR before reading about the study objectives (appendix 9.1.3).

All UK participants were required to give informed consent prior to taking part in the research, this included both the patients and the HCPs. Whilst this was the case in the UK, each country had its own procedures regarding consent, for example most of the participating centres did not require obtaining consent for the HCP. Written informed consent was provided via the consent form which outlined the key statements for which participants needed to agree and sign. With the introduction of remote interviews as a direct result of the COVID-19 pandemic, the option of obtaining verbal consent was made available, for which the university guidelines were followed (reading the consent form, having them agree to the statements and agreeing to take part, audio recorded). Participants were able to ask questions about the study and specifically their consent, with every effort made to ensure participants felt comfortable in joining the study. All participants were aged 18+ so issues surrounding consenting minors was moot.

2.5.1.3 Protection from harm

As with all research that addresses sensitive topics, this study brings the same ethical considerations regarding protecting the participants from potential harm or distress. Whilst there was very limited risk of physical harm, in that it was an interview study with no invasive or physical procedures, the potential for psychological distress was apparent. Mitigating procedures were put in place to limit the impact this research had on the patient (outlined below).

Potential risks relating to the patient becoming upset were highlighted within the ethical review process and included, patients may have become upset during the interviews as they were asked to discuss their condition and the impact it has had on the lives. Patients were aware of this prior to the interview having read the PIS and spoken to the researcher, however if a patient became upset, they were reminded that they could pause or end the interview at any point if they felt the need to do so.

Following the completion of the interview, patients were then asked to complete a survey that contained issues that may or may not relate to their condition. This was identified as another area for which potential distress could occur. The issue being that the list of issues may have caused the patient to worry that the included issues may happen to them as the disease progresses. To help ensure this risk was minimised, prior to the interview and once again before the completion of the questionnaire, it was explained to the participant how the questionnaire had been created. It was explained that the list contained issues form various treatments and sources and that not all issues will be relevant to them and was highlighted to them that none of the items were mandatory, they were free to skip issues they didn't want to comment on. Further to this, patients were sign posted to information materials as and when was necessary. The lead supervisor on this project is a breast clinician and was available to refer patients recruited from Leeds Teaching Hospital Trust to their clinical team for support if necessary.

The protection of the researcher was an important factor to consider when conducting research within a sensitive area. Having a supportive team and points of contract to debrief after the interviews was key. This proved more difficult for remote interviews. Support was available from peers, senior colleagues and supervisors within the wider research team. A fieldwork risk assessment form for offsite working was completed as per university policy. Further to this, additional training and procedures were introduced during the COVID-19 pandemic. With the rules and regulations relating to social distancing, personal protective equipment (PPE), in the form of surgical masks, were mandatory in both office and clinical spaces. When entering clinical areas, additional

PPE was required, including eye protection, gloves and aprons. Training was provided by members of the clinical team.

2.5.1.4 Burden

Participants were asked to compete two main tasks during their time with the researcher. The interviews utilised a mixed methods approach where the patient was interviewed and then proceeded to complete a questionnaire. In total the time spent with the researcher was approximately 30-40 minutes, however this varied across the participants. This combined approach enabled participants to complete each task in one sitting and thus saving time and effort travelling to the hospital for two sessions. As with the steps taken to mitigate distress, participants were reminded that they could pause or end the interview at any point if they felt the need to do so.

One patient requested to complete the questionnaire in their own time following the interview, this was in a remote session.

2.6 Summary

This chapter has described the overarching design and methodology of this research, providing justification for the decisions made with regards to the research aims and underlying theoretical assumptions. As discussed in this Chapter, the impact of the COVID-19 pandemic caused significant time delays and resulted in amendments being made to the protocol, the introduction of virtual interviews being just on example of this. Specific methods are explored further in subsequent chapters. The next Chapter presents the first step in my research project, the systematic review of the quality-of-life related issues reported by MBC within the literature.

Chapter 3. Systematic Review

The assessment of quality of life in metastatic breast cancer research: A systematic review.

The previous Chapters have provided background on metastatic breast cancer (MBC) and the methodology of the thesis. This Chapter (3) outlines the initial piece of work conducted which was a systematic review of the literature relating to quality of life in MBC. The strengths associated with conducting a systematic review, opposed to rapid or scoping reviews was discussed in detail in Chapter 2, with the main benefits being the level of comprehension they offer [113]. To further the comprehensiveness, a mixed-method systematic review was conducted. A mixed methods review has been defined as the combination of qualitative and quantitative studies within a single systematic review to address the review questions [153]. This chapter outlines the aims and rational of the review, followed by the methods, results and overall discussion and conclusions.

Findings from the review were to be used as part of the development of a new EORTC module for assessing QOL in patients with MBC.

3.1 Aim

The aim of this review was to further our knowledge of quality of life in metastatic breast cancer patients via the synthesis of data systematically identified from the literature.

The objectives were to:

1. Provide a comprehensive overview of the QOL and psychosocial impact of metastatic breast cancer reported in published studies from:
    - Phase III Clinical Trials of Investigational Medicinal Products (CTIMPs)
    - Non-CTIMP studies
2. Summarise the range of QOL and patient reported outcome measures used across studies
3. Summarise the contribution made by patient reported QOL assessment to study findings

3.1.1 Rationale

Previous systematic reviews of the literature have been conducted whereby QOL was explored within the context of MBC. Many of the reviews focused on data provided by Phase III clinical trials, with little attention paid to studies of alternative methodologies [154]. An early review conducted by Bottomley (2002) examined the effect of systemic therapy on health-related quality of life in advanced breast cancer [155]. The impact of treatments on HRQOL were reported, however, the final conclusions highlighted the need for improved methodology and reporting of QOL within trials of MBC patients. Ghislain (2016) built upon this review by re-evaluating the publications in subsequent years [156]. Their primary aim was to evaluate the HRQOL methodology reporting in advanced breast cancer RCTs since 2001 and reported the QOL measures included in the papers, QOL as a study endpoint and the quality of the reporting of the QOL results. Willis (2015) conducted a mixed methods review, as they determined little was known about MBC experiences and thus needed to include all study designs to provide a comprehensive account [157].

Building on previous work conducted in this area, this Chapter reports the mixed-methods review conducted as part of my thesis to update and further expand the knowledge of the impact QOL has on women living with, and being treated for, MBC. Whilst it is widely accepted that RCTs are the gold standard for developing new treatments and interventions, the aim of this review required a wider exploration of the literature as it aimed to identify the full range of issues experienced by these patients. Therefore, findings from both CTIMP and non-CTIMP studies were included to best answer the research questions and provide comprehensive insight of the literature.

3.2 Method

Methods were informed by the Centre for Reviews and Dissemination's guidance for conducting reviews in healthcare [158]. A review protocol was developed, however, was not published on PROSPERO due to the fact too much progress on the review had been made prior to registering the protocol. In retrospect, alternative platforms for registering research could have been considered, such as the Open Science Framework [159], to increase the transparency of this research. The review formed part of the initial work package for the EORTC module development and whilst not required by the EORTC, a full systematic review of the literature was conducted.

3.2.1 Search strategy

The preliminary search strategy proved to be too unwieldy and was unable to identify the key research papers within the selected databases. As a result, two search strategies were developed to provide comprehensive coverage of the literature. Using Boolean logic, metastatic breast cancer, and its synonyms, were combined alongside relevant search terms to produce the two strategies, both of which were verified by an information specialist (Appendix 9.1.19.1.1). Searches were conducted in parallel, across Medline, EMBASE, PsychINFO, Central and CINAHL databases. The searches were restricted to identify papers published between 2000-2019. Table 1 shows the inclusion criteria developed using the PICOS framework [160].

Table 1. ***Inclusion criteria formed via the PICOS framework.***

PICOS Framework	Study inclusion criteria
Population	Adult females aged 18 or over with a diagnosis of metastatic breast cancer (Stage IV)
Intervention	Anti-cancer treatments (chemotherapy, hormone therapy, targeted therapy & combinations) and/or psychosocial interventions
Comparator	Not applicable
Outcome	Quality of life, psychosocial, emotional and physical symptoms, side effects and adverse effects
Study design	CTIMP Search Phase III therapeutic RCTs or Clinical Trials of an Investigational Medicinal Product
	Non-CTIMP Search High quality psychosocial studies (including RCT of psychosocial interventions) observational (cohort) and qualitative studies
	Published in English, in a peer-reviewed journal, with a sample size greater than 50, unless a qualitative study
Exclusions	Reports of conference proceedings, abstracts and case reports. Publications included primary and advanced breast cancer patients

The aim of the review was to synthesis evidence from a range of papers utilising various methodologies, therefore the two searches were designed to reflect this. The first of the two searches were restricted to identify Phase III Randomised Clinical Trials of an Investigational Medicinal Products (CTIMPs) only and referred to as the CTIMP Search. The CTIMP search aimed to capture adverse event, toxicity and QOL data associated with MBC treatments. The second search was not restricted by study design, it aimed to capture the wider psychosocial and emotional impact of MBC across multiple study designs (Table 1). This search was referred to as the ‘non-CTIMP’ search. The process

of reviewing, screening and data extraction for each search was conducted in parallel, with the final results combined to provide a complete overview of the literature. Search results were exported from the databases and managed in Endnote.

3.2.2 Data extraction and analysis

Prior to data extraction, all papers were reviewed for inclusion by two reviewers (CB & LS). To facilitate the screening process and overall management of the data, papers were exported into two Endnote files, one contained the results from the CTIMP search and the other the non-CTIMP search. This helped maintain the systematic approach by allowing the reviewers to assess the papers more easily against the inclusion criteria. The first stage was to screen the papers for inclusion based on their titles and abstracts. CB screened all papers while LS independently screened 20%. Those that did not meet the inclusion criteria were removed at this stage. Due to the extensive number of papers yielded from the searches, it was not possible to categories the specific reasons for removal further. Disagreements were resolved via discussion and papers selected by either reviewer were included for full-text screening.

The second round of screening involved a deeper investigation of the papers to further assess their eligibility. At this stage the full text was reviewed. Throughout this process, detailed reasons behind decisions to exclude papers were recorded. Having identified the papers for inclusion in the review, relevant data was then extracted. Data were entered and managed using an excel database. As with the Endnote files, each search had its own Excel file. The data extraction form was developed using the Cochrane template for the extraction of data from Randomised Clinical Trials (RCTs) and non-RCT studies [161]. I reviewed and evaluated the template for its appropriateness and modified the form accordingly to suit the aims and objectives of this review. The drafted extraction form was then reviewed by the supervisory team to ensure it best captured necessary information required, for example, author, publication date, journal, title, abstract, study population, intervention type, and relevant outcomes (Table 1). Data extraction was managed using an excel database, whereby each variable of interest from the form was mapped. All data was then subsequently used to synthesis the results of the review.

The primary objective of the review was to provide comprehensive overview of the QOL and psychosocial impact MBC has on women diagnosed with MBC. To achieve this, the outcomes of interest within the included papers were, the QOL related issues reported in PROMs, as well as the physical (adverse events, side effects, toxicities) and psychosocial issues reported. Objectively measured issues, such as leukopenia or liver

function tests were noted but not included in the analysis due to the inability for patients to self-report such issues. Therefore, although important in the wider context of the treatment and management of MBC, they were not relevant in the development of a new QOL questionnaire PROM. For quantitative studies, issues were extracted where they were experienced by 10% or more of the study sample and were grouped accordingly i.e. whether they were physical or psychosocial. For qualitative studies, there were no restrictions on the issues as the sample sizes were much lower. Instead, the key themes and issues were extracted from these types of studies.

The secondary objective was to summarise the range of PROMs utilised in the assessment of QOL across the literature. Data on the type and frequency a PROM was used were extracted to address this objective. Further to this, data on whether or not papers reported a significant difference in QOL scores was extracted to address the third objective which looked to determine the contribution of patient reported QOL assessment within the literature.

The quality of the studies was assessed with the Mixed Methods Appraisal Tool-2018 (MMAT-2018) as it allowed for the critical appraisal of multiple study designs within the same tool [162]. The MMAT-2018 facilitates the appraisal of quantitative, qualitative and mixed methods studies and has been validated and tested for its reliability [162]. The MMAT is categorised into five sections, (1) Qualitative, (2) Quantitative RCT, (3) Quantitative non-randomised controlled trials, (4) Quantitative descriptive and (5) Mixed methods, with each category having its own set of methodological quality criteria in which the included studies were assessed. Responses to these criteria included ‘yes’, ‘no’ or ‘cannot tell’. Other appraisal tools such as the Cochrane tool for assessing risk of bias in randomised clinical trials were considered, and those developed by the Joanna Briggs Institute, however these would have required the use of multiple tools to assess each of the included study designs [163, 164]. A limitation of the MMAT-2018 was that it did not produce a score or the ability to rank the papers.

3.2.3 Analysis

Due to the heterogeneity of studies, a narrative synthesis of the data was conducted. The narrative approach allowed for the exploration of findings from both within and between study designs and thus resulting in a rich source of data in which to answer the research questions. Other methods of analysis, such as meta-analysis was not appropriate or possible with the inclusion of non-CTIMP studies. QOL related issues, QOL measures used and data relating to QOL as an endpoint were recorded and

analysed using content analysis. Qualitative data was transformed, whereby the key themes and/or issues were extracted from the papers and refined down to their core issue to match the format of the data extracted in the quantitative studies. This allowed for the comparison between study designs. Further to this, each of the QOL issues extracted were categorised according to the Generic Choice Model to determine the conceptual domains in which each issue is linked, this aided the management and analysis of the results [109]. Data were collated and frequency tables produced to highlight the most common issues and measures used within the literature. Frequency data was used to analyse the extent to which QOL data contributed to the overall message of the study, for example its inclusion as a study endpoint and its contribution to the key results.

3.3 Results

After the removal of duplicated studies, the two searches resulted in a combined total of 11,416 papers. 10,767 papers were excluded, as they did not fulfil the inclusion criteria, leaving 649 studies (Figure 5). A total of 103 papers remained after full-text screening and were included in the review. Of the 103 papers, 70 Phase III RCTs were identified via the ‘CTIMP Search’ (Table 2), and 33 papers from the ‘non-CTIMP Search’. Non-CTIMP studies included six non-CTIMP RCTs, 18 non-RCT studies and nine qualitative studies (Table 3). The results of risk of bias assessment using the MMAT tool are provided in Appendix 9.1.3.

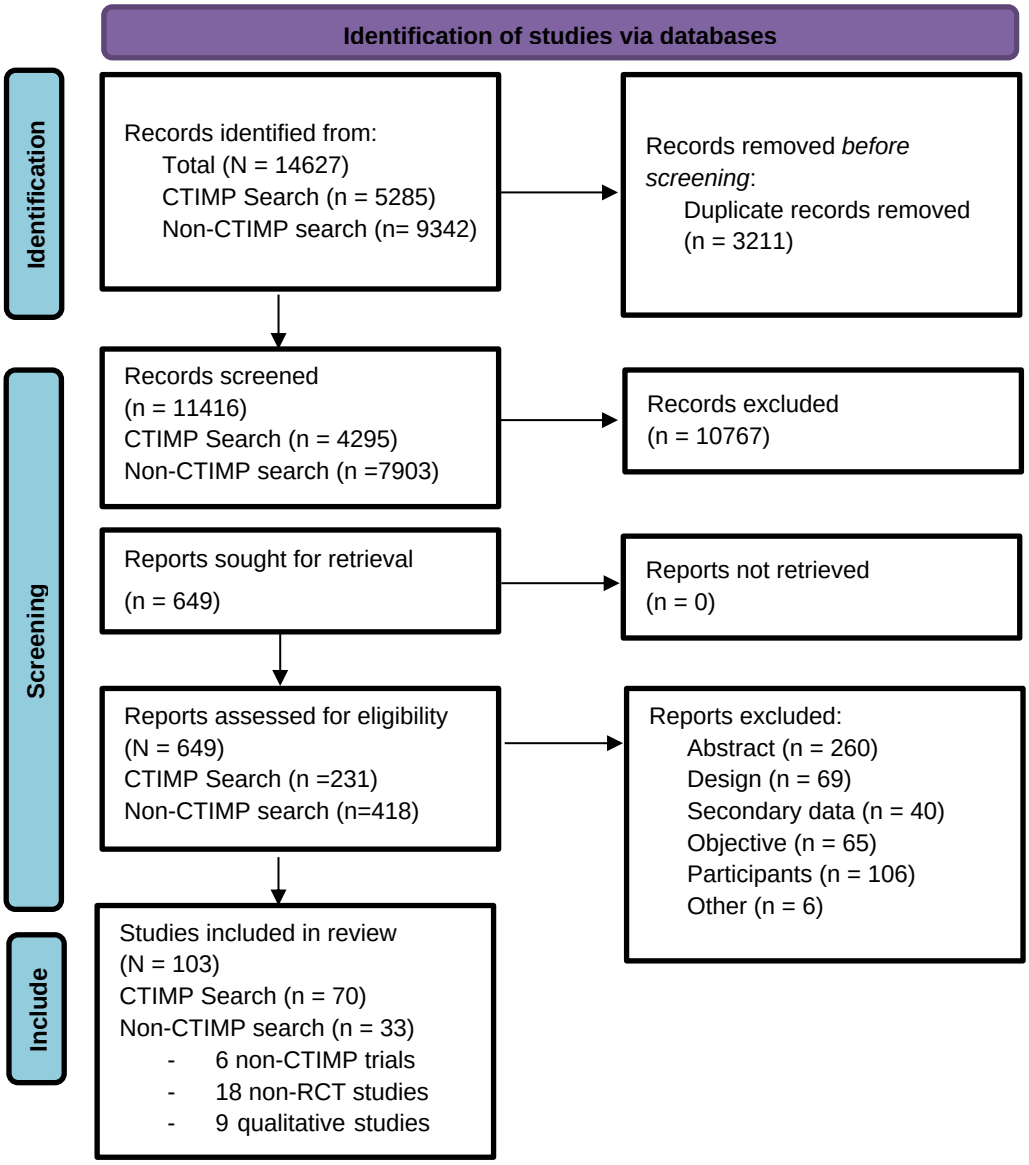


Figure 5. ***Flow chart showing the article selection process.***

Table 2. Summary of studies included in the CTIMP search.

First author and date	Objective	Treatment outline	Sample size	Measure	QOL assessed	Significant Difference in QOL	Key Findings – Most common issues*
Alba (2004) [165]	Evaluated haematological toxicity in first-line chemotherapy in MBC	Chemotherapy alone	144	NCI CTCAE	No	N/A	Febrile Neutropenia, Asthenia & Diarrhoea
Albain (2008) [166]	Compared the efficacy of gemcitabine plus paclitaxel versus paclitaxel in MBC	Chemotherapy + targeted agent	529	NCI CTCAE, Rotterdam Symptom Checklist (RSCL) and Brief Pain Inventory (BPI) short form	Yes	N/A	Alopecia, Anaemia, Arthralgia, Diarrhoea, Emesis, Fatigue, Myalgia, Nausea, Neutropenia, Sensory neuropathy
André (2014) [167]	Assessed whether the addition of the mTOR inhibitor Everolimus to trastuzumab might restore sensitivity to Trastuzumab.	Chemotherapy plus targeted agent	569	NCI CTCAE	No	N/A	Abdominal pain, Anaemia, Arthralgia, Asthenia, Back pain, Constipation, Cough, Decreased appetite, Diarrhoea, Dyspnoea, Epistaxis, Fatigue, Febrile neutropenia, Headache, Insomnia, Leukopenia, Mouth ulceration, Muscle spasms, Myalgia, Nasopharyngitis, Nausea, Neutropenia, Pain in extremity, Peripheral oedema, Pyrexia, Rash, Stomatitis, Thrombocytopenia, Upper abdominal pain, Upper respiratory tract infection, Vomiting, Weight decreased
Baselga (2012) [168]	Compared Everolimus and Exemestane versus Exemestane and placebo	Hormone therapy	724	EORTC-QLQ-C30 and BR23	Yes	No	Stomatitis, Rash, Fatigue, Diarrhoea, Decreased appetite, Nausea, Cough, Dysgeusia, Headache, Decreased weight, Dyspnoea, Arthralgia, Anaemia, Epistaxis, Vomiting, Peripheral oedema, Pyrexia, Constipation, Hyperglycaemia, Pneumonitis, Thrombocytopenia, Asthenia, Pruritus, Insomnia & Back pain
Beaver (2012) [169]	Examined the effects of Exemestane plus Everolimus on progression-free in postmenopausal, HR+ MBC.	Hormonal therapy plus targeted agent	724	EORTC QLQC30 + BR23 (BOLERO2)	Yes	No	Stomatitis, Anaemia, Fatigue & Pneumonitis

Blackwell (2010) [170]	Compared Lapatinib alone or in combination with Trastuzumab in patients with ErbB2-positive, Trastuzumab-refractory MBC.	Targeted agent	296	CTCAE FACT-B	Yes	No	Anorexia, Cough, Dermatitis acneiform, Diarrhoea, Dyspnoea, Fatigue, Headache, Nausea, Rash, Vomiting
Burris (2013) [171]	Analysed the treatment effects on health-related quality of life (HRQOL).	Hormone therapy	724	EORTC QLQ-C30 CTCAE	Yes	Yes	Yes - EVE + EXE was associated with a longer TDD in global HRQOL versus PBO + EXE
Campone (2013) [172]	The effect of visceral metastases on the efficacy and safety of Everolimus in postmenopausal women with MBC. BOLERO-2	Hormonal plus targeted agent	724	CTCAE EORTC QLQ-C30	Yes	No	Cough, Decreased appetite, Diarrhoea, Dysgeusia Fatigue, Headache, Hyperglycaemia, Nausea, Pneumonitis, Rash, Stomatitis, Weight decreased
Campone (2013*) [173]	Evaluated EVE + EXE impact on disease burden, and patient-reported HRQOL. BOLERO-2	Hormonal therapy plus targeted agent	724	EORTC QLQ-C30 + QLQ-BR23	Yes	No	No statistically significant overall difference between EVE þ EXE and PBO þ EXE for Global Health Status, breast symptom BRBS or arm symptom BRAS
Cassier (2008) [174]	Compared paclitaxel-doxorubicin and docetaxel-doxorubicin combinations.	Chemotherapy	210	NCI-CTC, EORTC QLQ-C30	Yes	No	Leukopenia, Neutropenia, Febrile neutropenia
Cella (2011) [175]	Examined health-related quality of life (HRQL) among women with MBC treated on E2100 with Paclitaxel or Paclitaxel plus Bevacizumab.	Chemotherapy plus targeted agent	670	FACT-B	Yes	Yes	Paclitaxel + bevacizumab resulted in fewer breast cancer-specific concerns in comparison to paclitaxel alone. Issues included pain and impact of side effects.
Chia (2008) [176]	Evaluation of Fulvestrant vs Exemestane in postmenopausal women with HR+ MBC	Hormonal therapy	693	Functional Assessment of Cancer Therapy–Endocrine Symptom (FACT-ES) and Trial Outcome Index (TOI)	Yes	No	Hot flashes & Fatigue

Conte (2004) [177]	To evaluate whether the sequential administration of Epirubicin and Paclitaxel were not markedly worse than the concomitant administration.	Chemotherapy alone	202	EORTC QLQ-C30	Yes	Yes	Anaemia, Neutropenia, Mucositis, Neuropathy. Emotional functioning significantly better in concomitant arm.
Cortes (2018) [178]	Compared vinflunine with physician's choice of alkylating agent (AA) for patients with heavily pre-treated MBC	Chemotherapy alone	594	NCI CTCAE QLQ-C30 + QLQ-BR23	Yes	Yes	Abdominal pain, Alopecia, Anaemia, Anorexia, Asthenia, Bone pain, Constipation, Cough, Diarrhoea, Dyspnoea, Fatigue, Injection-site reaction, Malignant neoplasm progression, Myalgia, Nausea, Neutropenia, Stomatitis, Thrombocytopenia, Vomiting, Weight decreased. Global health status decreased at all evaluations after baseline in both treatment arms, with a more pronounced decrease in the AA than the vinflunine arm.
De Luca (2019) [179]	Evaluated nab-paclitaxel in Italian patients with MBC.	Chemotherapy alone	90	CTCAE EORTC QLQ-C30	Yes	Yes	Anaemia, Neutropenia, Asthenia, Peripheral neuropathy, Stomatitis & Alopecia
Di Leo (2010) [180]	Compared fulvestrant 500 mg regimen with the approved dose of fulvestrant 250 mg per month for treatment of postmenopausal women with oestrogen receptor-positive MBC who experienced progression after prior endocrine therapy.	Hormonal therapy	736	NCI CTCAE FACT-B TOI	Yes	No	GI disturbances, Injection site reactions & Joint disorders
Ejlertsen (2004) [181]	To determine whether the addition of intravenous vinorelbine to epirubicin increased the progression-free survival in first-line treatment of MBC.	Chemotherapy alone	387	N/A	No	No	Leukopenia, Nausea, Vomiting, Anaemia, Infection & Stomatitis
Falandry (2009) [182]	Evaluated antitumor effects of cyclooxygenase-2 inhibitors in breast carcinoma and their ability to act synergistically with aromatase inhibitors (AIs).	Hormonal therapy plus targeted agent	157	NCI CTCAE	No	No	Arthralgia, Asthenia, Insomnia & Pain

Fountzilas (2004) [183]	Compared survival between patients treated with epirubicin/paclitaxel (Taxol) or paclitaxel/carboplatin (Cp) chemotherapy.	Chemotherapy alone	327	EORTC QLQ-C30	Yes	No	Neutropenia
Gligorov (2014) [184]	Maintenance capecitabine and bevacizumab vs bevacizumab alone (PFS, overall survival, safety, patients achieving an objective response or clinical benefit, time to progression, and quality of life.)	Chemotherapy plus targeted agent	185	CTCAE EORTC QLQ-C30	Yes	No	N/A
Guan (2013) [185]	Compared the addition of Lapatinib to Paclitaxel vs placebo plus paclitaxel in patients with HER2-overexpressing MBC.	Chemotherapy plus targeted agent	444	NCI CTCAE	No	No	Alopecia, Anaemia, Decreased appetite, Diarrhoea, Fatigue, Leukopenia, Nausea, Rash & Vomiting
Hagiwara (2018) [186]	Investigated the impact of adverse events on health utility and health-related quality of life (HRQOL) in patients with MBC undergoing first-line chemotherapy.	Chemotherapy alone	380	CTCAE EQ-5D-3L, EORTC QLQC30,	Yes	No	Fatigue, Alopecia, Anorexia & Sensory neuropathy
Harbeck (2016) [187]	The PALOMA3 trial assessed the safety and efficacy of the combination of palbociclib and fulvestrant in premenopausal or postmenopausal women with hormone-receptor–positive MBC that progressed during prior endocrine therapy	Chemotherapy plus targeted agent	508	CTCAE	No	No	Anaemia, Asthenia, Decreased appetite, Diarrhoea, Epistaxis, Fatigue, Leukopenia, Mucosal inflammation, Nausea, Neutropenia, Paronychia, Pyrexia (fever), Rash, Stomatitis, Vomiting & Weight decrease
Harbeck (2016*) [188]	Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative MBC	Hormonal therapy plus targeted agent	521	EORTC QLQ-C30 + QLQ-BR23	Yes	Yes	Yes - global QoL scores higher in palbociclib plus fulvestrant group, Significantly greater improvement from baseline in pain in intervention group. No significant differences were observed for other QLQ-BR23 functioning domains, breast or arm symptoms.
Harvey (2006) [189]	Evaluated whether a relationship exists between docetaxel dose and clinical response in the treatment of patients with MBC.	Chemotherapy alone	407	CTCAE	No	No	Asthenia, Leukopenia, Neutropenia & Febrile neutropenia

Hopwood (2008) [190]	Compared front line gemcitabine plus paclitaxel versus paclitaxel alone in patients with MBC	Chemotherapy alone	336	RSCL (Rotterdam symptom checklist) and brief pain inventory	Yes	No	Hair loss, tiredness, lack of energy, tingling hands and feet, sore muscles. Worrying, Despairing about future, Decreased sexual interest, Tiredness, Anxiety, Difficulty in sleeping, Tension, Lack of energy, Nervousness, Depressed mood, Hair loss, Tingling hands and feet & Sore muscles
Hortobagyi (2016) [191]	Evaluated the efficacy and safety of the combination of ribociclib and letrozole as initial therapy in patients with HR-positive, HER2-negative MBC	Hormonal therapy plus targeted agent	668	NCI CTCAE QLQ-C30	Yes – not reported	N/A	Alopecia, Arthralgia, Back pain, Constipation, Cough, Decreased appetite, Diarrhoea, Fatigue, Headache, Hot flush, Infections, Nausea, Rash & Vomiting
Inoue (2010) [192]	Randomized phase III trial of trastuzumab monotherapy followed by trastuzumab plus docetaxel versus trastuzumab plus docetaxel as first-line therapy in patients with HER2-positive MBC	Chemotherapy plus targeted agent	112	NCI CTCAE	No	No	N/A
Iwata (2017) [193]	Assessed efficacy and safety of Palbociclib plus Fulvestrant in Asians with endocrine therapy-resistant MBC.	Hormonal therapy plus targeted agent	105	NCI CTCAE, EORTC QLQ-C30	Yes	No	Alopecia, Arthralgia, Back pain, Constipation, Cough, Decreased appetite, Diarrhoea, Dizziness, Dyspepsia, Fatigue, Headache, Hot flush, Mucosal inflammation, Musculoskeletal pain, Nasopharyngitis, Nausea, Oropharyngeal pain, Pain in extremity, Pruritus, Pyrexia, Rash, Stomatitis & Vomiting
Janni (2018) [194]	Evaluated duration of response (DoR), tumour shrinkage, PFS by treatment-free interval (TFI), and health-related quality of life (HRQoL).	Hormonal therapy plus targeted agent	501	EORTC QLQ-C30	Yes	No	Improvement in pain symptoms (QLQ-C30 assessed) support the clinical benefit of ribociclib
Jones (2005) [195]	Compared docetaxel vs paclitaxel in patients with MBC that had progressed after an anthracycline-containing chemotherapy regimen.	Chemotherapy alone	449	NCI CTCAE FACT-B	Yes	No	Pain, Asthenia, Nausea, Diarrhoea, Stomatitis, Infection, Myalgia, Skin disorders & Vomiting

Kaufman (2009) [196]	Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive MBC	Hormonal therapy plus targeted agent	207	NCI CTCAE	No	No	Fatigue, Diarrhoea, Vomiting, Arthralgia, Pyrexia, Back pain, Dyspnoea, Nausea, Cough, Headache, Nasopharyngitis, Constipation & Chills.
Kaufman (2000) [197]	Compared the efficacy and safety of the oral aromatase inactivator exemestane (EXE) with megestrol acetate (MA) in women with MBC.	Hormonal therapy	768	EORTC QLQ-C30	Yes	Yes	Patients treated with EXE showed a statistically significant improvement in physical functioning, role functioning, global health, fatigue, dyspnoea, and constipation compared with patients who received MA. Patients treated with MA displayed a significant improvement in emotional function, appetite loss, and pain. MA therapy = less insomnia. No significant between-group differences were noted for cognitive function, social function, nausea and vomiting, diarrhoea, or financial difficulties. Hot flashes and Fatigue
Keller (2004) [198]	Compared the efficacy of pegylated liposomal doxorubicin (PLD) with that of a common salvage regimen (comparator) in patients with taxane-refractory MBC.	Chemotherapy alone	301	EORTC QLQ-C30	Yes	N/A – Not reported	Abdominal pain, Anorexia, Asthenia, Constipation, Diarrhoea, Fatigue, Fever, Mucositis, Nausea, Neuropathy, Neutropenia, Pain, Palmar-plantar, Rash, Stomatitis & Vomiting
Krop (2014) [199]	Compared trastuzumab emtansine with treatment of physician's choice in metastatic breast patients.	Targeted agent alone	602	EORTC QLQ-C30	Yes	N/A – Not reported	Abdominal pain, Anaemia, Asthenia, Diarrhoea, Dyspnoea, Fatigue, Neutropenia & Thrombocytopenia
Krop (2015) [200]	Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases	Targeted agent alone	95	NCI CTCAE	No	No	Diarrhoea, Haemorrhage, Hand foot syndrome, Hepatotoxicity, Hypokalaemia, Peripheral neuropathy & Thrombocytopenia

Langley (2005) [201]	Compared the effectiveness and tolerability of epirubicin and paclitaxel (EP) with epirubicin and cyclophosphamide (EC) as first-line chemotherapy for MBC (MBC).	Chemotherapy alone	705	AE measure not specified	No	No	Alopecia, Infection, Nausea, Vomiting & Pain
Liu (2006) [202]	Quality of Life Analysis of DPPE (tesmilifene) Plus Doxorubicin Versus Doxorubicin in Patients with MBC	Chemotherapy alone	271	EORTC QLQ-C30 + QLQ-BR23	Yes	No	Alopecia, Anorexia, Ataxia, Cardiac failure, Constipation, Diarrhoea, Dizziness, Extrapyramidal effects, Fatigue, Hallucinations, Headache, Infection without neutropenia, Injection site reactions, Nausea, Stomatitis & Vomiting
Lück (2013) [203]	Compared capecitabine plus paclitaxel (XP) with epirubicin plus paclitaxel (EP) as first-line therapy for MBC, regarding progression-free survival (PFS) as primary efficacy endpoint.	Chemotherapy alone	340	NCI-CTCAE EORTC QLQ-C30 + BR23	Yes	Yes	For the QLQ-C30 questionnaire statistically significant differences between treatment arms were found for difficulties taking a long walk, physical condition or medical treatment interfering with social activities, limitations in hobbies or leisure activities, worries over the last week all in favour for EP. However no significant differences between treatment arms were observed for results of the BR23 questionnaire. Alopecia, Anaemia, Arthralgia, Cardiotoxicity, Diarrhoea, Fatigue, Hand–foot syndrome, ypersensitivity reaction, Infection without Neutropenia, Leukopenia, Lymphocytopenia, Motor neurotoxicity, Mucositis, Myalgia, Nausea, Neutropenia, Sensory neurotoxicity, Stomatitis, Thrombocytopenia, Vomiting
Miller (2005) [204]	Compared the efficacy and safety of capecitabine with or without bevacizumab, in patients with MBC previously treated with an anthracycline and a taxane.	Chemotherapy plus targeted agent	462	NCI-CTCAE FACT-B	Yes	N/A – Not reported	Anorexia, Asthenia, Bleeding, Diarrhoea, Hand-foot syndrome, Headache, Hypertension, Infection, Nausea, Pain & Proteinuria
Miller (2007) [205]	Compared the efficacy and safety of paclitaxel with that of paclitaxel plus bevacizumab as initial treatment for MBC.	Chemotherapy plus targeted agent	722	NCI-CTCAE version 2.0, FACT-B	Yes	No	Sensory neuropathy & Hypertension

O'Shaughnessy (2002) [206]	Compared efficacy and tolerability of capecitabine/docetaxel therapy with single-agent docetaxel in anthra-cycline-pre-treated patients with MBC.	Chemotherapy alone	511	NCI-CTCAE EORTC-QLQ-C30 + QLQ-BR23	Yes	No	Diarrhoea, Stomatitis, Nausea, Vomiting, Alopecia, Fatigue, Pyrexia, Neutropenic fever, Myalgia, Arthralgia, Hand-foot syndrome & Asthenia
O'Shaughnessy (2018) [207]	Efficacy and safety of first-line ribociclib plus letrozole in patients with de novo MBC.	Hormonal therapy plus targeted agent	227	NCI CTCAE	No	No	Alopecia, Anaemia, Arthralgia, Back pain, Constipation, Cough, Decreased appetite, Diarrhoea, Fatigue, Headache, Hot flush, Hypertension, Leukopenia, Nausea, Neutropenia, Pyrexia, Rash & Vomiting
Osoba (2002) [74]	Compared the effects of treatment with a combination of trastuzumab (Herceptin) and chemotherapy versus chemotherapy alone on health-related quality of life (HRQL) in patients with HER-2/neu overexpressing, MBC.	HT, CT	431	EORTC QLQ-C30	Yes	Yes	Improvement was statistically significant only for fatigue in the intervention arm. Intervention arm (Fifty-one percent of patients reported an improvement of ≥ 10 in their global QOL scores in the combined therapy group as compared with 36%.
Pallis (2012) [208]	Compared the superiority of combination treatment in terms of progression-free survival (PFS).	Chemotherapy alone	158	NCI–CTCAE	No	No	Anaemia, Constipation, Diarrhoea, Fatigue, Hand-foot syndrome, Nausea, Neurotoxicity, Neutropenia, Thrombocytopenia, Vomiting
Paridaens (2000) [209]	Compared the efficacy of paclitaxel vs doxorubicin given as single agents in first-line therapy of advanced breast cancer (primary end point, progression-free survival PFS) and to explore the degree of cross-resistance between the two agents.	Chemotherapy alone	331	NCI CTCAE EORTC QLQ-C30 and Rotterdam symptom checklist	Yes	No	Neutropenia, Febrile neutropenia, Vomiting, Stomatitis
Park (2019) [210]	Investigated whether irinotecan plus capecitabine improved progression-free survival (PFS) compared with capecitabine alone in patients with human epidermal growth factor 2 (HER2) negative and anthracycline and taxane pretreated MBC	Chemotherapy alone	221	NCI-CTCAE EORTC QLQ-C30	Yes	Yes	Yes - Significant differences in favour of comparison arm were noted for diarrhoea and nausea/vomiting symptom scales. The differences observed between treatment arms in other functional scales and in the global health scale were not significant. Neutropenia, Anaemia, Hand-foot syndrome, Diarrhoea, Nausea, Vomiting & Insomnia

Park (2015) [211]	Examined QoL among women with MBC treated on KCSG-BR07-02 with maintenance of paclitaxel plus gemcitabine (PG) chemotherapy after achieving disease control to initial six cycles of PG chemotherapy or observation.	Chemotherapy alone	124	EORTC QLQ-C30 and BR-23	Yes	No	No significant differences between arms.
Park (2013) [212]	Evaluated whether maintenance chemotherapy with paclitaxel/gemcitabine (PG) was superior to observation in improving progression-free survival (PFS) in patients with MBC who achieved disease control with an initial six cycles of PG as their first-line treatment.	Chemotherapy alone	231	NCI CTCAE EORTC QLQ-C30 + BR23	Yes	No	Anaemia, Constipation, Diarrhoea, Nausea, Neuropathy, Neutropenia, Thrombocytopenia, Vomiting
Parnes (2003) [213]	Determined whether biochemical modulation with LV (leucovorin) enhances the efficacy of CAF (cyclophosphamide, doxorubicin, and fluorouracil) against MBC	Chemotherapy alone	241	CALGB expanded common toxicity criteria	No	No	Infection, Diarrhoea, Dyspnoea, Lymphocytopenia, Neutropenia & Leukopenia
Perez (2015) [214]	Assessed whether etirinotecan pegol is superior to currently available treatments for patients with previously treated, locally recurrent or MBC.	Targeted agent alone	852	EORTC QLQ-C30 + QLQ-BR23	Yes	Yes	Significant differences were noted in favour of etirinotecan pegol over 32 weeks for global health status and physical functioning scales of the EORTC QLQ-C30 Abdominal pain, Abdominal pain upper, Alopecia, Arthralgia, Asthenia, Blurred vision, Constipation, Cough, Decreased appetite, Decreased weight, Diarrhoea, Dizziness, Dyspnoea, Fatigue, Headache, Myalgia, Neuropathy-related events, Peripheral oedema, Pyrexia & Vomiting
Robert (2011) [215]	Sunitinib plus paclitaxel prolongs progression-free survival (PFS) compared with bevacizumab plus paclitaxel as first-line treatment for patients with HER2(-) MBC.	Chemotherapy plus targeted agent	485	NCI CTCAE	No	No	Alopecia, Anaemia, Anorexia, Arthralgia, Asthenia, Constipation, Diarrhoea, Dysgeusia, Dyspepsia, Dyspnoea, Epistaxis, Fatigue, Hand–foot Syndrome, Headache, Hypertension, Leukopenia, Mucosal Inflammation, Myalgia, Nail Disorder, Nausea, Neutropenia, Peripheral Neuropathy, Peripheral Sensory Neuropathy, Rash, Stomatitis, Thrombocytopenia, Vomiting

Rugo (2018) [216]	Impact of palbociclib plus letrozole on patient-reported health-related quality of life	HT + TT	666	FACT-B EQ-5D	Yes	Yes	Abdominal pain, Alopecia, Arthralgia, Asthenia, Back pain, Constipation, Cough, Decreased appetite, Diarrhoea, Dizziness, Dry skin, Dysgeusia, Dyspepsia, Dyspnoea, Fatigue, Headache, Hot flush, Infection, Insomnia, Musculoskeletal pain, Myalgia, Nausea, Pain in extremity, Peripheral oedema, Pyrexia, Rash, Stomatitis & Vomiting. Significantly greater improvement in pain scores was observed in the Int. arm. In both arms, deterioration of FACT-Breast Total score was significantly delayed in patients without progression versus those with progression and patients with partial or complete response versus those without.
Rugo (2019) [217]	Updated efficacy, safety, and patient-reported outcome (PRO) results for the overall PALOMA-2 study population	Chemotherapy plus hormonal therapy	666	FACT-B NCI CTCAE	Yes	No	
Schmid (2005) [218]	Compared up-front tandem HDCT and standard combination therapy in patients with MBC.	Chemotherapy alone	93	NCI CTCAE QOL measure not specified	Yes	N/A – not reported	Infection, Nausea, Vomiting & Stomatitis
Schröder (2011) [219]	Compared weekly single-agent docetaxel is preferable to 3-weekly docetaxel regarding its toxicity and efficacy profile.	Chemotherapy alone	161	NCI CTCAE EORTC QLQ C30 + QLQ BR23	Yes	No	Fatigue, Asthenia, Mucositis, Febrile neutropenia, Diarrhoea & Onycholysis (nail disorder)
Sherrill (2010) [220]	Quality-of-life and quality-adjusted survival (Q-TWiST) in patients receiving lapatinib in combination with paclitaxel as first-line treatment for MBC	Chemotherapy plus targeted agent	86	FACT-B	Yes	No	

Slamon (2018) [221]	Evaluated ribociclib plus fulvestrant in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy in the advanced setting.	Hormonal therapy plus targeted agent	726	CTCAE	No	No	Nausea, Fatigue, Diarrhoea, Vomiting, Constipation, Arthralgia, Cough, Headache, Pruritus, Alopecia, Rash, Back pain, Decreased appetite, Pain in extremity & Hot flush
Smorenburg (2014) [222]	Compared the efficacy and safety of first-line chemotherapy with pegylated liposomal doxorubicin (PLD) versus capecitabine in MBC	Chemotherapy alone	78	NCI CTCAE EORTC QLQ-C30, geriatric assessment	Yes	N/A – not reported	Fatigue, Hand foot syndrome & Stomatitis
Sparano (2010) [223]	Determined whether the combination of ixabepilone plus capecitabine improved overall survival (OS) compared with capecitabine alone in patients with MBC (MBC) previously treated with anthracyclines and taxanes.	Chemotherapy alone	1198	CTCAE	No	No	Alopecia, Anaemia, Anorexia, Arthralgia, Asthenia, Constipation, Diarrhoea, Fatigue, Hand-foot syndrome, Leukopenia, Mucositis, Myalgia, Nail disorder, Nausea, Neutropenia, Peripheral neuropathy, Peripheral sensory neuropathy, Stomatitis, Thrombocytopenia & Vomiting
Trédan (2016) [224]	Compared the efficacy of combining endocrine therapy with bevacizumab against continuation of the initial regimen in patients who had had a response or disease stabilization with first-line taxane and bevacizumab.	Chemotherapy alone	117	EORTC QLQ-C30	Yes	No	Alopecia, Anaemia, Arthralgia, Constipation, Diarrhoea, Fatigue, Hypertension, Mucositis, Myalgia, Nail disorders, Nausea, Neutropenia, Oedema, Peripheral motor neuropathy, Peripheral sensory neuropathy & Vomiting
Tripathy (2018) [225]	Assessede the efficacy and safety of ribociclib plus endocrine therapy in premenopausal women with advanced, HR-positive breast cancer. MONALEESA-7	Targeted agent alone	672	EORTC QLQ-C30 NCI CTCAE	Yes	Yes	Abdominal pain, Alopecia, Anaemia, Arthralgia, Asthenia, Back pain, Bone pain, Constipation, Cough, Diarrhoea, Fatigue, Headache, Hot flush, Insomnia, Leukopenia, Musculoskeletal pain, Myalgia, Nausea, Neutropenia, Pain in extremity, Pyrexia, Rash, Stomatitis, Upper respiratory tract infection & Vomiting Yes - Time to deterioration in QoL score not reached in ribociclib group, was 21.2 months in placebo.

Urrutic oechea (2017) [226]	Assessed the efficacy and safety of trastuzumab plus capecitabine with or without pertuzumab in patients with human epidermal growth factor receptor 2-positive MBC who experienced disease progression during or after trastuzumab-based therapy and received a prior taxane.	Chemotherapy plus targeted agent	452	NCI CTCAE	No	No	Diarrhoea, Nausea, Hand-foot syndrome, Rash, Nasopharyngitis & Insomnia
Verma (2012) [227]	Assessed the efficacy and safety of T-DM1, as compared with lapatinib plus capecitabine, in patients with HER2-positive MBC previously treated with trastuzumab and a taxane.	Targeted agent alone	991	FACT-B NCI CTCAE	Yes	Yes	Anaemia, Diarrhoea, Fatigue, Mucosal inflammation, Nausea, Palmar–plantar & Vomiting. Yes - median time to a decrease of 5 points or more in the FACT-B TOI score was delayed in the T-DM1 group (7.1 months, vs. 4.6 months) with lapatinib plus capecitabine.
Verma (2018) [228]	Evaluated patient-reported outcomes for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer treated with first-line ribociclib plus letrozole.	Hormonal therapy plus targeted agent	668	EORTC QLQ-C30 + QLQ-BR23	Yes	No	No significant difference, HRQoL maintained and similar between arms
Wu (2011) [229]	Focused on the impact of treatments on health-related quality of life (HRQOL).	Targeted agent (lapatinib plus trastuzumab vs lapatinib alone)	296	FACT-G + FACT-B	Yes	Yes	Patients on lapatinib had declining HRQOL at all the scheduled visits, which were significantly different from the combination arm at week 12 for the FACT-G score only.
Yamam oto (2017) [230]	Compared the efficacy and safety of low-dose capecitabine plus docetaxel combination therapy (XT) versus single-agent administration of docetaxel in anthracycline-pretreated HER2-negative MBC.	Chemotherapy alone	163	EORTC QLQ-C30	Yes	Yes	Alopecia, Hand-foot syndrome, Fatigue, Dysgeusia, Stomatitis, Nail changes, Anorexia, Nausea, Peripheral oedema, Diarrhoea, Neuropathy sensory, Vomiting & Constipation Less deterioration over time with low dose (intervention arm) during treatment administration.

Zhang (2017) [231]	Compared the efficacy and safety of utidelone plus capecitabine versus capecitabine alone in patients with MBC.	Chemotherapy alone	405	CTCAE	No	No	Peripheral neuropathy, Palmar-plantar, Nausea, Diarrhoea, Vomiting, Constipation, Insomnia, Asthenia, Alopecia, Leukopenia, Neutropenia & Anaemia
Zhou (2009) [232]	Assessed the effects of study treatments on quality of life (QOL) among patients in EGF100151.	Chemotherapy plus targeted agent	399	FACT-B and EQ-5D	Yes	No	The addition of lapatinib to capecitabine significantly increases TTP without any evidence of a deleterious effect on patients' QOL
Zielinski (2005) [233]	Compared the time to progressive disease, overall response rate, overall survival, and toxicity of gemcitabine, epirubicin, and paclitaxel versus fluorouracil, epirubicin, and cyclophosphamide as first-line therapy in patients with MBC.	Chemotherapy alone	259	WHO criteria	No	No	Alopecia, Nausea, Vomiting, Mucositis, Neutropenia, Thrombocytopenia & Anaemia

Table 3. Summary of studies included in the Non-CTIMP search grouped by study design.

First author and date of publication	Objective	Type of Study	Sample	Measure	Significant Difference in QOL	Key Findings
Aranda (2006) [234]	Addressed the psychosocial and quality of life needs of urban women with MBC. (Evaluating a nurse-led intervention)	non-CTIMP RCTs	105	EORTC QLQ-C30 Supportive Care Needs Survey (SCNS)	No	No significant differences between groups.
Low (2010) [235]	Evaluated the effects of emotionally expressive writing in a randomized controlled trial of MBC patients.	non-CTIMP RCTs	62	Centre for Epidemiologic Studies–Depression Scale (CES–D) Impact of Events Scale (IES) Negative somatic symptoms Pennebaker (1982) Pittsburgh Sleep Quality Index (PSQI)	No	Expressive writing did not produce reductions in psychological distress (i.e., general depressive symptoms and cancer-specific intrusive thoughts) or improvements in physical health.
Bordeleau (2003) [236]	Evaluatede the effect of a standardized group psychosocial intervention on health-related quality of life (HRQOL) in women with MBC.	non-CTIMP RCTs	215	EORTC QLQ-C30	No	No difference in HRQOL between groups. However, there was significant deterioration over time in the functional scales: global, physical, role, and cognitive functioning; and in symptom scales: dyspnoea, appetite loss, and fatigue.
Goodwin (2001) [237]	Assessed supportive-expressive group therapy on survival among women with MBC.	non-CTIMP RCTs	235	Profile of Mood States Pain and suffering or hurt scale	N/A	Women who were initially more distressed benefited from the intervention.
Hanser (2006) [238]	Examined the effects of music therapy (MT) on psychological functioning, quality of life, and physiologic stress arousal.	non-CTIMP RCTs	70	FACT-G Functional Assessment of Chronic Illness Therapy—Spiritual WellBeing (FACIT-Sp) Hospital Anxiety and Depression Scale (HADS)	No	No significant differences in QOL or psychological distress over time. Immediate effect of intervention - Significant improvements in mood, relaxation, and comfort. Significant decreases in heart rate after each session.

Kissane (2007) [239]	Assessed the impact of supportive-expressive group therapy (SEGT) on survival in MBC.	non-CTIMP RCTs	227	EORTC QLQ-C30 The Monash Interview for Liaison Psychiatry (MILP) Impact of Event Scale Mini- Mental Adjustment to Cancer Scale	Yes	QLQ-C30 = Significant improvement in intervention arm in Social Functioning for those with Depression. IES = Significant improvements in intervention arm for intrusive thoughts in patients with depression at baseline. Mini-MAC = Sig better attitudinal coping in intervention arm, reduced helplessness–hopelessness subscale.
Walker (2011) [240]	Evaluated the impact of disease progression and of specific sites of metastasis on patient reported outcomes (PROs) that assess symptom burden and health related quality of life (HRQoL) in women with MBC.	non-randomised studies	102	PCM, version 2.0 86-item self-report measure that asks patients to rate the severity of symptoms	Yes	Fatigue, physical pain and trouble sleeping were sensitive to either general effects of disease progression or to effects associated with specific sites of metastasis. Progression of disease was associated with modest but significant worsening of General Physical Symptoms, Treatment Side Effects, Acute Distress and Impaired Performance index scores.
Walker (2014) [241]	Examined the relationship between early discontinuation or switching of treatment (ETDS) and patient-reported symptom burden among patients receiving first-line treatment of MBC	non-randomised studies	797	PCM, version 2.0 86-item self-report measure that asks patients to rate the severity of symptoms	Yes	Symptoms that were at least a mild problem for the largest proportion of patients were fatigue, body weakness, and physical pain. Fatigue and pain were the only two symptoms endorsed as severe by at least 40% of patients.
Brems-Eskildsen (2019) [242]	Examined the efficacy and toxicity of Eribulin treatment in MBC patients	non-randomised studies	130	CTCAE v4	N/A	Fatigue, neuropathies, muscle and joint pain, nausea and loss of appetite, mucosal inflammation, diarrhoea, vomiting and fever.
Shin (2016) [243]	Studied quality of life (QOL), depression, anxiety, and prognostic understanding of patients with MBC.	non-randomised studies	140	FACT-B HADS Prognosis and Treatment Perceptions Questionnaire (PTPQ)	Yes	QOL and psychological symptoms Chemotherapy showed worse QOL than Endocrine therapy, with significantly lower physical well-being and higher depression and anxiety.

Ecclestone (2016) [244]	Examined symptom burden and quality of life (QOL) in patients with MBC.	non-randomised studies	174	Edmonton Symptom Assessment System (ESAS) FACT-B questionnaires	Yes	ESAS = found better well-being in in patients treated with bisphosphonate for bone metastases. When both metastatic groups were analysed together bisphosphonate treatment was significantly associated with lower appetite loss scores. Lower fatigue scores were also found in patients participating in a clinical trial. Lower scores of fatigue and dyspnoea were significantly associated with the presence of brain metastases.
Amado (2006) [245]	Evaluated changes in QOL among MBC patients receiving treatment derived from trials	non-randomised studies	40	SF-36 Beck Depression Inventory (BDI)	Yes	Increase in overall QOL, Pain, Social Functioning and Mental Health.
Muller (2014) [246]	Evaluated data on the quality of life (QoL) of patients treated with capecitabine as mono- or combination chemotherapy	non-randomised studies	735	EORTC QLQ-C30 CTCAE	No	QOL remained stable during the investigation.
Muller (2018) [247]	Examined the influence of disease progression on health-related quality of life	non-randomised studies	329	EORTC-QLQ-C30 V3.0	No	Comparisons of mean differences of QOL domains/scales yielded no differences.
Koopman (2002) [248]	Examined sleeping problems in women with MBC in relation to depression, social support, and salivary cortisol.	non-randomised studies	97	Stanford Sleep Questionnaire Centre for Epidemiological Studies Depression Scale (CES-D) Single-Item Measure of Social Support (SIMSS)	No	24.7% reported problems in falling asleep at night, 44.3% reported problems with waking in the night, 29.9% reported problems with waking and getting up in the morning, and 20.6% reported sleepiness during the day. 63% reported one or more sleep disturbance.
Walker (2013) [249]	Examined longitudinal health-related quality-of-life (HRQoL) among MBC patients with bone metastasis	non-randomised studies	321	PCM, version 2.0 86-item self-report measure that asks patients to rate the severity of symptoms	Yes	Patients that experienced bone fractures had increased Acute Distress (anxiety and distress), worse Despair and Depression scores, worsening of worsening of ambulation (walking) problems. There was a significant detrimental effect (higher scores) associated with pleural metastasis on impaired performance scores.

Karamouzis (2007) [250]	Evaluated quality of life (QoL) parameters in patients with MBC and assessed the potential differences between patients receiving chemotherapy and those undergoing supportive care interventions.	non-randomised studies	200	EORTC QLQ-C30 + BR23	Yes	Quality of life was found to be statistically better patients receiving chemotherapy than supportive care. Only. Statistically significant differences in favour of chemotherapy were also found in functioning subscales, symptom single-item questions and sexual functioning. Sig diff in Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning, Fatigue, Pain, Appetite loss, Financial difficulties, Body image, Sexual functioning, Future perspective, Breast symptoms, Arm symptoms, Upset by hair loss.
Reed (2012) [251]	Explored QoL, experience of care, and support needs of women living with MBC in the U.K.	non-randomised studies	235	FACT-B	Yes	Those receiving chemotherapy had lower functional well-being than those receiving hormone therapy. Social well-being was significantly better for those with bone metastases only. Bone metastases more likely to report pain, lack of energy, nausea and shortness of breath. Overall QOL was low when compared with normative data.
McClelland (2015) [252]	Aimed to identify factors affecting QoL in a sample of patients diagnosed with MBC, with particular attention to body image, disease site, and time since diagnosis.	non-randomised studies	113	EORTC QLQ C-30 + BR23	Yes	Higher pain and fatigue were associated with decreased global QoL. 50–65 year olds reported a significant increase in global QoL as body image increased. Women who had been diagnosed longer than 36 months reported a significant increase in global QoL as body image increased. Greater fatigue decreased physical function. Greater fatigue was associated with decreased emotional function, while greater body image was associated with increased emotional function.
Brufsky (2017) [253]	Explored emotional needs of patients at initial diagnosis of MBC and treatment change to increase awareness about gaps and facilitate communication between patients and oncologists.	non-randomised studies	359	MYDC survey	No	Between initial diagnosis of MBC and treatment change, some patients' attitudes and feelings adapted as their disease advanced. Fewer patients reported fear of the unknown, and distress over believing something could have been done to prevent disease progression. More patients reported hope of keeping the disease stable and confidence in treatment options. More women with children ≤17 years old were distressed because they believed something could have been done to prevent disease progression. Worries about running out of treatment options.
Aranda (2005) [80]	Investigated the quality of life and support and information needs of urban women with MBC.	non-randomised studies	105	EORTC QLQ-C30 Supportive Care Needs Survey (SCNS)	No	Between one quarter and a third of the women reported difficulties with their physical, role and social functioning, and a little over a quarter of the women reported poor global health status. Fatigue was a problem for most women. The highest unmet needs were in the psychological and health information domains.

Tometich (2018) [254]	Examined cancer patients' expectations, goals, and priorities for symptom improvement.	non-randomised studies	80	Modified The Patient-Centred Outcomes Questionnaire (PCOQ) - to include 10 common symptoms (pain, fatigue, anxiety, sadness, numbness/tingling in hands/feet, swelling of arms or legs, nausea, hot flashes, sleep problems, and attention/thinking/memory problems)	No	On average, patients reported low to moderate severity across the 10 symptoms and expected symptom treatment to be successful. Patients indicated that a 49% reduction in fatigue, 48% reduction in thinking problems, and 43% reduction in sleep problems.
Marschner (2018) [255]	Evaluated effectiveness and safety of nab-paclitaxel in 697 patients with MBC	non-randomised studies	697	FACT-B Taxane-specific module (FACT-Taxane) RKI Robert-Koch-Institute pain questionnaire	No	FACT-G and FACT-B global scores were almost not affected during the treatment with nab-P. Taxane-induced symptoms increased in a clinically relevant manner. Peripheral sensory neuropathy, fatigue, decreased white blood cells, nausea, peripheral motor neuropathy, alopecia, and diarrhoea.
ten Tusscher (2019) [256]	Aimed to identify the most prevalent physical symptoms and functional limitations that limit physical activity of patients with palliative treatment for MBC	non-randomised studies	114	EORTC QLQ-C30 Charlson Comorbidity Index The Physical Activity Scale for Elderly (PASE) Physical fatigue 4-item Short Fatigue Questionnaire Patient Specifics Complaints Instrument (PSC)	No	Fatigue, Muscle and joint pain, Shortness of breath, Neuropathy, Decreased shoulder mobility, Oedema, Muscle weakness, Pain (back), Nausea and Vomiting. Other physical issues included, Running, Standing, Lifting, Playing sport, Domestics tasks, Carrying objects, picking something of the floor, Sitting for long periods, Getting in/out the car, Working, Turning in Bed, Cycling, Sexual activities, Standing from chair and Going out.

Lee Mortensen (2018) [257]	Explored the long-term health-related quality of life (HRQOL) and support needs in MBC patients of all ages in the Danish context.	Qualitative (Focus groups)	18	N/A	N/A	Two main topics were discussed in the focus groups: The quality of life impact of living with MBC and patient needs for treatment and care. Impact on QOL - subthemes: (a) reactions to the MBC diagnosis (shock and fear of death, short life expectancy, end to ordinary life including family life, work, social and leisure activities), (b) cognitive (Memory issues, lack of concentration), (c) physical (pain, gastrointestinal upsets, flu symptoms, nausea, cardiovascular dysfunction, oedema, stomatitis, neuropathy, stiffness of muscles and joints, dyspnoea, dizziness, problems with sleep and gait, hair loss and menopausal symptoms. Fatigue limited role functioning and activities), (d) psychological (emotional impact, depression/anxiety, fear of further metastasis brain/vital organs, living on borrowed time was stressful, hyper-alertness to symptoms, anger), (e) social/relational QoL aspects of MBC (Concern over children's welfare importance of having a supporting family/partner, MBC heavy burden on relationships), (f) strategies to cope with MBC (planning for the future-funerals, regaining some control, constant adaptation of QOL standards- roles and social relations, maintaining normality/role functioning, loss of employment).
Chen (2014) [258]	The aim of this study was to explore the experience of altered functional status and social roles of women with advanced breast cancer.	Qualitative (interview)	10	N/A	N/A	Women described the need to modify the way they engaged in self-care, rest, work, exercise, food preparation, housework, and family and leisure activities. They explained how they adapted to these changes, both behaviourally and cognitively. Two main themes emerged describing the strategies used to make these modifications including: Redefining Social Roles, (encompassing the behavioural adaptations made by the women) and Transforming Perceptions (describing the cognitive adaptations). Fatigue, pain, nausea, and difficulty concentrating. Fear, stress, anxiety, irritability, and depression.

Krigel (2014) [259]	The aim of this study was to further explore the lived experiences of women with MBC(MBC)	Qualitative (Focus groups)	15	N/A	N/A	Role Function - unable to maintain full time employment or maintain family roles. Relationships & communication - Role reversal (help from children), Managing illness perceptions (Not sharing all details with everyone), Lack of relationship support (ending of marriages), supportive spouses, lack of/unhelpful support from friends (e.g. drink green tea), Maintaining privacy vs getting support, changed in physical intimacy (vaginal dryness, menopause and a decrease in libido). Self-image - Both physical and sense of self changes (loss of breast, surgical side effects (scars/lymphoedema), weight gain, hair loss), being labelled as a 'cancer patient', loss of femininity, cancer causes change in overall self. Dealing with uncertainty - Lack of information about their disease and its trajectory (MBC, treatment options and side effects. Not know who to call for what (GP vs Oncologist vs nurse), not knowing the survival impact of MBC, planning for the future (wills etc), fear and anxiety of advanced cancer (waiting for test results), fear of stress, guilt, financial burden, disrupting family life e.g. clinic visits, depression (no longer being able to do things), importance of hope.
Lewis (2015) [260]	Identified the healthcare, information and support needs of women living with MBC.	Qualitative (interview)	18	N/A	N/A	Side-effects of treatment (pain, fatigue, lack of energy, muscle weakness, nausea, infections and lymphoedema had the greatest negative impacts and placed limitations on their level of functioning and participation in daily life. Lack of information about side effects of treatment); Expressions of hope and trust (High trust in Drs was important, hope for new treatments. trust was important for maintaining hope); and the use of complementary and alternative therapies.
McClelland (2016) [261]	Examined patients' descriptions of resources needed to support their Sexual QoL in palliative care.	Qualitative (interview)	32	N/A	N/A	Issues - psychological aspects of breast loss, Perceptions of body image, loss of femininity, hair loss, loss of identity, impact of physical changes on relationships, sense of ongoing loss, declining ability to maintain 'normal', Lack of information, vaginal dryness, desire for normality.

Mosher (2018) [262]	Identified factors underlying perceptions of symptom importance among 25 symptomatic MBC patients	Qualitative (interview)	25	Patient Centred Outcomes Questionnaire (PCOQ)	N/A	Physical symptoms (i.e., sleep problems, pain or fatigue) reported more than psychological symptoms (i.e., anxiety or sadness). Concentration difficulties: Sleep problems, pain or fatigue/severe fatigue, anxiety about the cancer, treatment, side effects & life span. Exacerbation of other physical symptoms: Sleep problems and pain as treatment priorities because they exacerbated other symptoms. Symptom-related long-term health concerns: Concerns over sleep problems, pain in cancer site, stress and fear of pain, or fatigue. Negative impact on their relationships with others: increased irritability when experiencing sleep problems or pain. sadness about the cancer and anxiety - not enjoying social interactions.
Vilhauer (2008) [263]	Investigated the experiences of women diagnosed with MBC.	Qualitative (interview)	14	N/A	N/A	Body image, Sexuality, Worries about stress, Fear of disease progression, Fear of dying, Practical concerns, Loss of future, Reduced daily activity, Physical symptoms, Social constraints, Medicalised lifestyle, Stress avoidance, Reduced social support, Inadequate support from close circle, Fear/discomfort/lack of understanding from close circle, Unable to open up to others.
Luoma (2004) [264]	Investigated the meaning of MBC patient's quality of life (QoL).	Qualitative (interview)	25	EORTC QLQ-C30	N/A	Physical function, Daily activities, Dependency on others, Helplessness, Decreased autonomy, Change in appearance, Change in roles and responsibilities, Social functioning, Maintaining reciprocal relationships, Isolation, Managing illness perceptions, Anxiety, Role functioning, Employment, Domestic changes, Emotional functioning, Bad temper, Feeling down, Depression, Acceptance of fate, Anger, Lack of normality.
McClelland (2015) [265]	Identified the sexual health needs of women diagnosed with MBC.	Qualitative (interview)	18	N/A	N/A	Limited sexuality, physical frailty and painful intercourse, frustrated and worried about how to maintain sexual activity both alone and with their partners, became a source of stress and frustration. Other issues-'fingerprints falling off, nails turning black, your teeth breaking off, your thyroid going black. Uncertainty of physical limitations, Emotional impact of talking to partners/possible partners about sex. Patients' unmet information needs about sexual health - vaginal pain/dryness, Communication with medical providers about sexual concerns.

3.3.1 Overview of the quality-of-life impact of MBC

Across the 103 papers, 305 issues were identified spanning multiple domains such as physical, psychological, emotional, and social. Table 4 presents the domains of the conceptual model and the number of issues categorised according to the framework. The majority of issues were related to symptom burden, which included physical symptoms and treatment related side effects. Issues relating to the psychological experience were associated with MBC were also common, and included issues relating to worry and fear. The support pathway domain accounted for 10% of the issues identified in the review and included the issues linked with family and social life. The remaining domains (independent living, clinical services & work, finance and benefits) accounted for a limited number of issues Table 4.

Table 4. The number of issues categorised in accordance with the domains of conceptual framework, the Generic Choice Model.

Generic Choice Model domain	Number of issues	Percentage %
N	305	100
Symptom Burden	161	53
Psychological experience	91	30
Support Pathways	29	10
Independent Living	11	4
Clinical services	5	2
Work, Finance and Benefits	6	2

Table 5 presents the most frequently reported issues and the percentage of papers that reported them. With the exception of depression, all issues were associated with a physical domain, with fatigue (48%), nausea (44%), diarrhoea (40%), vomiting (34%) and alopecia (22%) amongst the most common issues. A difference was found between study types, CTIMP's reported a greater number of physical issues, whereas non-CTIMP studies reported a more varied set of issues including both physical and psychosocial issues.

Table 5. ***The most common QOL issues reported across all papers* (n=103 papers).***

Issue	Count N=103	Percentage %
Fatigue	49	48%
Nausea	45	44%
Diarrhoea	41	40%
Vomiting	35	34%

Alopecia	23	22%
Pain	22	21%
Stomatitis (inflammation of the mouth)	22	21%
Constipation	21	20%
Asthenia (weakness or lack of energy)	20	19%
Arthralgia (joint pain)	17	17%
Headache	16	16%
Rash	15	15%
Cough	13	13%
Dyspnoea (difficulty breathing)	13	13%
Hand–foot syndrome	12	12%
Decreased appetite	12	12%
Myalgia (muscle pain)	12	12%
Mucositis (Sore mouth)	11	11%
Depression	10	10%
Pyrexia (fever)	10	10%
Infection	10	10%

*issues reported by >10% of study sample

3.3.1.1 CTIMP Search – Clinical Trials

The findings from both searches were reviewed independently to provide greater context to the overall results. Papers included in the CTIMP search were all phase III RCTs of female participants diagnosed with metastatic breast cancer. A range of anti-cancer treatments were identified with the majority of trials investigating the use of chemotherapy agents alone (30/70) or in combination with a targeted agent (13/70). A further 13/70 papers explored combinations of hormone therapy and targeted agent. The remaining papers included Targeted agents alone (7/70), Hormone therapy alone (5/70) or chemotherapy plus hormone therapy (2/70).

The most frequently reported issues experienced by patients in these studies affected the gastrointestinal system. This included issues such as diarrhoea, nausea and vomiting were reported in around half of the papers (

Table 5). Other body systems that were found to be impacted by the disease and/or treatment included the musculoskeletal system (arthralgia & myalgia), the skin (alopecia, rash & hand–foot syndrome) as well as more general issues, such as fatigue, asthenia and headaches. These issues were all reported in at least 10% (7/70) or more of included papers. Less frequent issues included hot flushes, weight related issues (anorexia, weight decrease & lack of appetite), neuropathy and pain (bone, back & general pain). These issues were reported in less than 10% (7/70) of papers.

3.3.1.2 Non-CTIMP Search

Papers identified in the non-CTIMP search were more varied in their study design as the search was not limited to RCTs. The search identified 33 papers, which we categorised into three methodological groups, (1) non-CTIMP RCTs, (2) non-randomised studies (observational, quantitative descriptive & mixed methods) and (3) Qualitative studies (interviews & focus groups).

Overall, the most common issues reported within these papers were pain and fatigue, both of which were reported in over half of the papers (Table 6). Gastrointestinal problems were the third most common problem, with nausea reported in 30% (10/30) of papers. Psychological issues, such as depression, anxiety and difficulty sleeping were also found to be important, as well as issues relating to body image, fear of progression and hair loss Table 6. The breakdown of issues by study design is reported below.

3.3.1.2.1 Group 1 - Randomised Control Trials (non-CTIMP)

Non-CTIMP RCTs accounted for 18% (6/33) of papers within this search and involved the evaluation of psychosocial interventions such as supportive-expressive group therapy. A total of 34 QOL related issues were identified, however one paper did not report any common or significant issues. Fatigue was reported in 40% (2/5) of these papers. Other issues included, but were not limited to pain, feeling faint/dizzy, muscle soreness/stiffness and headaches; as well as psychosocial issues such as issues with sleep, loss of independence and hopelessness/helplessness.

3.3.1.2.2 Group 2 - Non-RCT studies

Non-RCT studies accounted for 55% (18/33) of papers in this search and included papers with observational, descriptive, and mixed method designs. One paper did not report any common adverse events or significant QOL issues, and of the 17 papers that did, the most frequently reported were pain (reported 11/17 times), fatigue (10/17), nausea (7/17), anxiety, diarrhoea and difficulty sleeping (4/17), followed by depression, lack of energy and shortness of breath (3/17).

3.3.1.2.3 Group 3 – Qualitative

Nine out of 33 papers were qualitative studies, two employed the use of focus groups and seven were interview studies. Overall, the range of QOL issues reported were more varied than in the non-qualitative studies. Over 166 different issues were identified with the most commonly reported being, fatigue reported 5/9 times, followed by pain, anxiety

and depression each reported four times. Loss of normality, unknown prognosis, body image, nausea, difficulty concentrating, reduced daily activities, maintaining employment, hair loss and vaginal dryness, were each reported 3/9 times and the remaining issues were reported in two or less studies.

Table 6. ***The 15 most common QOL related issues reported by CTIMP vs non-CTIMP studies.***

Issue	Number of studies (%)	Issue	Number of studies (%)
CTIMP Search (n=70)		Non-CTIMP Search (n=33)	
Diarrhoea	37 (53%)	**Pain**	17 (51%)
Nausea	35 (50%)	**Fatigue**	17 (51%)
Vomiting	33 (47%)	**Nausea**	10 (30%)
Fatigue	32 (46%)	Depression	10 (30%)
Alopecia	22 (31%)	Anxiety	8 (24%)
Stomatitis	21 (30%)	Difficulty sleeping	7 (21%)
Asthenia	20 (29%)	Body image	5 (15%)
Constipation	20 (29%)	Fear of progression	5 (15%)
Arthralgia	17 (24%)	**Hair loss**	5 (15%)
Rash	15 (21%)	Shortness of breath	4 (12%)
Headache	15 (21%)	**Lack of energy**	4 (12%)
Cough	13 (19%)	**Diarrhoea**	4 (12%)
Myalgia	12 (17%)	Difficulty concentrating	4 (12%)
Hand–foot syndrome	12 (17%)	Unemployment	4 (12%)
Mucositis	11 (16%)	Reduced daily activities	3 (9%)

Issues in **bold** highlight those identified by both searches.

3.4 Measures of Quality of Life in MBC studies

No metastatic breast cancer specific measures were found. A total of 34 Patient Reported Outcome Measures (PROMs), including generic, multi-dimensional and disease and treatment specific tools were used across the papers. Four clinician reported outcome measures were also identified Table 7.

Table 7. *Complete list of measures identified in the review*.

Measure	CTIMP search N=70	Non-CTIMP search N=33	Combined searches N=103
Patient Reported Outcome Measure	Count (%)	Count (%)	Count (%)
EORTC QLQ-C30	20 (28.6)	8 (24.4)	28 (27.2)
EORTC QLQ-C30 + QLQ-BR23	14 (20)	2 (6.1)	16 (15.5)
FACT-B	12 (17.1)	4 (12.1)	16 (15.5)
EQ-5D + (-3L/-5L)	4 (5.7)	0	4 (3.9)
Rotterdam Symptom Checklist (RSCL)	3 (4.3)	0	3 (2.9)
Brief Pain Inventory (BPI) + (short form)	2 (2.9)	0	2 (1.9)
Geriatric assessment	1 (1.4)	0	1 (1)
Functional Assessment of Cancer Therapy–Endocrine Symptom (FACT-ES) TOI	1 (1.4)	0	1 (1)
Measure not specified	1 (1.4)	0	1 (1)
Patient Care Monitor (PCM) assessments	0	3 (9.1)	3 (2.9)
Impact of Events Scale (IES)	0	2 (6.1)	2 (1.9)
Hospital Anxiety and Depression Scale (HADS)	0	2 (6.1)	2 (1.9)
Supportive Care Needs Survey (SCNS)	0	2 (6.1)	2 (1.9)
Centre for Epidemiologic Studies–Depression Scale (CES–D)	0	2 (6.1)	2 (1.9)
FACT-G	0	1 (3)	1 (1)
The Monash Interview for Liaison Psychiatry (MILP)	0	1 (3)	1 (1)
Functional Assessment of Chronic Illness Therapy—Spiritual WellBeing (FACIT-Sp)	0	1 (3)	1 (1)
SF-36	0	1 (3)	1 (1)
Physical fatigue 4-item Short Fatigue Questionnaire	0	1 (3)	1 (1)

The Physical Activity Scale for Elderly (PASE) questionnaire	0	1 (3)	1 (1)
Patient Specifics Complaints Instrument (PSC)	0	1 (3)	1 (1)
Pittsburgh Sleep Quality Index (PSQI)	0	1 (3)	1 (1)
RKI Robert-Koch-Institute pain questionnaire	0	1 (3)	1 (1)
Stanford Sleep Questionnaire	0	1 (3)	1 (1)
Prognosis and Treatment Perceptions Questionnaire (PTPQ)	0	1 (3)	1 (1)
Single-Item Measure of Social Support (SIMSS)	0	1 (3)	1 (1)
Profile of Mood States	0	1 (3)	1 (1)
MYDC survey**	0	1 (3)	1 (1)
Edmonton Symptom Assessment System (ESAS)	0	1 (3)	1 (1)
Modified The Patient-Centered Outcomes Questionnaire (PCOQ)	0	1 (3)	1 (1)
Mini-Mental Adjustment to Cancer Scale (Mini-MAC)	0	1 (3)	1 (1)
The taxane-specific module (FACT-Taxane)	0	1 (3)	1 (1)
Beck Depression Inventory (BDI)	0	1 (3)	1 (1)
Pain and suffering or hurt scale	0	1 (3)	1 (1)
Negative somatic symptoms Pennebaker (1982)	0	1 (3)	1 (1)
Clinician reported measure			
NCI CTCAE	44 (62.9)	2 (6.1)	46 (46.6)
WHO Toxicity Grading Criteria	2 (2.9)	0	2 (1.9)
CALGB expanded common toxicity criteria	1 (1.4)	0	1 (1)
Charlson Comorbidity Index	0	1 (3)	1 (1)
Measure not specified	1 (1.4)	0	1 (1)

Quality of life measures were commonly used, with 73% (75/103) of papers including at least one measure. The EORTC QLQ-C30 was most frequently used measure, included in 37% (28/75) of papers and was supplemented with the QLQ-BR23 in a further 21% (16/75). The FACT-B was also used in 21% (16/75) of the papers, followed by an EQ-5D in 5% (4/75) and the Rotterdam Symptom Checklist and Patient Care Monitor (PCM) assessments in 4% (3/75). The remaining measures were used in two or fewer papers. Non-patient reported measures included the NCI-Common Terminology Criteria for Adverse Events (NCI-CTCAE) which was included in 45% (46/103) of all papers.

3.4.1 CTIMP Search – Clinical Trials

Of the 70 papers included, 20 did not include QOL measures. In total, 12 measurement tools were identified, eight PROMs and four clinician-reported measures (Table 7). The most common PROM was the EORTC QLQ-C30, followed by the QLQ-C30 in combination with the breast specific module (QLQ-BR23). The FACT-B was the third most common questionnaire. The remaining measures were used four or less times and included the EQ-5D, Rotterdam Symptom Checklist (RSCL), Brief Pain Inventory (BPI) and Geriatric assessment. Of the clinician reported measures, the NCI CTCAE was most frequently included followed by WHO Toxicity Grading Criteria and the CALGB.

3.4.2 Non-CTIMP Search

Seven papers (24% 7/33) did not include a QOL related outcome measure as they were qualitative studies. The non-CTIMP studies utilised a wider range of PROMs. A total of 31 different measurement tools were identified, with all but two being a PROMs (Table 7). The most frequently used was the EORTC QLQ-C30, followed by the FACT-B and the Patient Care Monitor (PCM) assessment. The PCM was used only by studies in the Netherlands. The EORTC QLQ-BR23, Impact of Events Scale (IES), Hospital Anxiety and Depression Scale (HADS), Supportive Care Needs Survey (SCNS) and Centre for Epidemiologic Studies–Depression Scale (CES–D) were each used in two papers (8% 2/25). The remaining measures were used just once. The NCI-CTCAE and Charlson Comorbidity Index were the only clinician reported measurement tools.

3.5 Contribution of QOL data to study findings

Patient reported QOL was included as a study endpoint in 68% (70/103) of papers, and was stated as a primary outcome in 27% (19/70) and as a secondary outcome in 64% (45/70) of papers. Despite being a study endpoint, six papers did not report any QOL data. The contribution the QOL data had on the overall message of the paper was examined, with 45% (29/64) reporting an overall impact on QOL scores.

3.5.1 CTIMP Search

The inclusion of patient reported QOL as a study endpoint in CTIMP papers was high, 71% (50/70). QOL was specified as a primary endpoint in 10% (5/50) of papers, as a secondary endpoint in 78% (39/50) of papers, the remaining 12% (6/50) did not state whether it was a primary or secondary endpoint. Overall, 88% (44/50) of papers reported this data within the results section. Of the papers that reported QOL data, 36% (16/44)

presented a statistically significant result. These results were found across a variety of measurement tools, including the EORTC QLQ-C30, EORTC QLQ-C30 + QLQ-BR23, FACT-B, EQ-5D-3L and the Rotterdam symptom checklist (Table 8). Of note, the Global health status/overall QOL were sensitive enough to detect differences between study groups.

3.5.2 Non-CTIMP Search

Quality of life was included as a study endpoint in 61% (20/33) of papers: 70% (14/20) included it as a primary endpoint and 30% (6/20) as a secondary endpoint. Overall, 65% (13/20) of papers reported a difference in QOL. Table 8 highlights the frequency each measure was used within the literature and how often a significant result was detected by each of the measures. The domains in which a difference was found are also displayed in Table 8.

Table 8. ***Measures that detected a significance in at least one QOL domain/scale.***

Measure	Number of studies with statistically significant result	Which QOL domains	Studies that found differences
CTIMP Search			
EORTC QLQ-C30 Used in n=20 publications	35% (7/20)	Global Health Status[74, 171, 186, 197] <u>Symptom scales</u> Pain [179, 197] Fatigue [74, 197] Dyspnoea[197] Constipation[197] Diarrhoea[210] Nausea[210] Vomiting[210] Appetite loss[197] <u>Functional scales</u> Physical [186, 197] Role[186, 197] Emotional [177, 186, 197] Cognitive[186] Social[186]	Burris (2013) [171] Hagiwara (2018) [186] Kaufman (2000) [197] Osoba (2002) [74] De Luca (2019) [179] Park (2019) [210] Conte (2004) [177]
EORTC QLQ-C30 + QLQ-BR23	35.7% (5/14)	Global Health Status [178, 188, 203, 214, 225] Physical functioning [203, 214] Pain symptom scale [188, 225]	Cortes (2018) [178] Harbeck (2016) [188] Lück (2013) [203] Perez (2015) [214] Tripathy (2018) [225]
FACT-B	25% (3/12)	FACT-G total score[229] Breast symptom scale[175] FACT-B TOI scale[227]	Cella (2011) [175] Verma (2012) [227] Wu (2011) [229]

Rotterdam symptom checklist	33% (1/3)	Overall quality of life[190]	Hopwood (2008) [190]
EQ-5D-3L	25% (1/4)	Disutility[186]	Hagiwara (2018) [186]
Non-CTIMP Search			
EORTC QLQ-C30	13% (1/8)	Social Functioning[239]	Kissane (2007)* [239]
EORTC QLQ-C30 + QLQ-BR23	100% (2/2)	Global Health Status[252] <u>Functional scales</u> Physical [250, 252] Role[250] Emotional [250, 252] Social[250] Cognitive[250] <u>Symptom scales</u> Fatigue[250] Pain[250] Appetite loss[250] Financial difficulties[250] <u>BR23 domains[250]</u> Body image [250] Breast & arm symptoms [250] Systemic therapy side effects [250] Sexual functioning & satisfaction [250]	Karamouzis (2007) [250] McClelland (2015) [252]
FACT-B	75% (3/4)	<u>Symptom scales</u> Pain [251] Lack of energy [244, 251], 21 Nausea [251] Shortness of breath [244, 251] Appetite[244] <u>Well-being</u> Functional [251] Social [251] FACT-B TOI [243]	Reed (2012) [251] Ecclestone* (2016) [244] Shin (2016) [243]
Patient Care Monitor (PCM) questionnaire	100% (3/3)	<u>Symptom scales</u> Fatigue [240, 241] Pain [240, 241] Trouble sleeping [240] Anxiety Depression [249] General Physical Symptoms [240, 249] Treatment Side Effects [240] Acute Distress [240, 249] Impaired Performance index [240]	Walker (2011) [240] Walker (2013) [249] Walker (2014) [241]

Edmonton Symptom Assessment System	50% (1/2)	Well-being[244] Fatigue[244] Appetite[244]	Ecclestone* (2016) [244]
Impact of Event Scale	100% (1/1)	Intrusive thoughts[239]	Kissane* (2007) [239]
Mini-MAC	100% (1/1)	Coping[239] Helplessness-hopelessness[239]	Kissane* (2007) [239]
SF-36	100% (1/1)	Overall QOL[245] Pain[245] Social Functioning[245] Mental Health[245]	Amado* (2006) [245]
Beck Depression Inventory	100% (1/1)	Depression[245]	Amado* (2006) [245]

*Paper reported differences across multiple measures within the same paper

3.6 Discussion

This review was designed to provide a comprehensive overview of the Quality of Life (QOL) issues associated with living with, and being treated for, Metastatic Breast Cancer (MBC) and to further our understanding of the measurement tools used with this patient group. In over the 103 papers included in the review between 2000-2019, women with MBC reported over 305 issues across the spectrum of QOL domains. The Generic Choice Model was used as the conceptual framework from which the issues were categorised [109]. The use of the framework provided an important insight into the types of issues that impact the lives of women with MBC at a conceptual level. As a result, physical issues associated with the symptoms and side effects of treatment were identified as the most commonly reported issues within the literature.

Thirty-five Patient Reported Outcome Measures (PROMs) and four non-patient reported measures were used with this patient group, the most common being the EORTC QLQ-C30, followed by the QLQ-C30 + BR23 and the FACT-B. However, there were no MBC QOL specific questionnaires identified. The inclusion of QOL as an outcome measure of clinical trials was common, with 68% of included papers reporting QOL as either a primary or secondary endpoint. Between 36% (CTIMP RCTs) and 65% (non-CTIMP) reported statistically significant differences in various QOL domains highlighting the added value QOL data provides [156, 266]. Interestingly, the generic cancer measures were more sensitive to detecting differences in QOL aspects, despite not being designed for MBC.

The heterogeneous nature of the treatments and disease trajectory resulted in a wide spectrum of reported issues. Physical issues were the most commonly reported, such as those affecting the gastrointestinal system, with nausea, diarrhoea and vomiting

amongst the most prevalent issues. Such issues were expected, as the population of the review were receiving active treatment e.g. chemotherapy and targeted agents [68, 267] which are typically associated with such physical side effects. A recent review, investigating the QOL of MBC patients in the palliative phase of the disease, further highlighted the importance of the management of such issues in an attempt to limit the negative impact they have on the individuals QOL [268]. Whilst not directly comparable to the findings of the review presented in this chapter, it is important to consider the impact MBC has on QOL across the disease trajectory.

With the inclusion of non-CTIMP and CTIMP studies in this current review, noticeable differences in the types of issues identified were found between the two study types. A greater number of psychosocial issues, such as, fear of progression, anxiety and depression, difficulty sleeping and issues relating to body image were reported in non-CTIMP studies. Non-CTIMP studies included a wider range of measures, therefore increasing the variation of potential issues for which patients could report. They also included qualitative studies whereby patients could freely report problems without the constraints of a structured questionnaire. These observations suggest current measures for assessing QOL in CTIMP studies may not fully capture the experiences of women with metastatic disease as shown by the increased reporting of psychosocial issues in non-CTIMP studies. The inclusion of qualitative sub-studies within RCTs may prove a valuable addition as QOL is a multi-dimensional concept that incorporates the wider impact of disease and not just the physical symptoms and side effects, and is therefore crucial to consider these psychosocial complications [269].

In the absence of a MBC specific QOL questionnaire, the number of measurement tools used was varied. Despite the availability of two breast cancer specific questionnaires, the EORTC QLQ-C30 proved to be most frequently used measure across all studies, a finding supported by a previous review [155]. However, a more recent review found the FACT-B to be the most frequently within Phase III RCTs [156]. The methodological strengths of the EORTC QLQ-C30 may account for its popularity; however, with the availability of a breast specific module, the use of the QLQ-C30 alone raises questions as to why the additional module is not also included within these studies. In light of this, an MBC-specific questionnaire may help to address this issue, as it would target the specific needs of the patient and provide better measurement of QOL in this patient group.

The number of papers including QOL as a study endpoint was considerably higher in the current review than seen in previous reviews (68% vs 39%) [156]. In fact, when

compared to the data from CTIMP studies only, the difference was even greater, with 71% of studies reporting QOL as an endpoint. The level of inclusion also surpasses that of research into early breast cancer, which found QOL to be reported as an outcome in just 54% of studies over a 10-year period between 1990-2000 [266]. This suggests that over time, and likely due to the recent availability of methodological guidelines, that QOL is increasingly becoming a key endpoint across MBC research, and thus further highlighting the importance of better measurement [270, 271]. It is important to note that in 12% of the CTIMP studies the QOL results were not reported. Findings are similar, but lower, than a study of a cohort of cancer trials showing that 38% of trials never reported the results of their QOL studies [272, 273].

The QOL results contributed to the main findings in around 1/3 of CTIMP and 2/3 of non-CTIMP studies, but it was not possible to identify a sub-set of QOL measures that were more likely sensitive to between group differences. Notably, the overall QOL scores of several measures seemed to be capturing well the overall impact on QOL of different treatments. The breast cancer specific questionnaires used within the included papers were designed to capture the relevant and important issues associated with the disease; however few studies that included such measures found a difference in the breast domains, with the majority of papers reporting differences in the core domains only (QLQ-C30 or FACT-G). This alludes to potential insensitivities of the breast cancer specific measures when used in a metastatic population. This is likely due to the fact MBC differs significantly to early breast cancer, and the existing measures were primarily validated in early breast cancer. Therefore, the development of an internationally validated, and methodologically sound, PROM for MBC is an important step order to help to improve the quality of measurement in research and provide more meaningful information in clinical practice.

The inclusion of multiple methodologies enabled the exploration of QOL beyond the reporting of CTIMPs (Phase III RCTs). Whilst RCTs offer robust methodologies, their scope to generate new information regarding the issues and experiences of patients may be somewhat limited due to the focus on objective treatment outcomes and the use of structured quantitative QOL methods. A strength of this review was the inclusion of qualitative studies as they provided a greater depth of information in which to answer the research questions. This was highlighted by the fact that 166 issues, spanning physical, psychological, emotional and social domains, were identified from the nine qualitative papers. Without the inclusion of such studies, results may have been heavily loaded towards the physical symptoms and side effects reported in clinical trials, and whilst toxicity data provides a great insight into the effects of the cancer and its treatments, it

does not tell the full story of the impact they have on the individual's quality of life. It may be argued that the wider range of psychological issues is not relevant when evaluating the efficacy and toxicity of new treatments. However, it has been increasingly recognised that patient-reported measures add value to cancer trials [274]. Capturing the broader patient experiences and feelings may not directly influence regulatory drug approvals but will provide future patients with valuable data to make treatment decisions, give clinicians evidence to support changes to clinical practice and shared decision-making and give information to regulators, policy-makers and health technology assessors and regulators.

The inclusion of multiple study designs led to the development of a complex search strategy to capture relevant CTIMP and non-CTIMP studies. This inclusion of both quantitative and qualitative papers made drawing comparisons somewhat more difficult due to the nature in which the data was reported. For example, the use of a single, structured questionnaire within CTIMPS unified the data in a way in which was not seen in non-CTIMPs whereby non-CTIMPS reported a wider range of issues, that were more broadly defined due to the less structured methods or use of multiple measure.

There were also more than double the number of CTIMP papers included compared to non-CTIMPs and therefore the overall frequencies are largely driven by this. However, to highlight this limitation and preserve the richer data provided by non-CTIMP studies, the two types of studies were reported separately. Despite the systematic and robust approach adopted by this review, it was subjected to the same limitations as seen in similar reviews, including issues relating to publication bias, study population and the exclusion of non-English papers.

Further to the challenges discussed above, this was a fast-moving area of research with an exceptional number of successful RCTs in the MBC setting being published since 2019, and these new drugs entered clinical practice. This influx of new trials resulted in new data being made available, after having completed the initial search for this systematic review. In light of the new evidence, and for the purpose of the module development, it was necessary to review the data to ensure all issues had been included. A full update of the systematic review was not conducted due to time limitations; however, I conducted an update of the new investigators' brochures of the drugs entering clinical practice and a supplementary review of the additional CTIMP studies published from 2019-2022. Whilst this update was important for the publication of the review and development, it was decided not to include this supplementary data in my thesis, due to time limitations. Instead, data from 18 papers published between 2019-2022 was used

to verify that the issues included in Phase I was in fact still comprehensive and representative of the issues related the new treatments. No new issues were identified, however the prevalence of mucositis across the new treatments was noted.

In the time since completing this work, additional reviews have been published investigating QOL and patient reported outcome measures in MBC. A recent review of QOL in MBC patients receiving palliative care included both quantitative and qualitative papers within their search strategy, and whilst no qualitative papers were included in the review, it highlights the need to consider the wider literature if we are to further our understanding of the issues and experiences of this patient group [268]. A second review of PROs in advanced breast cancer clinical trials was published in 2021, which supported the finding that multiple PROMs are used within the literature and that the EORTC QLQ-C30 was the most used measure [85]. The review concluded that many of the included trials did not include details of the PRO administration, scoring, analyses, and interpretation of results within the papers, further supporting the need for improved reporting of QOL in MBC patients.

On reflection, it was clear that the scope of the review was too broad. Whilst the aims of the review were clear, the practicalities of undertaking such a review with the time and resources available within my PhD were challenging. The broad nature of the aims resulted in a wide set of inclusion criteria and complex search strategies that identified thousands of publications for review. Adapting the timeframe in which papers were searched between would have significantly reduced the number of papers identified. For example, limiting the CTIMP search to within 5-10 years, rather than the past 20 years would have made this aspect of the review more contemporary. The combination of multiple study designs in one review was also a challenge, particularly in the synthesis of the results. Future reviews would focus on a more specific topic or refined inclusion criteria, however in the current review I met the aims and was able to answer the research questions that I set out to answer.

This review has taken an important step in furthering our understanding of the quality-of-life issues associated with metastatic breast cancer. From the identification of issues to the exploration of the current measures, there is a gap in the literature for a MBC-specific, QOL measure to be developed to unify the research and facilitate the comparison of results between studies. Such a measure should cover a wider range of QOL issues to be useful in both CTIMP and non-CTIMP studies. The issues identified from this review were considered in the development of a new metastatic breast cancer module, to supplement the EORTC QLQ-C30.

Chapter 4. Phase I: Issue Generation

As described in Chapters 1 and 2, the structure of the thesis was guided by the European Organisation for Research and Cancer's (EORTC) approach to questionnaire development, which consisted of three phases of development, followed by a fourth phase to internationally validate the questionnaire [99]. Chapter 4 builds upon the systematic review conducted in Chapter 3 and presents the research activities completed during the Phase I of the project. Whilst the systematic review was part of the issue generation process, and forms part of the Phase I development process, it was presented as a standalone chapter to showcase the work which underpinned and facilitated the research conducted throughout the thesis.

The review was instrumental in building the foundation from which the provisional questionnaire was developed. It provided an insight into the range and complexity of issues women with MBC experience as a result of the disease and/or treatment, and identified over 300 potential issues spanning multiple domains. The most common types of issues reported within the literature related to symptom burden, for instance fatigue, nausea and diarrhoea [166, 178], followed by psychological related issues, such as anxiety, depression and issues associated with body image [250, 261]. Results of the review have shown that CTIMP studies often focus on the physical symptoms and side effects experienced as a result of the cancer and/or treatment [167, 200, 207], however quality of life (QOL) related issues were also commonly reported within these types of studies via PROMs [170, 179, 187]. On the other hand, non-CTIMP studies, such as qualitative studies, were shown report a wider array of issues [260, 261]. Qualitative studies were beneficial in the generation of new data specifically within the area of QOL research [115], particularly in issues that go beyond those of symptom burden. The findings from the review were used as a framework from which a comprehensive issue list was created to quantifiably assess the relevance and importance of the issues women with MBC experience. The objective of Phase I (Chapter 4) was to explore and assess this comprehensive set of QOL related issues via a mixed methods approach to identify the issues most relevant and important to the patient.

Chapter 4 resulted in the identification of a core set of issues which were prioritised by patients for inclusion in the new questionnaire. The findings of this chapter were later used in Phase II which sought to develop the issues into fully formed questionnaire items, this data is presented in Chapter 5. Chapter 4 begins with an overview of the methodological approach adopted in Phase I. It details the process in which a second review of the treatment investigator brochures was conducted and integrated into Phase

I, as well as the methodological approach adopted across participant recruitment, data collection, management, and analysis. The chapter concludes with the discussion of the results.

4.1 Methods

4.1.1 Overview

The generation of QOL related issues impacting MBC patients consisted of multiple components to ensure a full range of issues were identified. Three core sources were reviewed resulting in the generation of an exhaustive list of relevant issues experienced by women with MBC. Sources included, 1. The literature, 2. Patients living with MBC and 3. Healthcare Professionals (HCPs) with clinical expertise within the area of MBC. This was in line with version 4 of the EORTC Module Development Guidelines.

Presented in Chapter 3, the scientific literature was first searched with the aim of identifying and extracting the relevant symptoms, side effects and wider psychosocial issues women living with MBC experience. To supplement the systematic review, a second review of the investigator brochures (IBs), presented in section 4.2, was conducted to ensure full coverage of the treatments and their respective adverse events and issues were obtained. Results of the reviews were amalgamated to produce the 'issue list questionnaire, the methods of which are discussed in section 4.3.4.1.

Moving beyond the published literature, patients and HCPs were consulted to further explore the issues and ensure the issue list questionnaire was inclusive of all the relevant issues. To achieve this, semi-structured interviews were conducted, during which, a quantitative assessment of the relevance and importance of the issues was obtained via the administration of the issue list questionnaire.

4.2 Investigator Brochure review

Investigator Brochures (IBs) are a collection of clinical and non-clinical data about investigational medical products, which in this case are anti-cancer treatments for MBC. IB's are designed to enable a clinician, or potential investigator, to understand and make unbiased decisions around the appropriateness of the treatment [275]. They contain pertinent information associated with each treatment, and include details on dosage, mode of delivery and adverse events, making them a highly valuable source of data [275]. The use of IBs within the realm of questionnaire development is somewhat limited, however the approach was included within the update of the breast specific EORTC

module. Although, the methodological approach of the review remains to be known [98]. The objective of this review was to identify and extract the most common adverse events associated with the treatments currently used in MBC as part of the issue generation stage of Phase I. The results aimed to supplement those of the systematic review in an attempt to capture all of the most relevant issues impacting women with MBC.

4.2.1 Method

A scoping review was conducted following the methods outlined by the Arksey and O'Malley framework [114]. Having first established the aim of the review, the second stage was to identify relevant data sources from which to answer the research questions posed. This included searches for clinical practice guidelines such as those published by NICE and ESMO [5]. Key CTIMP trials from the systematic review were also reviewed to ensure newly emerging treatments were included. In order to determine the most common AE's associated with the treatments used within MBC, the identified drug therapies were extracted and outlined for inclusion in the data extraction phase.

4.2.1.1 Data extraction

The current treatments for MBC were extracted from the identified sources and entered into an excel database. The listed treatments were categorised according to their clinical profile, for example chemotherapy, targeted therapy, hormone therapy and immunotherapy, before being searched for on the electronic medicines compendium (EMC) website. The EMC provides up to date, approved and regulated prescribing information and patient information for licensed medicines, and the associated IBs of each treatment [276]. Having identified the individual IB's, data relating to the most common adverse events were extracted, entered and cross referenced alongside their corresponding treatment within the excel database.

AE data were extracted according to their prevalence. In the highest level of data extraction, all AE's classified as common (≥ 1% to < 10%) or very common (≥ 10%) were extracted. However, in line with the methods utilised in the systematic review, only the 'very common' AEs were included in the final analysis and those impacting less than 10% of the sample were excluded. The remaining very common AE's were reviewed to determine whether they were consisted to feasibly be self-reported by the patient. These decisions were made based on the clinical characteristics of the associated AE, such as the body system it impacted and the PRO-CTCAE item library [277]. Each issue was categorised according to the CTCAE body system profile, therefore, AEs that impacted systems that required objective measurement for example, 'Blood and lymphatic', were

not considered to be ‘self-reportable’ as patients are unable to determine their blood counts without objectively measured assessments. Each AE, was reviewed by myself and supervisory team which conducted with a medical oncologist whose specialty was breast cancer to determine its inclusion.

The final dataset consisted of the most common AE’s that were considered to be patient reported outcomes. These data, along with their associated treatment and conceptual domain, were then extracted to form an overall list of issues which was comparable with the data extracted from the systematic review. This list was combined with the systematic review data to produce a master list of issues and later formed the issue list questionnaire presented to participants during the semi-structured interviews (see section 4.3.4.1).

4.2.1.2 Analysis

Due to the nature of the data, the CTCAE body systems framework was used to categorise the issues as it provided the most suitable framework from which to map the data. All AEs were categorised according to the relevant CTCAE body system criteria (e.g. Gastrointestinal), the individual drug treatment in which they were related (e.g. Paclitaxel) and by the overall drug classification (e.g. chemotherapy). Frequency data was calculated to determine the most common AEs reported across the available treatments. The overall aim of the review was to extract the issues associated with MBC drug treatments to supplement those found by the systematic review and therefore, the data produced by the IB review was cross referenced, and later combined resulting in the development of an extensive list of QOL related issues.

4.2.2 Results

Overall, 29 treatments were identified and reviewed. The most common treatments types included chemotherapy (12), targeted therapy (9), hormonal therapy (7) and immunotherapy (1). The individual drugs included are presented in Table 9. The majority of treatments were chemotherapies and included various cytotoxic agents from multiple classes, including taxanes, anthracyclines and anti-metabolites. A range of targeted agents were included, including monoclonal antibodies, antibody-drug conjugates and tyrosine-kinase inhibitors. There are several classes of hormone therapies with distinct mechanisms of action, of which this review captured seven, including selective oestrogen receptor modulators (SERMs), aromatase inhibitors and luteinizing hormone-releasing hormone (LH-RH) agonists. Atezolizumab was the only immunotherapy included.

Table 9. Individual drug therapies included within the review categorised by treatment type.

Chemotherapy	Targeted Therapy	Hormone therapy	Immunotherapy
Carboplatin	Trastuzumab	Tamoxifen	Atezolizumab
Cisplatin	Pertuzumab	Faslodex	
Doxorubicin	T-DM1	Anastrozole	
Epirubicin	Lapatinib	Letrozole	
Capecitabine	Everolimus	Exemestane	
Gemcitabine	Denosumab	Goserelin	
Fluorouracil	Bevacizumab	Megestrol acetate	
Methotrexate	Palbociclib		
Docetaxel	Ribociclib		
Eribulin			
Paclitaxel			
Vinorelbine			

The results from the initial data extraction are documented within Appendix 9.1.3, which highlights both the common, and very common AEs for each of the treatments shown in Table 9. This data was further assessed to identify only the 'very common' patient reported AE's. Each AE was categorised in accordance with the body system in which it was associated (Table 10). The treatments included within the review were shown to impact a range of body systems, the most commonly affected were the gastrointestinal (GI) system, for example nausea, vomiting, diarrhoea, general systems (fatigue, asthenia & pyrexia) and those that were skin related (alopecia, rash, itchy skin).

Table 10. The count of Adverse Events reported across the investigator brochures, categorised according the CTCAE body systems framework.

CTCAE Body System	Count of Adverse Events (n368)
Gastrointestinal	96
General	67
Skin	49
Respiratory	31
Nervous system	31
Musculoskeletal	31
Infections	17
Metabolism and nutrition	13
Vascular	10
Psychiatric	9
Eye disorders	5
Reproductive	4
Immune system	2
Blood and lymphatic	2
Cardiac disorders	1

An excerpt of the results are presented in Table 11. A total of 98 different issues were identified across the 29 treatments reviewed. Thirty-seven AEs were found to be frequently reported (more than 10% of IBs) across the various treatment categories. The adverse events were cross-checked against those identified in the systematic review, resulting in the development of a master list of issues that have been found to impact the QOL of women living with, and being treated for MBC. The issue list was subsequently reviewed and formatted into a survey that was later presented to participants during the semi-structured interviews. The development of the issue list questionnaire is detailed in section 4.3.4.1.

Table 11. The most frequent 'very common' adverse events reported across the reviewed investigator brochures*.

Adverse Events**	Count of AE	% coverage (n=29)
Nausea	21	72.41
Vomiting	17	58.62
Fatigue	16	55.17
Diarrhoea	15	51.72
Stomatitis	13	44.83
Asthenia	13	44.83
Alopecia	12	41.38
Dyspnoea	12	41.38
Rash	11	37.93
Headache	10	34.48
Hot flushes	10	34.48
Arthralgia	10	34.48
Abdominal pain	10	34.48
Cough	9	31.03
Constipation	9	31.03
Pyrexia	8	27.59
Infections	7	24.14
Myalgia	7	24.14
Decreased appetite	6	20.69
Epistaxis	6	20.69
Insomnia	5	17.24
Dysgeusia	5	17.24
Pain	5	17.24
Pruritus	5	17.24
Anorexia	5	17.24
Mucosal inflammation	5	17.24
Palmar-plantar	4	13.79
Back pain	4	13.79
Dizziness	4	13.79
Dyspepsia	4	13.79
Weight decreased	4	13.79
Dry skin	3	10.34
Injection site reaction	3	10.34

Peripheral sensory neuropathy	3	10.34
Nail disorders	3	10.34
Urinary tract infection	3	10.34
Pain in extremity	3	10.34

*Adverse events present in 10% or more of the included investigator brochures.

**included self-reportable adverse events only.

4.2.3 Discussion

The objective of this review was to identify and extract the most common adverse events associated with MBC treatments, and aimed to supplement the findings of the systematic review in an attempt to provide comprehensive coverage of the most relevant issues impacting women with MBC. In total, twenty-nine investigator brochures of the treatments used within the MBC setting were reviewed, and data relating to the most common PRO-adverse events were extracted and analysed. A range of treatments were reviewed, including chemotherapies, targeted agents, hormonal treatments and immunotherapy. The gastrointestinal system was by far the most affected body system, which saw a high frequency of AEs impacting the patients and included nausea, vomiting and diarrhoea. Overall, a wide array of AEs were prevalent in the treatment of MBC spanning multiple body systems and domains.

The use of the CTCAE body systems framework facilitated the conceptualisation of the AEs and provided insight into the prevalence of the various different types of issues associated with MBC treatments. Its selection was largely determined by the way in which data was presented within the IBs, whereby AEs were reported and presented in accordance with the CTCAE classification. The inclusion of the Generic Choice Model framework in this review was not appropriate as the GCM lacked the sensitivity to categorise the issues in a meaningful way, for example the AEs would have all been classified within the symptom burden domain of the model.

The findings of the review provided complimentary data that was cross-checked with that of the systematic review to ensure a comprehensive list of issues was generated. This process was conducted as part of the development of the ‘issue list questionnaire’ presented to participants in the Phase I interviews and is discussed further in section 4.3.4.1. The result of which determined no novel AEs or QOL related issues were identified by this review. Whilst no new issues were identified, a strength of this methodology and its inclusion in the wider methods for developing questionnaires was seen via its efficient and streamlined approached to identifying relevant issues impacting the lives of MBC patients. As such, this method has a high potential for its use as an alternative approach to identifying issues when developing or updating PROMs. Despite

not providing as comprehensive data as the systematic review, for example, the identification of psychosocial issues, a IB review coupled with a review of the qualitative literature could provide the necessary data for phase I of the EORTC development process. Further to this, any potential issues that were missing would be identified within the interviews, and amalgamated into the issue list, resulting in the comprehensive coverage of the QOL related issues experienced.

Investigator brochures provide a convenient and accessible source of data from which research can be conducted. Whilst a wealth of AEs were extracted in this review, only the very common issues, for instance those experienced by 10% or more of the sample, were included in the analysis to maintain comparability with the systematic review, and therefore the extraction of both common and very common data within this review was unnecessary. However it highlights the scope this methodology has for future research in this area. Particularly when reviewing emerging treatments, such as new immunotherapies for TNBC, which may have limited data of this nature available [278]. This method could be a quick way to update toxicity and adverse event knowledge as and when new treatments become available.

In summary, the results of the review provided complimentary data to that found by the systematic review, and highlighted the value of the methodology within the development of PROMs due to its streamlined yet comprehensive approach. The inclusion of this method, coupled with a qualitative review of the literature, within the issue generation phase may prove to be a beneficial approach to questionnaire development moving forward. The remainder of this chapter is focused on the methods and results of the Phase I interview study conducted with both patients living with MBC and Healthcare Professionals (HCPs) with clinical expertise within the area of MBC.

4.3 Phase I - Methods

4.3.1 The research setting

The context of the setting in which the research has taken place is an important factor to consider, particularly in a large-scale international project, as it can facilitate the generalisation and interpretation of the research findings [279, 280].

I led the coordination of this project with support from supervisory team based at the Leeds Cancer Centre (LCC) in the UK. The research took place across eight countries including the UK, France, Spain, Italy, Germany, Poland, Japan, and Jordan. A ninth country (The Netherlands) was also enrolled in the project, however, did not contribute to the recruitment of participants due to delays caused by the COVID-19 pandemic. The

inclusion of a range of cultures and languages was a crucial element of the research to increase the cross-cultural validity of the overall findings. The language of the participants was also a factor carefully considered with the inclusion of the various nations several languages were included, including English, West-Germanic (Germany), Slavic (Poland), Romance (France, Spain & Italy) and non-European (Japan & Jordan).

In total, 12 centres, across eight countries, actively contributed to the recruitment of participants. Active centres recruited participants, in line with the study protocol, from within the local breast cancer units at their sites. An additional seven centres within these countries expressed interest in participating but were not activated due to local permissions not being obtained.

In the UK, research activities were conducted across two centres, the LCC and Mount Vernon Hospital. The LCC is one the largest cancer centres in the UK, treating patients from across the Yorkshire region. Patients were recruited from breast oncology clinics, outpatient and day-case units within the Bexley Wing. In addition to this, the study was also advertised at a local breast cancer charity in Leeds (Breast Cancer Haven). The Haven provide support for all breast cancer patients and offered specific services dedicated to those living with metastatic disease. With support from the Haven staff, adverts for the study were place on their online bulletin with the hope of reaching a wider network of participants, for example, those no longer required to attend hospital appointments on a regular basis.

Prior to the commencement of the study, I completed the research governance actions for obtaining ethical approval for the project. This included developing the study protocol and supporting documents, such as consent forms and information sheets. Study materials, including the protocol, were submitted to the Health Research Authority (HRA) for approval by the Research Ethics Committee (REC). Having been granted a favourable opinion from the REC, local approvals were sort and obtained from the LCC Research and Innovation department.

In the case of the international centres, each country had differing requirements and procedures for conducting research of this nature. As the study coordinator it was my role to support the centres, however ultimately the responsibility of obtaining approvals was down the Principal Investigator (PI) at each of the respective centres. A large proportion of this work was the translation of the study documents, which were originally developed in English. It was the responsibility of the PI to translate and submit the documents. I was able to prove support and guidance at the key milestones of the review process. This included coordinating contracts between the relevant parties, establishing

clear lines of communication, and assisting with translation procedures for the study documents. My main role at this stage was resolving problems relating to the bureaucracy surrounding establishing international research.

4.3.2 The study sample

Sampling is the process of selecting a proportion of the target population when it is not feasible to study the entire population. Due to the heterogeneity of the study population, a purposive sample method was employed to facilitate the collection of a representative sample. Sample size was determined by three defining factors, that characterise the target population, this included, age (<50; 51-69; >70), time since diagnosis of metastasis (<6months; 7 – 24months & >25months) and treatment type (chemotherapy, hormone, targeted therapy, immune therapy, radiotherapy & combinations). A sampling matrix was developed to categorise and manage the recruitment of patients. Based on this, a sample size of 180 patients was calculated for this phase of the study. The sampling matrix is presented in Table 12.

Table 12. ***Purposive sampling strategy for patient recruitment in each country included in Phase I.***

Time from Diagnosis of MBC	Current Treatment**	Age range		
		<50	51-69	>70
< 6 months	HT only	1	1	1
	HT+TT	1	1	1
	CT or CT+ TT*	2	2	2
7-24 months	HT only	1	1	1
	HT+TT	1	1	1
	CT or CT+ TT*	2	2	2
>25 months	HT only	1	1	1
	HT +TT	1	1	1
	CT or CT+ TT*	2	2	2

HT- Hormone Therapy; CT- Chemotherapy; TT- Targeted Therapy (anti-HER2, CDK4/6 inhibitors, mTOR inhibitors, PARP inhibitors, immune therapy).
*Those receiving TT for maintenance should be grouped using their previous treatment.
**Radiotherapy will be recorded as part of patient's treatment.

When selecting the patients for inclusion, care was taken to ensure a balanced group in terms of sites and number of metastatic disease (bone only, visceral metastases; and single vs multiple sites), lines of treatment, as well as pathology (luminal type, HER2 positive, and triple-negative patients). This was managed via running preliminary reports on the dataset as the data was entered. This was not part of the formal sampling strategy, however, was used to monitor the characteristics of the sample. Baseline characteristics

and demographic variables were obtained from medical records and through a demographic questionnaire which was completed by the patient.

With regards to the recruitment of international patients, it was proposed that each country recruit approximately 20 patients however, this was flexible and monitored throughout as it was important to include a range of cultures and languages.

Inclusion criteria

Female patients with a confirmed diagnosis of metastatic breast cancer were eligible for enrolment in this study.

Inclusion criteria

1. Adult females aged 18 years or over.
2. Had a diagnosis of MBC (Breast cancer that had spread to another part of the body). Patients with brain metastases were included, providing there was no associated cognitive impairment.
3. Had received (patients under observation) or were receiving treatment for MBC, including chemotherapy, hormone therapy, targeted agents (anti-HER2, CDK4/6 inhibitors, mTOR inhibitors, PARP inhibitors, immune therapy), radiotherapy and combinations.
4. Conversant in the language of questionnaire administration.
5. Had the capacity to give informed consent.

Exclusion criteria:

1. Patients diagnosed with early-stage breast cancer.
2. Patients with any psychiatric condition or cognitive impairment, as determined by the treating physician, that would hamper participation in interviews.

Healthcare Professionals

The target sample size for the HCP was 25 with each country to recruit 2-3 participants. The sample was to include a range of professions, including oncologists, nurses and other allied health professionals with a range of experience in the treatment and/or care of MBC patients to ensure a well-balanced and representative group.

4.3.3 Recruitment

Recruitment for the Phase I interviews took place across the included centres and followed the processes outlined in the study protocol. I prepared the protocol to cover phases I-III, based on the original grant application and EORTC guidelines with support from my supervisory team. To appease the various requirements across the different countries, the protocol contained a generic outline of the procedures which was supplemented with an appendix for the specific activities carried out in the UK. This approached was adopted to ensure each country followed the overall recruitment process but could supplement the procedure with additional information if required. This was the case in the UK due to the rigorous approval processes for conducting research in an NHS setting. This section outlines the recruitment procedure at Leeds Cancer Centre.

Patients were recruited with support from the breast cancer clinical team at the Leeds Cancer Centre. Members of the clinical team first screened the appointment lists against the inclusion criteria for eligible patients attending clinics, outpatient and day-case units. This was a curial component in the recruitment process as this was not a task that could be completed by members of the research team due to the GCP guidelines in place to protect the privacy of patients and their medical records. Identified patients were approached, informed of the study, and invited to participate at their subsequent appointment by the clinical team. Patients interested in taking part were only then introduced to the researcher who provided further information about the study and answered any questions. A detailed information sheet was provided, which contained the relevant study information as well as the GDPR statements and contact details of the study team. Patients were invited to take this away with them to read further and encouraged to get in contact with the study team if they had any questions.

Patients were given the opportunity to consent at the point of invitation if they wished or alternatively, they were followed up at their next appointment, and/or over the telephone, regarding their participation. Patients that declined to participate were thanked for their time and where possible the reason for declining was recorded. Each centre was responsible for recording this information, in Leeds, a detailed account of the number of patients approach, consented and declined was logged as part of GCP guidelines. For the individuals that were interested in taking part in the study, an interview was scheduled for a time and place convenient to the patient. Participants were given the option of completing the interview face to face, either in a private room at the Leeds Cancer

Centre or an alternative location convenient to them, or virtually, via Zoom or MS Teams or the telephone.

Prior to the interviews taking place, an overview of the interview schedule was provided, and time given for any questions the participant may have had. This included informing participants of their right to withdraw as well as reassuring them that there were no right or wrong answers, simply that the interview was about developing a greater understanding of their experiences of living with and being treated for MBC. Following this, informed consent was obtained from the participant. In the face-to-face interviews, this was provided in the form of written informed consent, however, for the virtual interviews, verbal consent was given by the participants. The University of Leeds policy for collecting verbal consent, whereby the consent form was read aloud to the participant who then agreed to each statement and agreed to participate in the study was followed. This was an amendment to the original protocol due to the impact of the COVID-19 pandemic. The amendment was approved by the study sponsor.

Following informed consent, the participant completed the social demographics form. The clinical information form was completed by the researcher following the interview and informed consent. Interviews were audio recorded using an encrypted device. Verbal consent was recorded separately to the interview and interview notes. It was not a requirement for the interviews conducted in the collaborating centres to be audio recorded, however interviewers were required to take field notes throughout.

The recruitment of participants from non-clinical environment was conducted with the support of Breast Cancer Haven Yorkshire. This was a specific protocol for recruitment in Leeds, no other centres aimed to recruit patients from non-clinical settings. The study was advertised via the Haven's website, social media activities and mailing lists. This was completed by a member of staff at the Haven who had the required permissions to communicate with the patients via the above methods. The advertisement for study involvement was placed online and directed interested parties to contact the researcher for further information. An invitation letter and information sheet were provided via email/post to patients who directly expressed an interest. A single reminder was sent after two weeks to those that did not respond after the initial contact with the researcher was made. All advertisement materials were approved by the REC.

Following the publication of the initial advertisement, the centre was forced to closed due to the impact of COVID-19 and the national lockdown. As a result, this method of recruitment became unviable as the majority of its staff were placed on the furlough scheme. With the reduced staff levels at the Haven, it was not possible to maintain this

method of recruitment. During the short advertisement period there was one expression of interest, however, the patient did not respond to the initial contact or the subsequent reminder.

Healthcare professionals

Eligible HCP were identified in discussion with the breast cancer multi-disciplinary team at the LCC. An invite, consent form and information sheet, detailing the study and the specifics of their involvement, was provided via email, telephone or face-to-face. Following contact with the HCPs that expressed an interest, interviews were arranged at a time and location convenient to them. A difference noted between the recruitment of HCP in the UK verse recruitment across the collaborating centres was the requirements for obtaining informed consent. Many of the international sites did not require HCP to sign written consent forms for studies of this nature as the topic and level of information collected was categorised as low risk. This however was not the case in the UK, whereby all participants were required to provide written, or verbal consent prior to enrolment to the study.

4.3.4 Data collection

4.3.4.1 Quantitative measures

Quantitative data collection was conducted using a questionnaire based methodology, and included the development and administration of an 'issue list questionnaire, as well as sociodemographic and clinical data collection forms (Appendix 9.1.8). The aim of the quantitative assessment used within Phase I was to provide an objective account of the most relevant and important issues patients with MBC experience as a result of their cancer and/or treatment. To achieve this, findings from the systematic and investigator brochure reviews were amalgamated and refined, resulting in the development of a comprehensive list of MBC specific QOL issues reported across the literature. Further to this, issues extracted from the EORTC's Core questionnaire (QLQ-C30) were incorporated into the list to provide a relevance and importance assessment for MBC patients.

A key stage in developing this assessment tool was the refinement of the issue list to produce a manageable, patient friendly, tool to objectively assess the issues. Firstly, the issue list was reviewed for duplications, whereby I screened, highlighted and extracted the overlapping issues from the list. As part of the refinement process, issues were translated from medical terminology into everyday terms. This process facilitated both the identification of duplicated issues, for example stomatitis and sore mouth, as well as

reduced the required level of reading comprehension for the patient sample. This was an iterative process and used a hierarchical decision approach overseen and reviewed by the supervisory team, which consisted of experienced clinical and non-clinical academics [281]. Throughout this process, great care was taken not to alter the original meaning of the issue to maintain the validity of the content. The final list consisted 185 issues spanning multiple domains, the design of the questionnaire is outlined below.

With the inclusion of 185 issues, the tool was designed to be as simple and intuitive as possible. Unlike traditional questionnaires were participants are presented with a list of items, or questions about a particular topic, this tool was simply a list of 185 issues, of which many were presented as one or two words such as 'pain' or 'back pain'. The structure of the questionnaire was defined by the conceptual framework of the Generic Choice Model for long term conditions (GCM), whereby each issue was categorised according to the domain in which they were associated [109]. Further to this, physical issues were subcategorised by the CTCAE body system framework [282], and by subdomains for the remaining issues. The included issues spanned multiple domains including, physical, psychological, emotional and social domains.

In keeping with the minimalistic and intuitive approach, the tool was formatted using the EORTC structure which consisted of a 4-point Likert scale response system (*not at all', to 'a little', to 'quite a bit', to ' very much'*) to assess the relevance of the issue and a 'check box' column where participants could indicate the issues they deemed to be most important and thus a priority for inclusion in the final questionnaire [99, 283]. A free text space was available at the end of the questionnaire to capture additional issues missing from the issue list questionnaire.

The issue list questionnaire, or 'issue list' as it is also referred to, was developed using the outlined methods by me and my supervisory team as a method to quantitatively assess the issues identified by the systematic and information brochure reviews, the data from which was later used to determine the issues included in the final questionnaire.

Social-demographic and clinical characteristics forms

For the patient sample, a basic socio-demographic information form was developed by the study team for the collection of key demographic information, including month and year of birth (MM/YYYY), current living situation, employment status and education level.

A clinical characteristics form was used to capture critical information relating to the patient's treatment and diagnosis. Data extracted from this form included, date of

diagnosis (primary & metastatic), site(s) of metastasis and their current treatment. Clinical data was obtained via the patient's medical record following their consent. A separate demographic form was used to capture relevant data about the HCP sample. This information included age, gender, country of residence, profession, and the number of years' experience.

4.3.4.2 Interviews

The semi-structured interviews consisted of two key stages, and employed a mixed methods design with the inclusion of both qualitative and quantitative methods. In the first stage of the interview, qualitative methods such as open-ended concept elicitation were used to explore the issues the participants had experienced. Across each of the participating sites, interview notes were taken throughout to provide additional information on the issues and perceptions of issues from the participant. This was a pragmatic decision aimed to facilitate the collection and analysis of data in Phase I by reducing the demands placed on the collaborators. For example, the completion, transcription and analysis of interview data is a very time consuming process and in addition to this, sites would have also had to translate the data into English. In the UK, the interviews were audio recorded to facilitate the analysis conducted on this data as part of this thesis. Due to the time pressures and wider demands of the project, the UK interviews were not transcribed, however they proved to be an extremely useful data source when cross referencing the data provided by the interview notes.

An interview guide was developed to support the interviewers by providing prompts and questions to ensure the relevant topics were discussed (appendix 9.1.6). The interview began with a series of open questions that related to their experience of living with and being treated for MBC. Participants were asked questions such as *"What are some of the (most important) issues you have experienced since being diagnosed with metastatic breast cancer?"* and "*Can you tell me about the experiences you have had as a result of your treatment?"*. During this line of questioning, probes and follow up questions were used to facilitate the discussion and encourage the participant to mention as many issues as they could think of. This continued until no new issues were raised. At the point of saturation when no new issues were mentioned, stage two of the interview began.

The second stage involved participants completing the issue list questionnaire. Instructions were given regarding how the list was generated, as well as information on its format and its method of completion. This was to ensure participants had an understanding that not all issues would be relevant to them and nor were they expected to experience all of the listed issues. This was of particular importance for those recently

diagnosed as they had less experience of the types of issues and problems women with MBC may experience. Further to this it was explained that it was not mandatory to answer all questions, as some related to very personal issues. The interviews were structured in this two staged format in order to avoid potential confirmation bias from patients only discussing the issues presented within the 'issue list questionnaire'.

When the participant was ready, they were first asked to rate each issue for its relevance, *and by "relevance" it was meant 'how closely connected is the issue to your cancer, for example is the issue something you have experienced'*. This was done for each of the 185 issues within the questionnaire. During this process they were encouraged to think aloud and verbalise their reasoning for particular scores to provide greater context, for example, if they scored an issue as not relevant then why was this the case. Equally if an issue was very much relevant, they were encouraged to explain why this was.

Following the completion of the questionnaire, participants were asked to indicate the importance of the issues, and b*y "importance" it was meant 'how much do you care about that issue'.* They were asked to select around 10-15 issues they felt were most important and that should be a priority for inclusion in the final questionnaire. As with the relevance scores, they were asked to talk aloud their reasoning behind their choices.

At the end of the interview participants were provided the opportunity to discuss further any issues they felt were missing and/or issues they feel should be removed. Patients were thanked for their time and sharing their experiences and feedback on the issue list. As the list of issues was lengthy, qualitative assessment of each issue was deemed too burdensome for the patient. The inclusion of quantitative methods at this stage of the interview aimed to reduce patient burden and facilitate the evaluation of the issues.

Healthcare professionals

Semi-structured interviews were also conducted with Healthcare Professionals (HCPs). These interviews followed the same structure and procedure as outlined above. An interview guide was developed to support the interviewers by providing prompts and questions to ensure the relevant topics were discussed (Appendix 9.1.7). The interview began with a series of open questions that explored the patient's experience of MBC from the HCP perspective, this included identifying the issues patients most frequently report during their consultations with the HCP. Participants were asked questions such as *"What are some of the (most important) issues patients report as a result of being diagnosed with metastatic breast cancer?".*

As with the patient interviews, the second stage involved the participants completing the issue list questionnaire. HCPs were asked to rank the relevance (how closely connected the issue was to the cancer and/or treatment) and the importance (the issues that most affect the patients). At the end of the interview participants were provided the opportunity to discuss further any issues they felt were missing and/or issues they feel should be removed amd were thanked for their time.

4.3.4.3 Data management

Data was managed by the coordinating site at the Leeds Cancer Centre. Each site was responsible for the recruitment of its own participants, and therefore responsible for the storage of files that contained personally identifiable information. Personal information was not used in research outputs or shared across the collaborating sites. Prior to completed study materials being returned to the study coordination centre, all sensitive information, such as their name and address, was removed, and the data was pseudonymised using a unique study ID. Each site held their own link code document for the patients they recruited, which was used only to identify patients for quality assurance of data, and corrections of errors during the statistical analyses.

Data sent by collaborators included the participant's demographic and clinical information, any study notes taken during the interview and the completed issue list questionnaire. This data was transferred via email and securely stored on a password protected online university server. I created a master database containing all participants study ID codes that was used to manage the data, monitor recruitment and was used for statistical purposes.

Data collected from the LCC were stored in a locked filing cabinet in a secure research office and digital data stored on a password protected university server. Signed consent forms were kept in a separate locked filing cabinet within the research offices. Interviews were recorded on encrypted devices and after each interview, data from the digital recorder was downloaded and stored on a password protected online university server and deleted from the encrypted device. Only the research team had access to these data.

Quantitative data was analysed using SPSS software. For both the socio-demographic and clinical data forms, numerical codes were assigned to the responses to aid the interpretation of the results. For example, for highest education level, compulsory school or less was coded as 1 and the highest level (university level) coded as 3.

Data entry was conducted by me, as the method of data collection was pen and paper based so required a manual approach. As a result, steps were taken to ensure the data had been entered correctly, this included reviewing the data ranges to ensure all responses were within the possible limits. Following this, the accuracy of the data entry was also assessed. Using a randomised number generator, 10% of the data were reviewed against the original documents to ensure the data was entered correctly. Where data was not entered correctly, a further sample would have been reviewed, however the review found the data to have been entered into the database in a consistent manner.

Prior to Phase I, the patient facing study documents were translated into the relevant languages by the collaborating sites. Data was returned to the lead site in the language they were completed. As a result, it was critical the format of the documents was not altered during this process as the data was entered in the order of the original English document. This included the demographic and clinical data forms, as well as the issue list questionnaire. Any interview notes or comments made in the free text section of the questionnaire were translated into English by the collaborating site prior to being sent.

Regarding entering the data, close attention had to be paid to the documents to ensure the data were being entered correctly. This was of particular importance for the data received from sites in Japan and Jordan as they use an alternative alphabet and structure their language differently to the European countries. For example, Arabic is read from right to left opposed to left to right in the non-Arabic countries. As I am not multi-lingual, I used the google translate app to scan the documents to confirm the structure of the documents were consistent with the original. This process was easier for the European languages as some words and phrases have a commonality between the languages. These methods provided an additional level of assurance over the quality and accuracy of the data being received. For example, it was noted that the German translation of the issue list was in fact incorrect. Upon investigation, it was determined that a previous version of the questionnaire had been translated. This was found to impact two participants and was resolved with help from the German team and the questionnaire was reformatted to match the original.

4.3.4.4 Missing data

All missing data was recorded as missing; however, no imputations were made on the missing data. The range of missing data was from 0% (low end) for physical symptoms to 5% for sexual questions. Notable missing data was observed in the German participants where a previous version of the issue list questionnaire was administered. For these patients, data on the QLQ-C30 issues was not available. Further to this, one

participant interviewed virtually at the Leeds site failed to return their issue list questionnaire and therefore was not included in the analysis.

4.3.4.5 Participant characteristics

The sociodemographic and clinical data forms were analysed using descriptive statistics (means and frequency data) to provide information on the characteristics of the sample. Within in the patient sample, descriptive statistics were produced for each of the following, country of residence, age, living situation, employment status, level of education, time since metastatic diagnosis, treatment type and the number and sites of metastasis. For HCPs, descriptive data was provided on type of profession, sex and number of years' experience. For both samples, data on the country of residence was also analysed.

4.3.5 Data analysis

Analysis of objectives:

(1) the breadth of coverage
(2) the relevance of the issues
(3) the relative importance of the issues

The first objective was to establish the breadth of coverage of the issues identified in the initial stages of Phase I. Qualitative techniques such as concept elicitation were conducted during the semi-structured interviews to identify any new issues not included within the literature. Qualitative data analysis is a systematic process of sorting and classifying data that has been collected in the case of this research content analysis was conducted on the interview data. As this stage was focused on identifying issues, rather than looking for themes, content analysis was better suited as the mode of analysis for this data. Interviews were not transcribed, however where available, audio files were reviewed, and data provided from the interview notes were coded. Whilst a qualitative interview approach to data collection was used, a full qualitative analysis was not performed on the data, rather, the quantitative data of the relevance and importance scores collected during the interviews was the primary analysis focus. Qualitative data from the interviews were however used to support the quantitative analysis and decision making process. This was a pragmatic decision based on the expected number of participants expected to be enrolled on the study, over close to 200 participants therefore the quantitative data was prioritised and the qualitative data used to supplement and elevate this data further by providing further context to the issues selected.

Objectives two and three looked to determine the relevance and importance of the included issues. Descriptive statistics were used to gain a better understanding of how the issues were perceived by patients and HCPs. The relevance of an issue, i.e. whether or not it was experienced or not, was evaluated using the mean relevance scores calculated from responses on the 4 point Likert scale – (1) Not at all, (2) A little, (3) Quite a bit and (4) Very much. During the analysis, issues were ranked from most relevant, for example, those that were experienced a lot, to least relevant, those that were not experienced.

The importance of the issues, i.e., the degree to which participants wanted the issue included in the questionnaire was analysed using frequency data from the importance scores (yes/no format). The percentage of participants that rated an issue as important, or a priority for inclusion, provided data on which issue were to be included in the questionnaire. Issues were ranked from highest priority to lowest priority.

The analysis was conducted separately for the patient and HCP data. During the interpretation of the results, priority was given to the patient data. The analysis provided four scores, patient and HCP relevance and patient and HCP importance. This data was exported into an excel spreadsheet where it was analysed against a set of predefined inclusion criteria to determine which of the issues were to be included in the Phase II provisional questionnaire.

Items within the EORTC QLQ-C30 were also included in the analysis of the issues. Items 29 and 30 (global health and global quality of life) were not included as they required a different measurement scale, and the underlying issues could not be extracted and included for assessment within issue list questionnaire in the same manner in which the remaining 28 items could. Mean and frequency data were provided for each issue. To avoid the duplication of items, QLQ-C30 issues were not included in the main analysis, however were analysed independently to provide data on the relevance and importance the core questionnaire has to MBC patients. This sub-analysis is presented in section 4.4.4.2.

A sub-analysis of the patient data split by age was conducted to further explore the relevance and importance of the issues. This analysis was completed due to heterogeneity of the disease, with younger age being a determining factor on particular issues, such as stress, employment and family roles [284, 285]. Older patients being treated for MBC have been observed to have lower physical functioning when compared with other MBC patients, however score higher in emotional, cognitive and social functioning. Further to this, older MBC experience less nausea/vomiting, pain, insomnia,

appetite loss and fewer financial difficulties [286]. The dataset was split by age in two groups, group one consisted of the participants aged 50 or younger and group two those aged 51+. As with the main data set, descriptive statistics were conducted to evaluate the effect age had on the perception of the relevance and importance of the issues. This data was used to support the inclusion process in circumstances where the justification and selection of certain issues was necessary. This was to ensure important issues for younger patients were not excluded.

To be included in Phase II, each issue was reviewed against a pre-defined set of decision rules that outlined the empirical thresholds for the inclusion of an issue in the provisional questionnaire Table 13. The thresholds applied to both patient and HCP data and were set as a mean relevance rating of ≥ 2 and an importance rating of 15%. The thresholds were established using the *EORTC Module Development Manual v4,* whereby it recommends a mean relevance score of ≥ 2 and an importance score of 30%. Due to the inclusion of a large number of issues (185) in the issue list questionnaire, the decision to lower the threshold for the importance scores was taken. This decision was taken based on further recommendations by the EORTC that where a large number of issues are included, it is acceptable to lower the threshold [99].

Table 13. ***Decision rules for issue retention in Phase I.***

The following empirical thresholds were applied to consider an issue for inclusion in the questionnaire:	
(a)	Patient's relevance ratings ≥ 2 (on the 1 to 4 scale)
(b)	Healthcare professional relevance ratings ≥ 2 (on the 1 to 4 scale)
(c)	Patient importance ratings ≥ 15 % (15 % of the patients agreed that an issue should be included in the list)
(d)	Healthcare professional priority ratings ≥ 15 %.

Each issue was assigned a score between 0-4 to indicate the number of criteria it satisfied. Those meeting three or more of the criteria were marked as 'include', with the remaining issues reviewed further at an individual level. Issues were included if their scores were close to meeting the set threshold or issues that were of clinical importance. The remaining issues were excluded from the provisional questionnaire.

The selection of issues was an iterative process and involved multiple meetings with various stakeholders, including my supervisory team and collaborators from both the EORTC Quality of life group and EORTC Breast cancer group, to discuss the included and excluded issues. Regular meetings with my supervisory team were used to discuss, evaluate and make decisions the retention of the issues that did not satisfy the criteria

outlined above. Issues meeting two or fewer criteria were individually reviewed for inclusion. For example, issues that were noted to have been close to reaching a third criterion could then be considered for inclusion. Further to this, the clinical relevance of an issue was also examined to aid in the decision making process. EORTC collaborators were invited to provide feedback on the inclusion/exclusion of issues at the bi-annual meetings, where results of Phase I were presented. Feedback from all parties was collected, collated and used alongside the quantitative data to make decisions regarding the inclusion or exclusion of an issue. Decisions were documented throughout this process.

Key stage of the development process was cross checking the Phase I results with the EORTC QLQ-BR45. The EORTC QLQ-BR45 is the current measurement tool used to assess the QOL of breast cancer patients across all disease stages and therefore, to ensure the work completed as part of this project was original and not simply replicating this questionnaire, the two were evaluated [98]. The evaluation process consisted of reviewing and cross checking each of the issues identified for inclusion in Phase II of the MBC module development process against the items included in the QLQ-BR45. Microsoft excel was used to manage and facilitate this. Where a positive match was found, the Phase I MBC issue and the corresponding QLQ-BR45 item were extracted. The extracted issues/items were reviewed in collaboration with the BR45 development team to determine whether significant overlap between the two was present. As part of this process the remaining issues in the MBC dataset were also considered to highlight how the two sets of data differ. The outcome of the assessment was then agreed.

4.4 Phase I – Results

4.4.1 Recruitment response rate

Data was collected over a 20-month period where the sample target of 180 patients was met and exceeded with a total of 187 patients enrolled in Phase I of the study. A similar trend was observed in the recruitment of HCP, the recruitment target was 25, however a total of 41 were recruited. Due to logistical constraints, it was not possible to collect the recruitment details relating to the number patients identified, approached, and consented across all sites. Therefore, the overall consent rate is unknown, however, data were available from the recruitment conducted at the Leeds Cancer Centre. These figures are discussed below.

Overall, the two UK sites recruited 28 patents, with the Leeds Cancer Centre (LCC) accounting for 20 of these. The consent rate for patients recruited at the LCC was less

than 25%, a figure that was lower than anticipated. This was largely do due to the challenges and barriers faced as a result of undertaking recruitment during the COVID-19 pandemic (July 2020 – March 2021). Over the recruitment period 155 eligible patients were identified by the clinical team, and of these, 86 were approached to take part. Twenty-one of the approached patients consented to participate in the study, giving a consent rate of 24.42%; 65 declined. It is important to note that 21 patients consenting to participate, however only 20 were entered in the study as one patient withdrew from the study prior to completing the interview. Their withdrawal was due to no longer having the time. The patient was withdrawn, and their data not included in the analysis. Further to this, one patient, who took part in a remote interview, failed to return the issue list questionnaire, leaving a total of 19 participants entered in the analysis.

The leading cause of non-participation was patients declining (36/65 of the cases 55.38%). This was followed by 43.07% (28/65) of patients approached being considered as lost to follow-up. Individuals in this category were approached with the study information but did not contact the researcher or could not be followed up by the researcher at subsequent appointments. Unfortunately, one patient (1/65) passed away after having been approached.

Further breakdown of the recruitment indicated that 69 patients were considered eligible, but not subsequently approached to participate in the study. Analysis of these cases highlighted the most common reason being that the sampling target had been met (n=16). To ensure a balanced and representative sample was recruited, a sampling matrix was utilised to guide the recruitment at a global and local level and therefore, as the sampling matrix was satisfied, patients meeting the fulfilled criteria were then not approached. Other reasons for non-approach related to the clinician's decision, this accounted for 33% (23/69) of cases. Clinician's decisions included 'not appropriate' i.e., patient too upset cited 12/23 times and poor performance status cited 11/23 times.

General research activities category saw the largest number of considered not approached patients (30/69). A breakdown of these results indicated that 'Burden' and 'Timing' each accounted for 12 cases totalling 24/30. Burden refers to the demand placed on the individual when taking part in multiple research studies, this was the case for 12 patients that had recently been approach and enrolled in another research project. Timing included patients that were classified as being missed by either the researcher, clinical staff or did not attend their appointments. With the restrictions in place due to COIVD this was particularly challenging aspect of recruitment with the uptake of telephone consultations and patients spending less time in the clinical area making it

increasingly difficult to approach patients. Four (4/30) were identified but unable to be approached as their appointments were after the recruitment end date, one did not meet the inclusion criteria as they could not speak English and one patient was lost to follow up.

4.4.2 Patient characteristics

The recruitment of patients was conducted in 13 centres across eight countries, including UK, Poland, Germany, Italy, France, Spain, Japan and Jordan. In total, 187 adult female patients with a confirmed diagnosis of metastatic breast cancer were enrolled Table 14.

Table 14. ***Demographic and clinical characteristics of the patient sample.***

Demographics	N	Mean
Age	187	58.55
Age split	N	%
<50	57	30.5
51-69	79	42.2
>70	51	27.3
Country	N	%
English speaking		
UK	28	15.0
Northern Europe		
Germany	2	1.1
Southern Europe		
Italy	51	27.3
Spain	27	14.4
France	9	4.8
Eastern Europe		
Poland	9	4.8
Non-European		
Japan	37	19.8
Jordan	24	12.8
Total	187	100.0
Living situation	N	%
Living with partner/spouse	111	59.4
Living alone	35	18.7
Living with children	28	15.0
Living with others	7	3.7
Other	6	3.2

Employment	N	%
Retired	78	41.9
Unemployed	44	23.7
Full-time	24	12.9
Part-time	21	11.3
Other	19	10.2
Missing	1	
Education		
Post compulsory school, below university	87	47.0
Compulsory school or less	54	29.2
University level	39	21.1
Other	5	2.7
Missing	2	
Clinical Characteristics		
Treatments		
Chemotherapy	78	41.7
Hormone therapy only	40	21.4
Hormone therapy + Targeted therapy	39	20.9
Targeted therapy only	25	13.4
Immune therapy	3	1.6
Radiotherapy only	1	0.5
None	1	0.5
Metastatic sites #		
1	70	37.4
2	66	35.3
3	31	16.6
4	16	8.6
5	4	2.1
Locations of metastasis		
Bone	113	60.4%
Lymphatics	95	50.8%
Liver	66	35.3%
Lung	55	29.4%
Other	29	15.5%
Brain	21	11.2%
Time since metastatic diagnosis (months)		
<6	50	26.7
7-24	63	33.7
>25	74	39.6

The mean age of the sample was 58.6 years old with a range of ages between 29 and 85 years old. The overall distribution of the age range was in line with the sampling strategy, with the exception of the middle-aged patients (51-69) who accounted for a slightly higher percentage of the sample (42.2%) when compared with the younger (30.5%) and older (27.3%) groups.

Italian patients accounted for the largest percentage of the sample (27.3%), followed by Japanese (19.8%) and then British patients (15%). Several of the countries experienced large delays in obtaining local approval which led to the over recruitment at other sites. For example, the Brazilian site was unable to participate and was later replaced with a site from Jordan which strengthened the sample by increasing the number of non-European participants. Further to this, the Netherlands were unable to open this study within the required timeframe so were unable to participate in Phase I. This did not impact the (cross-cultural validity) as several of the key languages were adequately covered.

Other key demographics included almost a quarter (23.7%) of patients reported being unemployed. This is interesting as the education level of the sample was high, just 29.2% had completed compulsory school or less. It is likely that people were unable to work as a result of their diagnosis, or perhaps the impact of COVID on employment, such as being furloughed, was prevalent amongst this group. Future exploration of this would be beneficial as employment can hold benefits beyond simply providing a financial income and therefore supporting patients to find employment may help negate issues such as isolation for those that live alone, which in this study accounted for 18.7% of the sample.

The planned sample was to include patients at a ratio of 2:1:1 across the three main treatment types, these being chemotherapy, hormone therapy alone and hormone therapy plus targeted therapy. The overall ratio of participants receiving these treatments was in line with this aim, however a number of patients were found to be receiving targeted therapy alone (13.4%). This is important in the planning of future work (Phase III) to ensure the sample is as well stratified to the population as possible.

Patients with a range of metastatic sites were included as were patients with a multiple number metastases. The majority of patients had two or fewer metastatic sites. Overall, the most common sites included bone and lymphatics, with a small number of patients (11.2%) having brain metastases.

Time since diagnosis of metastatic disease was a key part of the stratification and was recorded in months. Results show a slight deviation from the proposed sample, with fewer patients having been diagnosed within the last 6 months when compared with 7-

24 months and >25months. This did not however impact the sample, which remained to be well balanced across the key domains. On reflection, recruiting those most recently diagnosed was going to be a challenge as these patients were still dealing with the diagnosis and what it meant for them. Their priorities were likely to have been focused on treatment whereas those with a longer time since diagnoses had time to process their condition and thus more willing to engage with research at that moment in time.

4.4.3 HCP characteristics

A total of 41 Healthcare Professionals (HCP) were recruited from nine different countries including the UK, as well as countries across Northern Europe, Southern Europe, and the Middle East. The HCP were well experienced with an average of 14.5 years (range from 0 to >30 years) and the majority of the sample were females (75.6%). The inclusion criteria were defined as having experience in the treatment and/or care of those living with metastatic breast cancer. The sample was representative of the field and included various disciplines and levels of experience, although the main groups were oncologists and nurses (Table 15).

Table 15. ***Demographic of the Healthcare professionals recruited to the study***.

Demographics	N	Mean
Age	40	42.55 (range 24-64)
Gender	N	%
Male	10	24.4
Female	31	75.6
Country	N	%
English speaking		
UK	8	19.5
Northern Europe		
Belgium	3	7.3
Sweden	1	2.4
Southern Europe		
Italy	6	14.6
France	5	12.2
Spain	5	12.2
Switzerland	2	4.9
Greece	1	2.4
Non-European		
Jordan	10	24.4
Profession	N	%
Oncologist	19	46.3
Nurse	14	34.1
Other	4	9.8
Psychologist	3	7.3
Surgeon	1	2.4

Experience in Years	N	%
0-4	4	10
5-9	8	20
10-14	14	35
15-19	3	8
20-24	2	5
25-29	3	8
>30	6	15
Total	40	100
Missing	1	

4.4.4 Quantitative results

The primary aim of Phase I was to determine which of the quality-of-life related issues were most relevant and important to patients and HCPs. Data were used to select the most relevant and important issues to be included within the questionnaire. The data were collected via the issue list questionnaire developed in the early stages of Phase I which was presented to participants to complete (see methods). Relevance scores were provided via a 4-point Likert scale, with the mean score used to determine the issue's relevance. The importance scores were dichotomised (0 = not important & 1 = yes important). The degree of importance was assessed using frequency data.

4.4.4.1 Overall results

Quantitative questionnaire data were analysed to determine the most relevant and important issues impacting the QOL of this patient group. Results from the issues included within the EORTC QLQ-C30 were analysed as part of the sub-analysis to evaluate the relevance of these core cancer-related issues for MBC patients and are presented in section 4.4.4.2. One interesting observation was that of the 185 issues included, HCPs rated all but one as being relevant whereas patients were much more selective of the issues they felt were relevant. The combined analysis of both patient and HCP data resulted in the selection of 44 issues suitable for inclusion in Phase II. Table 16 highlights the categorisation of the included issues according to the conceptual framework and subdomains. Excluded issues can be seen in appendix 9.1.9. As priority was given to the patient scores, Table 17 presents the results in order of patient priority/importance for inclusion as indicated by the priority percentage.

Table 16. ***Categorisation of 44 issues selected for inclusion in Phase II.***

GCM Domain	Issue category	Count
Symptom Burden	General (Fatigue/Pain)	10
Psychological	Future / future uncertainty	6
Psychological	Anxiety/depression	5
Psychological	Fear	5
Symptom Burden	Musculoskeletal (Fatigue/Pain)	5
Symptom Burden	Reproductive (Sexual)	4
Independent living	Independence	3
Psychological	Psychological experience	2
Symptom Burden	Infections	2
Support pathways	Support pathways	2

When the issues were categorised in accordance with the domains of the conceptual framework, the results show that the majority of issues were either physical symptoms and side effects or psychological. Interestingly, a large number of psychological were selected as being relevant and important by this patient group. Of the issues relating to the symptom burden domain, fatigue and pain related issues were prevalent (Table 16).

Table 17. ***Issues selected for Phase II based on patient and HCP relevance and importance scores. Table ordered by patient priority.***

	Patient Response			HCP Response			Filters
Issue	**N**	**Mean**	**Priority**	**N**	**Mean**	**Priority**	**Criteria fulfilled**
Q085 Hair loss	184	2.45	28.6%	40	3.38	42.5%	4 of 4
Q121 Fear of disease progression	187	2.68	27.8%	40	3.68	34.1%	4 of 4
Q152 Worried about family	186	2.68	25.8%	40	3.50	24.4%	4 of 4
Q018 Treatment side effects	186	2.41	25.1%	40	3.33	36.6%	4 of 4
Q155 Worries about the future	186	2.61	24.2%	41	3.73	39.0%	4 of 4
Q154 Fear leaving family behind	186	2.58	22.0%	41	3.54	19.5%	4 of 4
Q014 Fatigue	186	2.48	21.9%	40	3.58	43.9%	4 of 4
Q127 Long term health concerns	185	2.66	20.5%	41	3.05	4.9%	3 of 4
Q175 Medicalised lifestyle	182	2.27	19.8%	40	3.05	12.5%	3 of 4
Q063 Numbness tingling burning in hands feet	185	2.12	19.4%	41	3.24	24.4%	4 of 4
Q109 Anxiety about advanced aspect	187	2.42	19.3%	41	3.56	17.1%	4 of 4

Q120 Fear of dying	185	2.28	18.9%	41	3.63	26.8%	4 of 4
Q119 Feeling afraid	185	2.29	17.8%	41	3.20	14.6%	3 of 4
Q019 Health instability caused by treatment and symptoms	186	2.41	17.2%	41	3.10	14.6%	3 of 4
Q091 Hot flush	187	2.11	17.1%	41	3.15	19.5%	4 of 4
Q156 Unknown future	185	2.59	16.8%	40	3.38	7.3%	3 of 4
Q160 Uncertainty	186	2.47	16.1%	40	3.20	5.0%	3 of 4
Q123 Fear of making symptoms worse	187	2.53	16.0%	41	3.12	4.9%	3 of 4
Q050 Bone pain	187	2.10	16.0%	40	3.28	26.8%	4 of 4
Q013 Loss or lack of energy	186	2.47	15.6%	40	3.20	12.5%	3 of 4
Q046 Muscle aches pains	186	2.26	15.6%	41	3.24	19.5%	4 of 4
Q049 Joint aches pains and stiffness	187	2.20	15.5%	41	3.12	29.3%	4 of 4
Q075 Decreased sexual interest	180	2.21	15.0%	40	2.90	17.1%	4 of 4
Q102 Change in appearance	187	2.28	15.0%	41	3.12	9.8%	3 of 4
Q017 Impact of cancer symptoms	184	2.40	14.1%	39	3.28	25.0%	3 of 4
Q073 Decreased sexual activity	178	2.16	14.0%	41	2.90	19.5%	3 of 4
Q057 Decreased grip strength	186	2.03	14.0%	40	2.53	9.8%	2 of 4
Q051 Back pain	187	2.28	13.9%	41	2.98	12.2%	2 of 4
Q181 Needing help from family children	187	2.37	13.4%	41	3.15	4.9%	2 of 4
Q166 Dependency on others	186	2.02	12.9%	41	3.24	17.1%	3 of 4
Q157 Unknown prognosis	185	2.48	12.4%	41	3.34	17.1%	3 of 4
Q106 Depressed mood feeling sad down	187	2.17	12.3%	41	3.54	22.0%	3 of 4
Q153 Parenting worries	180	2.27	12.2%	41	3.44	12.2%	2 of 4
Q108 Anxiety	184	2.25	12.0%	41	3.66	24.4%	3 of 4
Q074 Decreased sexual enjoyment	177	2.07	11.9%	41	2.76	7.3%	2 of 4
Q165 Loss of independence	187	2.03	10.2%	39	3.31	30.0%	3 of 4
Q070 Vaginal dryness	187	1.98	10.2%	41	2.80	14.6%	1 of 4

Q182 Altered partner relationships	179	1.82	8.9%	41	3.12	17.1%	2 of 4
Q169 Isolation	186	1.83	8.1%	39	3.13	17.5%	2 of 4
Q159 Future perspective	186	2.19	7.5%	41	3.24	9.8%	2 of 4
Q016 Feeling unwell	186	2.09	5.9%	41	3.05	14.6%	2 of 4
Q104 Dissatisfied with body image	187	1.96	5.3%	41	2.95	14.6%	1 of 4
Q034 Infections	186	1.31	3.8%	41	3.00	14.6%	1 of 4
Q036 Fever	185	1.32	1.1%	40	2.83	17.1%	2 of 4

Mean = mean relevance score. Priority = proportion of participants selecting the issue as important for inclusion. Green represents values that met the decision rule.

The analysis identified 31 issues as being highly relevant and important, with these issues satisfying at least three of the four predefined criteria. These issues were therefore selected for inclusion in Phase II. Fifteen of the 31 issues met all four criteria, with the issues being relevant and important to both patients and healthcare professionals. The remaining 16 met three of four criteria. Of these, the criterion not met varied, with nine issues meeting all but HCP importance and seven meeting all but patient importance.

Issues fulfilling 2 of 4 criteria were reviewed on a case-by-case basis, by the study team and an expert group, plus a sub-group analysis by age (Table 18). Data beyond the mean relevance and importance scores were used during the decision-making process to ensure issues were not unduly removed at this stage (see below). This resulted in the inclusion of a further ten issues. Of the ten issues included that met two of four criteria, back pain, feeling unwell and decreased grip strength were included as they were close to meeting a third criterion. The sub-analysis of data by age was conducted as a supplementary addition to facilitate the validation of the issues selected for inclusion, as breast cancer in younger patients may have a different natural course and the QOL issues experienced may be specific to this. Needing help from family children and parenting worries were included with support from the Age-related data as they were found to be important for younger patients and were close to meeting the overall importance threshold (Table 18).

Table 18. ***The 44 issues selected for inclusion in Phase II split by age and ranked by priority to younger patients.***

	Younger (<50)			Older (51+)		
Issue	N	Mean	Priority	N	Mean	Priority
Q152 Worried about family	54	3.06	33.3%	132	2.52	22.7%
Q154 Fear leaving family behind	54	3.04	33.3%	132	2.39	17.4%
Q155 Worries about the future	54	2.94	31.5%	132	2.48	21.2%
Q120 Fear of dying	53	2.49	28.3%	132	2.20	15.2%
Q121 Fear of disease progression	54	2.89	27.8%	133	2.59	27.8%
Q085 Hair loss	54	2.61	27.8%	130	2.38	29.0%
Q175 Medicalised lifestyle	53	2.53	26.4%	129	2.16	17.1%
Q014 Fatigue	54	2.57	25.9%	132	2.44	20.3%
Q153 Parenting worries	51	2.80	25.5%	129	2.06	7.0%
Q119 Feeling afraid	53	2.55	24.5%	132	2.19	15.2%
Q109 Anxiety about advanced aspect	54	2.69	24.1%	133	2.32	17.3%
Q018 Treatment side effects	54	2.69	22.2%	132	2.30	26.3%
Q091 Hot flush	54	2.61	22.2%	133	1.90	15.0%
Q127 Long term health concerns	53	2.92	20.8%	132	2.55	20.5%
Q075 Decreased sexual interest	54	2.65	20.4%	126	2.02	12.7%
Q050 Bone pain	54	2.37	20.4%	133	1.99	14.3%
Q017 Impact of cancer symptoms	52	2.69	19.2%	132	2.28	12.1%
Q019 Health instability caused by treatment and symptoms	53	2.75	18.9%	133	2.27	16.5%
Q073 Decreased sexual activity	53	2.66	18.9%	125	1.95	12.0%
Q160 Uncertainty	53	2.62	18.9%	133	2.41	15.0%
Q074 Decreased sexual enjoyment	53	2.51	18.9%	124	1.88	8.9%
Q102 Change in appearance	54	2.61	18.5%	133	2.14	13.5%
Q049 Joint aches pains and stiffness	54	2.39	18.5%	133	2.13	14.3%
Q156 Unknown future	53	2.92	17.0%	132	2.45	16.7%
Q046 Muscle aches pains	53	2.58	17.0%	133	2.13	15.0%

Q106 Depressed mood feeling sad down	54	2.43	16.7%	133	2.06	10.5%
Q182 Altered partner relationships	52	2.15	15.4%	127	1.69	6.3%
Q108 Anxiety	53	2.55	15.1%	131	2.13	10.7%
Q063 Numbness tingling burning in hands feet	53	2.26	15.1%	132	2.06	21.1%
Q123 Fear of making symptoms worse	54	2.80	14.8%	133	2.43	16.5%
Q157 Unknown prognosis	53	2.72	13.2%	132	2.38	12.1%
Q013 Loss or lack of energy	53	2.45	13.2%	133	2.48	16.5%
Q169 Isolation	53	2.00	13.2%	133	1.76	6.0%
Q051 Back pain	54	2.65	13.0%	133	2.13	14.3%
Q070 Vaginal dryness	54	2.24	13.0%	133	1.87	9.0%
Q016 Feeling unwell	54	2.41	11.1%	132	1.96	3.8%
Q057 Decreased grip strength	54	2.19	11.1%	132	1.96	15.2%
Q165 Loss of independence	54	2.17	11.1%	133	1.97	9.8%
Q166 Dependency on others	54	2.15	11.1%	132	1.96	13.6%
Q159 Future perspective	54	2.44	9.3%	132	2.09	6.8%
Q181 Needing help from family children	54	2.41	9.3%	133	2.35	15.0%
Q104 Dissatisfied with body image	54	2.26	7.4%	133	1.83	4.5%
Q034 Infections	54	1.44	3.7%	132	1.26	3.8%
Q036 Fever	54	1.46	1.9%	131	1.26	0.8%

Mean = mean relevance score. Priority = proportion of participants selecting the issue as important for inclusion. Green represents values that met the decision rule.

The remaining issues were included with support from the expert review process. Isolation was felt to offer an important insight into the patients social, emotional, or physical isolation. Similarly, altered partner relationships was supported by the expert review. Future perspective was included for its inclusion in the proposed 'Future' scale and decreased sexual enjoyment included as it forms part of the sexual scale of the QLQ-BR45. Fever was included for its clinical importance.

The issues that met only 1 of 4 criteria, were then reviewed for inclusion. Despite failing to meet the predefined inclusion criteria, the review identified three issues to be included. Dissatisfied with body image and vaginal dryness were both extremely close to reaching 3 of 4 criteria and were therefore included. The third issue was infections, this issue was

close to meeting 2 of 4 and was deemed to have high clinical relevance and importance by the expert review panel and thus warranted its inclusion.

To avoid the duplication of work, the current breast cancer module used by the EORTC (QLQ-BR45) was cross checked for overlap with the new, metastatic specific module. Results indicated that the modules shared 13 issues, which covered domains such as, musculoskeletal related pain, reproductive and sexual issues and general symptoms (Table 19). The remaining 31 issues were not included in the in the BR45. These issues are specifically important to patients with MBC and are currently not being assessed as part of QOL assessment in clinical trials of MBC. Meetings were held with the development team in charge of the QLQ-BR45 and it was deemed that the level of overlap was satisfactory for the continuation of the MBC specific questionnaire low.

Table 19. The 13 issues identified in both Phase I development and the EORTC QLQ-BR45.

Issue	Domain
Dissatisfied with body image	Body image
Long term health concerns	Future uncertainty
Feeling unwell	General-Treatment impact
Muscle aches pains	Musculoskeletal-Pain
Bone pain	Musculoskeletal-Pain
Joint aches pains and stiffness	Musculoskeletal-Pain
Vaginal dryness	Reproductive
Decreased sexual enjoyment	Reproductive
Decreased sexual activity	Reproductive
Decreased sexual interest	Reproductive
Numbness tingling burning in hands feet	Symptoms
Hot flush	Symptoms
Hair loss	Symptoms

4.4.4.2 Analysis of the EORTC QLQ-C30

The patient and professional ratings for EORTC QLQ-C30 issues were excluded from Table 17 to avoid the duplication of items within the final questionnaire. Results from the analysis of the QLQ-C30 issues are provided in (Table 20). It is important to note that the items 29 and 30 (global health and global quality of life) were not included in the issue list questionnaire. The remaining 28 items were included in the relevant sections of the "issue list" and analysed descriptively. Item 6 from the QLQ-C30, 'Were you limited in doing either your work or other daily activities', was included as two separate issues resulting in 29 issues that were included in the analysis.

Table 20. ***Patient and healthcare professionals' relevance and importance score for the issues included within the EORTC QLQ-C30.***

	Patient Response			HCP Response			
Issue	**N**	**Mean**	**Priority**	**N**	**Mean**	**Priority**	**Criteria met**
Q007 Pain	182	2.30	22.0%	41	3.76	65.9%	4 of 4
Q006 Reduced Daily Activities	184	2.39	20.7%	39	3.28	30.8%	4 of 4
Q045 Feeling weak	184	2.33	20.1%	41	3.27	24.4%	4 of 4
Q176 Impact on family life	187	2.40	19.8%	41	3.63	34.1%	4 of 4
Q135 Difficulty sleeping	183	2.19	19.1%	41	3.44	36.6%	4 of 4
Q094 Difficulty concentrating	185	2.07	17.3%	41	3.00	17.1%	4 of 4
Q001 Strenuous Activities	185	2.70	31.9%	41	3.12	12.2%	3 of 4
Q096 Worrying	185	2.61	22.2%	41	3.27	14.6%	3 of 4
Q002 Difficulty Walking Long Distances	185	2.53	20.0%	41	3.00	9.8%	3 of 4
Q008 Need Rest	184	2.50	19.0%	40	3.20	7.5%	3 of 4
Q009 Pain Affecting Daily Activities	185	2.17	14.6%	39	3.51	26.8%	3 of 4
Q170 Reduced ability to work	182	2.31	13.7%	41	3.05	19.5%	3 of 4
Q171 Financial difficulties	184	1.74	14.1%	41	3.12	22.0%	2 of 4
Q177 Impact on social activities	184	2.48	13.0%	41	3.32	4.9%	2 of 4

Q098 Depression	184	1.92	12.5%	40	3.45	48.8%	2 of 4
Q039 Decreased appetite	185	1.85	12.4%	41	3.17	31.7%	2 of 4
Q164 Limited in pursuing hobby leisure activities	184	2.32	11.9%	41	3.02	4.9%	2 of 4
Q076 Shortness of breath	185	1.79	11.4%	41	3.20	43.9%	2 of 4
Q004 Need Stay Bed Chair	185	1.99	10.8%	41	3.37	17.1%	2 of 4
Q023 Nausea	185	1.70	10.8%	41	3.20	43.9%	2 of 4
Q136 Tiredness	183	2.51	10.4%	41	3.32	14.6%	2 of 4
Q097 Feeling irritable	185	2.13	9.2%	41	2.95	7.3%	2 of 4
Q026 Diarrhoea	183	1.54	7.1%	41	3.15	19.5%	2 of 4
Q095 Feeling tense	185	2.18	6.5%	40	2.98	5.0%	2 of 4
Q005 help eating dressing washing	185	1.48	5.4%	41	3.15	22.0%	2 of 4
Q024 Vomiting	185	1.40	4.3%	41	3.27	34.1%	2 of 4
Q025 Constipation	185	1.84	10.8%	41	2.93	14.6%	1 of 4
Q099 Memory issues	185	1.99	9.8%	41	3.00	12.2%	1 of 4
Q003 Difficulty Walking Short distances	185	1.75	5.4%	41	2.98	14.6%	1 of 4

Mean = mean relevance score. Priority = priority for inclusion/importance score. Green represents values that met the decision rule.

The results indicate that the issues included within QLQ-C30 score highly for relevance and importance with patients and HCPs in the context of MBC, with 12 issues meeting at least three of the four criteria for inclusion. Pain was ranked as the most important issue by both cohorts, with almost two thirds of HCP indicating this as a priority issue.

The majority of issues (14) met two of four criteria, of which the HCP data was the driving factor. Of these 14 issues, five were close to reaching a third threshold and were considered as key issues. Financial difficulties and impact on social activities were within 2% of the threshold for patient importance/priority, with depression and need to stay in bed or chair within 0.08 of reaching the threshold for patient relevance. Tiredness was within 0.4% of reaching the importance criteria for HCPs.

Gastrointestinal related issues saw the largest discrepancies between the patient and HCP data as issues such as diarrhoea, vomiting and nausea were all highly rated by HCP but were perceived to be far less relevant and important to the patients.

Of the three issues that met just one of four criteria, constipation and difficulty walking short distances were within 0.4% of reaching the threshold for HCP importance. Memory issues was within 0.01 of being relevant to patients. To the best of our knowledge, this is the first empirical evidence that the EORTC core questionnaire is relevant for MBC patients.

4.5 Discussion

The findings from Phase I furthered our understanding of the quality-of-life related issues experiences by women with (MBC), as well as highlighting the significance they held. A total of 44 core issues were selected for inclusion in the questionnaire, spanning multiple domains including physical and psychosocial. The Generic Choice Model (GCM) was used as the framework from which the issue were mapped, and enabled the conceptualisation of the issues that were to be included in the provisional questionnaire. The GCM provided an excellent framework however this stage of the development process required greater detail in order to more accurately conceptualise the issues and was therefore enhanced by the further subcategorization within each domain to provide additional context behind the issues.

The included issues were different to those assessed within existing measures. This was highlighted in the comparison of the core issues identified in this study with those included in the EORTC QLQ-BR45 [98]. Although the total number of issues included were similar (44 vs 45 respectively), the number of 'new' issues i.e., those not already included in the QLQ-BR45, was high (31). The fact that so many of the issues differed highlights the potential shift in priorities compared to those diagnosed with primary breast cancer. This is also highlighted by the types of issues MBC patients deemed to be important. For example, issues relating to fear and worry were frequently scored highly, and were similar to those issues reported across the literature in the different phases of MBC disease trajectory, perhaps as a result of knowing they were living with a long-term life-threatening condition [70, 157]. Further to this, when comparing the results of Phase I to those of the systematic review (Chapter 3), it was clear that when patients are not limited by the constraints of the current PROMs used within the literature, and are presented with the issues relevant to them, their responses to which issues are relevant and important differ to those currently being assessed within the literature [168, 170,

186]. The results of Phase I are in line with results from non-CTIMP studies whereby a greater emphasis was placed on psychological or non-symptom burden related issues [259, 263].

An interesting observation from the results was that HCPs rated all but one (increased appetite) of the 185 issues as being relevant. This was important as the decision rules used to select the issues were inclusive of this criterion. On reflection this observation was not surprising as HCPs think very differently to patients as they have never experienced any of these issues first hand, perhaps this more expansive approach to rating the issues was a reflection on the training and mind set of HCP. For example, they are trained to capture as much information as possible to determine how to best help the individual, therefore to them, all the issues are relevant because if a patient experiences it, they want to know so they can fix it.

Whilst only exploratory, the data on Age offers an insight into how patients perceptions change as they get older. Worries and fears were highly rated by the younger patients, and whilst still of importance to the older group, suggests that younger patients need more support in dealing with the psychological aspects associated with living with and being treated for MBC. Similarly, previous research has found that younger patients are more prone to feelings of distress [284], and therefore, this type of information could be beneficial when reviewing and developing clinical care pathways as having a better understanding of what each patient deems to be important can help facilitate the delivery of more patient centred care.

To our knowledge, the sub-analysis of the EORTC QLQ-C30 data provides the first evidence of this Core questionnaire being relevant to MBC patients. As highlighted by the systematic review in Chapter 3, the QLQ-C30 is a very popular measure used within MBC research, therefore this is an important finding as it provides support to the studies that have used this measure, as well as support for its inclusion in future MBC research. Whether or not this subtracts from the need for an additional module is something to be reflected upon. The QLQ-C30 alone is relevant in this patient group, however, it is clear from the findings in Phase I, that many important issues are missing that directly relate to living with advanced cancer. The addition of an MBC specific module further strengthens the EORTC's strategy for assessing QOL in cancer patients and provides a platform for future work to build on. For example, the development of ad-hoc lists, referred to as 'Item lists' created via the EORTC Item Library to supplement the EORTC QLQ-C30 and, when relevant other EORTC modules.

Phase I was successfully delivered, with the recruitment of a large, international sample of patients that were recruited during an unprecedented time during the COVID-19 pandemic. The strength of the sample improved the cross-cultural validity of the findings, strengthened further by the inclusion of non-European countries within this first phase of development. In the future phases of development, additional details of the sample should be collected to ensure a diverse and representative sample is obtained. For example, the collection of ethnicity data as well as additional clinical details such as performance status, as this would facilitate and strengthen the how the final questionnaire may be used.

An obvious limitation of the interviews is the pragmatic decision to focus on the collection and analysis of the quantitative data, rather than inviting a more detailed discussion of each issue with recording and transcribing of this potentially insightful qualitative information. This decision was made due to the long list of issues leading to patient burden, as well as the challenges of translating interviews in multiple languages (for which we did not have available resources). However, notes taken by the interviewers were collected and considered when making the selection of issues.

As discussed, recruitment for Phase I commenced during a time of global uncertainty surrounding the COVID-19 pandemic. The first national lockdown in the UK began the same month (March 2020) I planned to start patient recruitment and I was unable to approach patients until July 2020. During this time, many of the appointments took place remotely rather than face to face. For those that did attend in person, they were faced with a large number of new obstacles and barriers both physical (2 meter rule, and personal protection equipment) and psychological (fear of meeting many people), all of which I feel played a large role in the low consent levels for this study. Patients did not want to wait around in the hospital for longer than necessary, nor did they want to speak to additional people and overall were looking to reduce their contact and risk of getting COVID. This made approaching patients in the traditional sense very difficult. Patients who attended the hospital were generally those who were more ill and required medical review and examination to allow treatment delivery. Patients who were well generally had telephone consultations. These exceptional circumstances led to the predominant recruitment of more ill patients.

Furthermore, finding suitable clinic rooms for the interviews was difficult with the existing strict measures on hygiene and social distancing. For those patients that were willing to talk to me directly, I experienced the challenges of trying to communicate and build rapport whilst wearing full personal protective equipment (mask, goggles, apron and

gloves), this was extremely challenging at first as I was not used to wearing it and/or seeing patients in masks as I am not a clinical member of staff. This being said, I feel that those people I spoke to directly were more likely to agree to take part in the study although no objective measure of this was recorded. I am extremely grateful of those who took part in this research during such a challenging time.

Overall, Phase I resulted in a core set of 44 issues being selected for inclusion in the first draft of the questionnaire. The conceptual characteristics of the included issues highlighted the wider impact MBC and its treatments have on the QOL of patients with a large number of the 44 issues categorised as either psychological or social domains. The more general physical issues, such as those related to pain and fatigue, were also prevalent within the issues set. The results of Phase I were integrated in Phase II of the development process whereby the core issues were operationalised into fully formed questionnaire items. The methods and results of Phase II are discussed in detail in the next chapter.

Chapter 5. Phase II: Item Development

Chapter 5 presents the methods and results of Phase II of the module development process. Phase II was aimed at operationalising the core set of quality of life (QOL) related issues, identified in Phase I, into fully formed questions (or items). The result of which produced a provisional questionnaire specific to the assessment of QOL in MBC, in a format consistent with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30. This phase adopted an iterative, multi-step method to facilitate the development of suitable, well-formed, items.

The development of questionnaire items is a specialist and complex process that requires the careful consideration of multiple components, such as language, phrasing and scale structure, in order to successfully deliver well-constructed items [132, 140, 142]. This is particularly true when developing questionnaires intended for international use, as the items need to be translatable, as well as culturally appropriate in each of the included countries [143]. Considering this, the methods set out in Phase II are designed to mitigate these factors as well as to provide the greatest strength to the resulting provisional questionnaire, for example, the utilisation of pre-existing items, such as those within item repositories (EORTC Item Library or the PRO-CTCAE item library) to facilitate the selection of validated and translated items within the final provisional questionnaire [277, 287]. Chapter 5 describes the methods undertaken to develop and presents the resulting provisional questionnaire.

Objectives included, (1) operationalise the selected issues from Phase I into items, (2) review of the selected items for duplication and (3) the development of the provisional questionnaire.

5.1 Methods

5.1.1 Operationalisation of issues

Building upon the work conducted in Phase I, the first objective of Phase II was to operationalise the 44 issues identified in Phase I. Operationalisation of the issues into fully formed questionnaire items was an iterative process and consisted of several key stages. The development process is discussed below.

The first stage involved establishing a database from which the 44 issues could be developed. Within this database, each of the individual issues were listed and categorised against the conceptual framework [109]. Having the issues grouped in this

way enabled a closer comparison of the issues with regards to the underlying concept they addressed. Each issue was then reviewed and assigned an item (or items) wording.

The review process was an important step in the development process as it helped to build a database of items for each of the included issues. During this process, issues were reviewed against pre-existing questionnaires and searched for in EORTC Item Library. The EORTC Quality of Life Group (EORTC QLG) has spent numerous years developing questionnaires assessing QOL within the cancer population, and as a result, have accrued a wealth of items spanning multiple languages and domains. The Item Library was subsequently developed to harness this existing knowledge to facilitate the development of high-quality questionnaires. At the time of writing, the library consists of 1028 items, many of which are available in a multitude of different languages. The item library has also been shown to have an excellent coverage of items, including those relating to adverse event/toxicities, as well as a wealth of other cancer related issues [288]. Its use has also been demonstrated in the development of bespoke questionnaires, which elevate the use, and flexibility, of static questionnaires via the customisation and development of specific item lists [289].

Access to the library was granted to the research team. The keyword search function was used to identify items that corresponded to each of the 44 included issues. The relevant items were extracted and entered into the database. Within the library, the wording of the items were categorised as being either ‘recommended’ or ‘other’. The recommended wording was the most up to date and grammatically correct versions, and those classed as ‘other’ were either previous iterations or items that have not warranted an update. Where possible both the recommend and other wordings of items were extracted to provide the research team with a comprehensive dataset from which to make the final decisions on which items to include. The recommended wording was used as a priority as these items were the most current and up to date versions and endorsed by the EORTC for inclusion within new questionnaires.

Following the review of the EORTC item library, the first assessment of the database was conducted. Each of the issues were assessed and categorised accordingly depending on whether a corresponding item had been assigned to the issue. Those that did not have a corresponding item were selected for further review. For these items, it was necessary to develop new, or modify existing items.

Following recommendations from within the literature, new items were clear, concise, unambiguous, as well as formed appropriately with regards to the available response options. Where new items were conditional i.e. not experienced by all patients, a not

applicable or N/A response was included. The direction of the question was also considered, with new items relating to limits in functioning or negative experiences worded negatively, and positive issues, in terms of ability or capability, worded positively. The new items were developed in a similar style to the QLQ-C30 to ensure uniformity across the questionnaires. For each instance of a new or modified item being developed, advice and feedback from experts were sought to ensure the items were suitable for both translation into their language as well as being culturally appropriate. Further to this, the items were reviewed by the EORTC Quality of life departments translation unit who are leading experts in the field.

5.1.2 Review of items for duplication

The second assessment of the database involved the selection of items to form the first draft of the provisional questionnaire. During this assessment, the items were independently reviewed by members of the supervisory team, whereby the most relevant and appropriate items were shortlisted for inclusion. The supervisory team consisted of myself, as well as both academic and clinical members of staff to ensure a global perspective was maintained throughout the initial selection process. This consensus style process was an iterative approach and decisions were made over the course of several meetings until a consensus was reached. To facilitate the shared-decision making process, a priority decision tool was used [290, 291]. The key aspects to consider when selecting the issues were (1) closeness to the core issues, selected items were to capture the core issue in its entirety, this was a priority to ensure content validity was maintained; (2) Phrasing of the item, the recommended wording was to be selected except in cases where alternative items better satisfied ‘Priority (1)’; (3) Translatability, items that included translations for each of the collaborating centres were preferred where possible. Reasons for selection and/or non-selection were noted.

The selected items were reviewed for overlap and duplication, this included a comparison with the recently updated breast cancer module (QLQ-BR45). The conceptual framework was used to group the items, which were then further categorised to reflect the core issue they assessed. Items that were deemed to be duplicates were noted and reviewed further to establish whether a more appropriate item could be selected.

The final step in this stage was the development of the timeframes for which patients would respond to when completing the questionnaire. In keeping with other EORTC measures, two timeframes were utilised, ‘during the past week’ and ‘during the past four weeks’. The inclusion of both timeframes was important as the physical issues were likely

to see changes over a shorter period of time, whereas the psychosocial issues needed a wider timeframe to detect change. The proposed timeframe for each item was established resulting in the development of the first draft of the provisional questionnaire.

5.1.3 Finalising the provisional questionnaire

The third objective of this phase was to confirm the provisional questionnaire that would be pre-tested in Phase III. To achieve this, an international consensus exercise was conducted. This process followed an iterative approach and was a two-step process that involved experts from various backgrounds including academics and clinicians from across the globe. Members of the consensus group included those with expertise and knowledge of questionnaire development, experience in the treatment and care of MBC patients as well as all collaborators and members of the supervisory team. The first round of the consensus exercise was conducted remotely. Documents were prepared and emailed to the group, and included an excel file containing data from the review of the item library and the initial decisions behind the selection of the proposed items. A word document containing a table of information relating to the original issue, its conceptual domain, the proposed item(s) and a comments section containing free text space for collaborators to add their comments was also provided. The conceptual framework was used to facilitate the review process by providing the structure in which the issues and items were categorised, presented and reviewed by the group and thus ensuring a wider perspective of the questionnaire content was maintained.

The group were asked to review the first draft of the provisional questionnaire. Each member reviewed the items for their acceptability and appropriateness. As this was an international project, members were asked to consider potential issues with the translations, as well as the cultural appropriateness of each of the items. Further to this, a focus was placed on generating feedback on the new and modified issues to ensure they were suitable for inclusion in the questionnaire. For problematic items, members were advised to offer alternative solutions included new phrasings and or new items. All members had access to the database developed in the earlier stage of this phase and were able to see comments and the decisions made by the research team in Leeds when developing the first draft of the questionnaire.

The feedback was collated, formatted according to the country of origin in which the expert was located. An overall summary of the results was produced for each item which was reviewed by the lead site in Leeds. The summary of results included the consensus result and used to determine if any actions were necessary in order to finalise the questionnaire. For example, items with a majority in favour of inclusion were retained;

items with mixed feedback were reviewed to address any potential concerns raised by the group; for those with negative feedback, the items were considered for exclusion.

Round 2 was conducted face to face whereby the results of the first consensus exercise and the second draft of the provisional questionnaire were presented to the project stakeholders at a meeting in Cyprus 2022. This included both, the collaborators involved in round 1, as well as senior members of the EORTC QLG. Each item and its reason for inclusion was presented and discussed by the group, once a consensus was reached, the next item was reviewed. Any required changes were agreed upon and corrected proceeding the meeting, resulting in the development of the finalised provisional questionnaire. The questionnaire was then formatted to match that of the EORTC measures, with the 4-point Likert scale and response timeframes.

A report of Phase I+II was written and submitted to the EORTC QLG for review. A final review of the items was conducted by the QLD translation unit, before being approved by the EORTC Projects and Modules Development Committee (PMDC).

5.2 Results

5.2.1 Item Library Review

The review of the item library yielded a total of 119 items covering 41 out of the possible 44 issues searched. Table 21 presents an overview of the number of items extracted from each core issue, as categorised by the GCM. The table highlights the core issue, type of item identified, for example whether it was a recommended item wording or not, and the total number of items extracted from the item library. I n total, 29 items extracted were the 'recommended wording' and 90 were classified as 'other wording'.

Table 21. ***The number of items extracted from the item library for each of the included issues as categorised by the conceptual framework.***

Core issue	Recommended wording N	Other wording N	Item Library total
Symptom Burden	**21**	**43**	**64**
Numbness tingling burning in hands feet	2	8	10
Joint aches pains and stiffness	3	4	7
Loss or lack of energy	1	4	5
Bone pain	1	3	4
Hair loss	1	3	4
Decreased sexual enjoyment	2	2	4
Feeling unwell	2	1	3
Impact of cancer symptoms	0	3	3
Muscle aches pains	1	2	3

Treatment side effects	1	2	3
Fatigue	1	2	3
Fever	1	1	2
Vaginal dryness	1	1	2
Medicalised lifestyle	0	2	2
Decreased sexual activity	1	1	2
Infections	0	2	2
Back pain	1	1	2
Decreased grip strength	0	1	1
Decreased sexual interest	1	0	1
Hot flush	1	0	1
Health instability caused by treatment and symptoms	0	0	0
Psychological	**6**	**38**	**44**
Worried about family	1	4	5
Parenting worries	0	5	5
Future perspective	1	4	5
Depressed mood feeling sad down	0	4	4
Fear of disease progression	0	3	3
Change in appearance	1	2	3
Uncertainty	0	3	3
Dissatisfied with body image	1	2	3
Anxiety about advanced aspect	0	3	3
Fear of dying	1	1	2
Long term health concerns	1	1	2
Unknown future	0	2	2
Fear leaving family behind	0	1	1
Unknown prognosis	0	1	1
Worries about the future	0	1	1
Feeling afraid	0	1	1
Anxiety	0	0	0
Fear of making symptoms worse	0	0	0
Independent living	**2**	**7**	**9**
Isolation	0	5	5
Loss of independence	1	1	2
Dependency on others	1	0	1
Needing help from family children	0	1	1
Support pathways	**0**	**2**	**2**
Altered partner relationships	0	2	2

Many the core issues searched for in the library had multiple items associated with it. The number of items was dependent of the type of issue, as certain issues were found to be better represented than others. Variations in item wording were a result of the ongoing developmental work of the EORTC in updating its modules over the years, with common issues, included across various modules, receiving multiple iterations in their

wording. Three of the core issue were found not to have had a corresponding item within the library. These issues included anxiety, fear of making symptoms worse and health instability caused by treatment and symptoms. Nine issues were found to have just one corresponding item. The data produced by this review were used to facilitate the selection of items included in the provisional questionnaire.

5.2.2 First draft development

Having identified 119 items from the Item Library, a review of the items was conducted by me and my supervisors to shortlist the items to be included in the provisional questionnaire. The process involved the development of several new items, as well as the modification of certain items extracted from the Item Library.

5.2.2.1 Item development (NEW)

Nine new items were developed and included within the first draft of the provisional questionnaire. Three of these items were developed due to the lack of a pre-existing item within the Item Library and included anxiety, fear of making symptoms worse and health instability. The six remaining items were developed for issues whose corresponding items from the Item Library did not address the original core issue identified and thus new items were needed to better address the issue. The items developed are shown in Table 22 alongside the original issues for context. The items are grouped by domain.

Table 22. ***The development of new items selected for inclusion in the first draft of the provisional questionnaire.***

Issue	**New items**
General-Treatment impact	
Medicalised lifestyle	Did having hospital visits and treatments interfere with your daily life?
Health instability caused by treatment and symptoms	Has your health been unpredictable as a result of your disease or treatment?
Body image	
Change in appearance	Has your appearance changed as a result of your disease/treatment?
Anxiety/depression	
Anxiety	Have you felt anxious?
Family impact/concerns	
Fear leaving family behind	Have you worried about leaving your family or children behind?
Independence	

Needing help from family children	Have you needed help from your family or friends for managing daily life?
Fear/ uncertainty	
Fear of making symptoms worse	Have you been concerned that your daily activities may make your symptoms worse?
Feeling afraid	Have you felt afraid of what the future may bring?
Unknown prognosis	Have you found it hard to cope with the uncertain prognosis of your disease?

5.2.2.2 Review of items for duplication

The selection process involved several rounds of discussion between myself and my supervisory team in order to determine which items best represented the core issue and therefore be included in the first draft of the questionnaire. Table 23 highlights the results from this selection process, with the core issue, identified items and selected item displayed in each column. For clarity, items extracted from the item library, modified items and new items created are all shown in the table. The issues/items are categorised by the domain in which they are related, as this facilitated the identification of repetitive or duplicated items. In total 50 items were selected and formed the first draft of the questionnaire.

Table 23. ***The selection of items for inclusion in the provisional questionnaire – first draft.***

Core issue	Identified items	Proposed Item	Decision
	Fatigue		
Loss or lack of energy	(R) Have you lacked energy? Have you lacked the energy to do things? Have you had a feeling of overwhelming and prolonged lack of energy? Have you felt lacking in energy? Have you had a lack of energy?	Q272. Have you lacked the energy to do things?	Practical wording best complimented the core issue.
Fatigue	(R) Have you lacked energy? Have you had a feeling of overwhelming and prolonged lack of energy? Have you felt exhausted?	Q502. Have you felt exhausted?	Fatigue items within the QLQ-C30. This was chosen to compliment these items across the severity spectrum
	Musculoskeletal-Pain		
Muscle aches pains	(R) Have you had aches or pains in your muscles or joints? Did you have aches or pains in your muscles or joints? Have you had aches or pains in your muscles?	(R) Q289. Have you had aches or pains in your muscles or joints?	Recommended wording
Joint aches pains and stiffness	(R) Have you had problems with your joints? (R) Have you had aches or pains in your muscles or joints? (R) Have you had pain in your joints? Did you have aches or pains in your muscles or joints? Have you had aches or pains in your joints? Have you had stiffness in your joints? Have you had trouble with your joints (e.g. stiffness, pain)?	Q909. Have you had stiffness in your joints?	Supplements item above without duplication.

Bone pain	(R) Have you had aches or pains in your bones? Have you had bone aches or pain? Have you had aches or pain in your bones? Have you had aches or pains in your muscles or bones?	(R) Q356. Have you had aches or pains in your bones?	Recommended wording
Back pain	(R) Have you had pain in your back? Have you had pain in your lower back?	(R) Q162. Have you had pain in your back?	Recommended wording
	Symptoms		
Fever	(R) Have you had a fever? Have you had fevers or chills?	(R) Q400. Have you had a fever?	Recommended wording
Numbness tingling burning in hands feet	(R) Have you had tingling or numbness in your hands or feet? (R) Have you had tingling hands or feet? Have you had tingling or numbness in your fingers or toes? Have you had numbness in your fingers or toes? Did you have numbness in your fingers or hands? Did you have tingling fingers or hands? Did you have tingling toes or feet? Have you had tingling in your fingers or toes? Did you have shooting or burning pain in your fingers or hands? Did you have shooting or burning pain in your toes or feet?	(R) Q462. Have you had tingling or numbness in your hands or feet?	Recommended wording
Decreased grip strength	Did you have difficulty opening a jar or bottle because of weakness in your hands?	Did you have difficulty opening a jar or bottle because of weakness in your hands?	Matched the core issue
Hair loss	(R) Have you lost any hair?* Have you lost hair as a result of your treatment? Have you had hair loss? Have you been upset by how the treatment has affected your hair?	Q457. Have you been upset by how the treatment has affected your hair?	Aimed to capture more than just ‘hair loss’ as treatments can cause hair thinning. *Have you lost hair? Was included in a later stage.
Hot flush	(R) Have you had hot flushes?	(R) Have you had hot flushes?	Recommended wording

Infections	Have you worried about getting an infection? Have you had trouble with other infections? KA. Have you had trouble with infections?	Q354. Have you worried about getting an infection?	Signs of infection covered by 'Fever'. So this items addresses the psychological impact of infections.
	General treatment impact		
Feeling unwell	(R) Have you felt ill or unwell? (R) Have you felt ill? Did you feel ill or unwell?	(R) Q126. Have you felt ill or unwell?	Recommended wording
Treatment side effects	(R) Have you had side effects from your treatment? To what extent have you been troubled with side-effects from your treatment? Have you had side effects from your treatment?	(R) Q168. To what extent have you been troubled with side-effects from your treatment?	Recommended wording
Impact of cancer symptoms	How much has your disease been a burden to you? How much has your illness been a burden to you? KA. How much has your illness and symptoms been a burden to you? Q46. Modified. How much has your disease and treatment been a burden to you? How much has your treatment been a burden to you?	Q46. Modified. How much has your disease and treatment been a burden to you?	Modified the item to include the burden of disease and treatment to reduce the overall number of items included in the questionnaire
Medicalised lifestyle	Did having to take your drugs regularly interfere with your daily life? Have you worried about having to take drugs for the rest of your life? KA. Did having hospital visits and treatments interfere with your daily life? GV Have you worried about having treatments for the rest of your life? Q555 modified- Did having hospital visits and treatments interfere with your daily life?	NEW. Did having hospital visits and treatments interfere with your daily life?	Existing items within the Item Library were not suitably phrased. New item developed.

Health instability caused by treatment and symptoms	KA. Has your general health felt/been unpredictable? CB. Has your health felt/been unpredictable as a result of your disease or treatment?	NEW. Has your health been unpredictable as a result of your disease or treatment?	No existing item in the library
	Body image		
Change in appearance	(R) Have you had problems with your appearance? Have you worried about your appearance? Has your appearance bothered you? NEW. Has your appearance changed as a result of your disease/treatment?	NEW. Has your appearance changed as a result of your disease and/or treatment?	Selected as best fit for the core issue e.g. 'change'.
Dissatisfied with body image	(R) Have you been dissatisfied with your body? Have you felt dissatisfied with your body as result of the disease or treatment? Have you been dissatisfied with your physical appearance?	SURV100. Have you been dissatisfied with your physical appearance?	Item from the survivorship questionnaire was deemed to better cover the core issue.
	Anxiety/depression		
Depressed mood feeling sad down	Did you feel depressed? Have you felt sad? Have you felt that nothing could cheer you up? Have you had mood swings?	Q660. Have you felt that nothing could cheer you up?	Included to supplement items in the QLQ-C30
Anxiety	GV/KA. Have you felt anxious?	NEW. Have you felt anxious?	To supplement items in the QLQ-C30. Anxiety is now a more common term used in day to day language
	Family impact/concerns		

Worried about family	(R) Have you worried about your family in the future? GV. Have you worried how your family may cope in the future? Have you worried about your family coping with your illness and treatment? Have you worried about the future of people who are important to you? How distressing, do you think, your illness or treatment has been to those close to you? I have worried about the future of people who are important to me	ELD-37. Have you worried about the future of people who are important to you?	Item from the elderly questionnaire was selected to capture the worry, and was more inclusion than that of the recommended wording. This was influenced by the remaining items in this domain.
Parenting worries	Have you worried about your family coping with your illness and treatment? Have you been worried about your family or children? Not seeing children growing up? Q39 Modified. Have you worried about your family or children coping with your illness and treatment? Have you been concerned about disruption to your family life because of your treatment? Have you worried about the impact of your cancer on your children?	SURV100 Have you worried about the impact of your cancer on your children? OR (If you do not have children, please select N/A) Q39. Modified. Have you worried about your family or children coping with your illness and treatment?	Two items proposed for consideration. Further feedback required on these items.
Fear leaving family behind	Were you worried about your family in the future? KA Have you been concerned about how your family or children will cope in the future? GV Have felt sad/worried about leaving your family behind?	NEW. Have you worried about leaving your family or children behind?	New item addressed the core issue
Altered partner relationships	Has your physical condition or medical treatment interfered with your relationships with your family or friends? GV. altered the relationships with your partner? Has your physical condition or medical treatment altered the relationships with your partner? (N/A)	Q721. Modified. Has your physical condition or medical treatment altered the relationships with your partner? (N/A) OR Q172. Has your physical condition or medical treatment interfered with	Two items proposed for consideration. Further feedback required on these items.

		your relationships with your family or friends?	
Isolation	Have you felt isolated from those close to you (e.g. family, friends)? As a result of your physical condition or medical treatment, have you felt isolated from your family or friends? Elderly M. Have you felt able to talk to your family about your illness? High-dose Have you felt a need to keep your fears/ concerns from family or friends? SURV100 Do you feel that people treat you differently?	207. Have you felt isolated from those close to you (e.g. family, friends)? AND Elderly M. Have you felt able to talk to your family about your illness?	Included both items to cover psychological and social isolation as well.
	Independence		
Needing help from family children	Have you worried that you are a burden to other people? KA. Have you felt that you are a burden to family or friends? GV. Have you needed help from your family or friends for managing daily life?	NEW. Have you needed help from your family or friends for managing daily life?	New item addressed the core issue
Loss of independence	(R) Have you worried about becoming dependent on others? Q294. Have you worried that you are a burden to other people?	Q294. Have you worried that you are a burden to other people?	Recommended wording included below. Item selected to supplement this.
Dependency on others	(R) Have you worried about becoming dependent on others?	(R) Q299 Have you worried about becoming more dependent on others?	Recommended wording
	Fear/ uncertainty		

Fear of disease progression	Have you been afraid of tumor progression? Have you worried about your health in the future? Have you worried about the results of examinations and tests?	Q587. Have you been afraid of tumor progression? AND Q186. Have you worried about the results of examinations and tests?	Included both to cover to different aspects of disease progression
Fear of making symptoms worse	KA. Have you been concerned about making your symptoms worse CB. Do you worry about making your symptoms worse? GV - NEW. Have you been concerned that your daily activities may make your symptoms worse?	NEW. Have you been concerned that your daily activities may make your symptoms worse?	No existing item in the library
Feeling afraid	Have you felt afraid? GV Have you felt afraid of what the future may bring?	Q661. Have you felt afraid? OR NEW Have you felt afraid of what the future may bring?	Two items proposed for consideration. Further feedback required on these items.
Anxiety about advanced aspect	Have you been afraid of tumor progression? Have you worried about your health in the future? Have you worried about the results of examinations and tests? (R) Have you worried about what might happen towards the end of your life?	(R) Q43. Have you worried about what might happen towards the end of your life?	Selected as best fit for the core issue.
Fear of dying	(R) Have you worried about what might happen towards the end of your life? Have you been worried about dying?	Q460. Have you been worried about dying?	Selected as best fit for the core issue.
Unknown prognosis	Have you been worried about your health in the future? NEW. Have you found it hard to cope with the uncertain prognosis of your disease?	NEW. Have you found it hard to cope with the uncertain prognosis of your disease?	Selected as best fit for the core issue.

Worries about the future	I have had worries and/or concerns about the future	To be removed	Covered by other items within this domain
Long term health concerns	(R) Have you worried about your health in the future? Q368 - Have you worried about your treatment causing future health problems? Have you been worried about your health in the future?	(R) Q41. Have you worried about your health in the future?	Recommended wording
Unknown future	Did you feel uncertain about the future? SURV100. Have you felt uncertain about the future?	Q42. Did you feel uncertain about the future? OR SURV100. Have you felt uncertain about the future?	Two items proposed for consideration. Further feedback required on these items.
Future perspective	(R) Have you worried about what might happen towards the end of your life? I have had worries and/or concerns about the future I have wondered whether anything can be done for me SURV100 Have you had to limit your life plans or goals? SURV100 Has the experience of cancer helped you to distinguish between important and unimportant things in life?	SURV100 Have you had to limit your life plans or goals? AND SURV100 Has the experience of cancer helped you to distinguish between important and unimportant things in life?	Included both to cover to different aspects of the core issue.
Uncertainty	Did you feel uncertain about the future? I have felt able to plan for the future Do you feel that your life has been on hold?	SURV100. Do you feel that your life has been on hold?	Previous items covered ‘uncertainty’ this item was included to supplement these.
	Reproductive		
Vaginal dryness	(R) Have you experienced a dry vagina during sexual activity? (BR45-73) Have you had a dry vagina? (BR45-70 wording)	Q912. Have you had a dry vagina?	Matched the QLQ-BR45 wording and is suitable for breast patients.

Decreased sexual activity	(R) Have you been sexually active? Have you been sexually active (with or without sexual intercourse)?	BR45-45. Have you been sexually active (with or without sexual intercourse)?	Matched the QLQ-BR45 wording and is suitable for breast patients.
Decreased sexual enjoyment	(R) Has sexual activity been enjoyable for you? (R) Have you felt less sexual enjoyment? To what extent did you feel sexual enjoyment? Has sex been enjoyable for you?	(R) Q84. Has sexual activity been enjoyable for you?	Recommended wording
Decreased sexual interest	(R) Have you been interested in sex?	(R) Q72. Have you been interested in sex?	Recommended wording

(R) Recommended wording, New – New items developed by the research team

The 50 items selected corresponded to 43 of the 44 issues. One issue, ‘worries about the future’, was selected for removal at this stage due to duplication of similar issues. There were seven instances where multiple items were proposed for a single issue. In the majority of cases (4), two items were included where consensus between myself and my supervisor team could not be agreed. These items were flagged for further evaluation during the expert consensus round. For the three remaining issues, it was agreed that the issues would be best assessed with the inclusion of two items.

With regards to the wording of the included items, 13 issues were assigned the recommended wording as stated in the Item Library. Interestingly, each of these related to the symptom burden domain. Whilst every effort was made to include the recommended wording, this was not always possible due to the items not assessing the key concept of the original issue. As a result, the wording of 25 of the included items were classed as other. These items were widely accepted and developed with rigor as with all EORTC items. In three cases where pre-existing items did not match the original core issue, the decision was taken to modify these items rather than to develop new ones. These were cases where just one or two words were modified to enable the item to better address the issue. As mentioned above, nine issues were assigned new items developed by the research team to address the gaps within the item library.

5.2.2.3 Time frames

Two possible timeframes were included, ‘within the past week’ or ‘past 4 weeks. These timeframes were selected due to the inclusion of items spanning multiple domains. Items relating to physical issues were better suited to a more frequent response time as they are often more variable compared with issues relating to psychosocial domains that are less susceptible to change over the one-week period. Psychosocial items were assigned the past 4 weeks’ timeframe. The timeframes were consistent with those used across all EORTC measures.

The first draft of the questionnaire was complete at this stage. It contained 44 issues, one of which was marked for removal pending the expert consensus, and a total of 50 items. The drafted questionnaire was then presented and reviewed by an expert group, from which the provisional questionnaire was finalised.

5.2.3 Expert consensus review

An expert consensus review of the data was conducted. The group consisted of the international collaborators involved in the project, as well as members of the EORTC QOL group and the breast cancer group. The sample consisted of eight individuals with a range of backgrounds including both clinicians and academics. The first draft of the questionnaire was reviewed by experts from around world including the UK, Germany, Poland, Italy, France, Japan and Jordan. Feedback was provided on the overall acceptability of the proposed items in terms of being culturally appropriate and translatable. Results of the consensus exercise are presented below.

5.2.3.1 Round 1: Review of results by email discussion

The results from the first round of expert feedback (conducted virtually) resulted in 39 out of 44 issues being selected for inclusion. Twenty-five of the issues were included as a consensus was achieved. Five issues were removed at this stage having reached a consensus within the group for their exclusion. These items are discussed below. The nine remaining issues required further action before the items were agreed. The results from this feedback are presented, alongside the action taken, in Table 24, which presents the 14 core issues that required further evaluation prior to their inclusion/exclusion.

Table 24. ***The 14 actionable issues highlighted in Round 1 of the expert review.***

Core issue	Item proposed by coordinating centre	Results - feedback
	Symptoms	
Hair loss	Have you been upset by how the treatment has affected your hair?	Also include the physical issue of hair loss. Agreed Have you lost any hair? AND Have you been upset by how the treatment has affected your hair?
	General treatment impact	
Impact of cancer symptoms	Modified. How much has your disease and treatment been a burden to you?	Agreement - Modify item to include ‘treatment’

Medicalised lifestyle	NEW. Did having hospital visits and treatments interfere with your daily life?	Translation issue – new wording proposed and agreed. NEW 2.0. Did attending hospital visits and treatment interfere with your daily life?
Health instability caused by treatment and symptoms	NEW. Has your health been unpredictable as a result of your disease or treatment?	Translation issue – new wording proposed and agreed. NEW2.0. Has your health been unstable as a result of your disease or treatment?
	Family impact/concerns	
Parenting worries	(1) Have you worried about the impact of your cancer on your children? (If you do not have children, please select N/A) OR (2) Modified. Have you worried about your family or children coping with your illness and treatment?	Agreement – Keep (1) 'Have you worried about the impact of your cancer on your children? (If you do not have children, please select N/A)'
Fear leaving family behind	Were you worried about your family in the future? KA Have you been concerned about how your family or children will cope in the future? GV Have felt sad/worried about leaving your family behind?	Disagreement on proposed items. Translation issue and duplicate item
Altered partner relationships	(1) Modified. Has your physical condition or medical treatment altered the relationships with your partner? (N/A) OR (2) Has your physical condition or medical treatment interfered with your relationships with your family or friends?	Agreement - Modify item to specify 'partner' Agreement – Keep (1) Modified. Has your physical condition or medical treatment altered the relationships with your partner? (N/A)
	Fear/ uncertainty	
Fear of disease progression	(1) Have you been afraid of tumor progression? AND (2) Have you worried about the results of examinations and tests?	Agreement - Keep both Modify (1) - tumor to disease. Modified. Have you been afraid of disease progression?

Fear of making symptoms worse	NEW. Have you been concerned that your daily activities may make your symptoms worse?	Translation issue – new wording proposed and agreed. NEW.2.0. Have you worried that your daily activities might worsen your symptoms?
Feeling afraid	NEW. Have you felt afraid of what the future may bring?	Agreement - Remove Duplicate item (Have you felt uncertain about the future? Have you been afraid of disease progression?)
Worries about the future	I have had worries and/or concerns about the future	Agreement - Remove Duplicate item (Have you felt uncertain about the future? Have you worried about what might happen towards the end of your life?)
Long term health concerns	(R) Have you worried about your health in the future?	Agreement - Remove. Duplicate item (Have you been afraid of disease progression? Have you felt uncertain about the future?)
Unknown future	(1) Did you feel uncertain about the future? OR (2) Have you felt uncertain about the future?	Agreement – Keep (2) 'Have you felt uncertain about the future?'
Uncertainty	Do you feel that your life has been on hold?	Agreement - Remove. Duplicate item (have you had to limit your life plans or goals?)

Purple text: proposed modifications.

5.2.3.1.1 Duplication

A key result of the consensus exercise was the removal of issues from the questionnaire. The first removed was 'worries about the future'. This issue was highlighted as a potential duplicate in the preliminary review conducted by the study team. Members of the expert consensus group confirmed this decision; therefore, it was removed from the questionnaire. Subsequently, four other issues were found to be repetitive and/or duplicates. The issues included, 'Fear leaving family behind' (translational issues Japan/Jordan and duplication), 'Worries about the future' (duplication), 'Long term health concerns' (duplication) and 'Uncertainty' (duplication). These issues were found to be relevant and important to patients in Phase I, however when the items were reviewed in full, as part of the questionnaire, clear overlaps between the issues were identified.

5.2.3.1.2 Cultural differences

Cultural concerns were raised by the Jordan site in relation to the sexual items as they felt these types of issue would be inappropriate in a Muslim culture and suggested such items to have a 'prefer not to answer' option or for them to be removed in certain cultures. Discussions around this took place at the Spring 2022 meeting and it was decided that these items would remain and reviewed again in Phase III. This is a common issue found within the literature regarding the cultural differences and interpretation of questionnaires. Overall, these are very important issues to patients so the removal of them completely is less than ideal. The inclusion of a N/A response was an option in the development of such measurement tools. However, it is important to limit the number of items that have an N/A response when it comes to interpretation of missing data [292]. An option was discussed to move these items to the end of questionnaire as optional, a president for this has been set in existing EORTC modules [293-295].

Based on the comments and feedback received during the first round of the expert consensus, four issues were removed. This resulted in a second draft of the provisional questionnaire which included 39 issues. This version of the questionnaire was then presented to the EORTC collaborators' group at a face-to-face meeting to finalise the questionnaire.

5.2.3.2 Round 2: Review via face-to-face meeting (Spring 2022)

The provisional questionnaire was presented to key stakeholders at the EORTC quality of life group meeting where it was discussed and evaluated in more detail. This round aimed to validate the decisions made in previous rounds, as well as to finalise the questionnaire. The group consisted of 22 individuals from a range of specialties including clinicians, methodologists and QOL researchers. The group agreed on the inclusion of all but one of the issues presented. The item relating to 'Feeling afraid' was discussed in detail, which resulted in the removal of this item. The group agreed on its removal as the item selected for this issues referred to 'being afraid of what the future may bring' and was removed on the basis that this item did not add value beyond the other items which reference to 'the future'. On reflection, an alternative item could have been selected rather than removing the issue, however this could potential be reviewed again in Phase III of the study.

With regards to the remaining issues, specific attention was paid to 'Hair loss'. It was agreed that this issue was to include two items as it was a highly important problem for patients. The items previously selected were, 'Have you lost any hair?' and 'Have you

been upset by how the treatment has affected your hair?'. However, it was suggested these items should match those included in the QLQ-BR45. After much discussion, the decision not to change the items to match the QLQ-BR45 was made. This was largely due to the second item for hair loss in the QLQ-BR45 being conditional on the patient having lost hair, whereas many of the new targeted treatments used in MBC do not cause complete hair loss, but rather hair thinning. The avoidance of the conditional item would allow more patients to respond.

The omission of sore mouth was discussed as the group noted that this was a common issue seen within their clinical practice and would have expected it to have ranked higher. No decision was taken to include this issue at this point as the priority for inclusion remained focused on the patient. However, the feedback from collaborators proved to be significant in the justification of including the issue of sore mouth following the update of the systematic review. Therefore, as a result of the data from the updated review and feedback from collaborators, sore mouth was included in the provisional questionnaire.

This resulted in a final questionnaire consisting of 44 items to assess 40 core issues. The selected items and their corresponding core issue can be seen in Table 25. The finalised formatted provisional questionnaire along with the proposed time frames set out in the EORTC format can be seen at the end of this chapter. A wider discussion took place on the predominance of psychosocial and future uncertainty items included in the measure and the impact this may have with regards to its use in clinical research. Whilst this did not impact the removal of items, it was an important topic to discuss.

Table 25. ***Provisional questionnaire grouped by domain, including the original issues and their corresponding item(s).***

Issue	Proposed Items
Fatigue	
Q013 Loss or lack of energy	Q272. Have you lacked the energy to do things?
Q014 Fatigue	Q502. Have you felt exhausted?
Musculoskeletal-Pain	
Q046 Muscle aches pains	(R) Q289. Have you had aches or pains in your muscles or joints?
Q049 Joint aches pains and stiffness	Q909. Have you had stiffness in your joints?
Q050 Bone pain	(R) Q356. Have you had aches or pains in your bones?
Q051 Back pain	(R) Q162. Have you had pain in your back?
Symptoms	

Q034 Infections	Q354. Have you worried about getting an infection?
Q036 Fever	(R) Q400. Have you had a fever?
Q063 Numbness tingling burning in hands feet	(R) Q462. Have you had tingling or numbness in your hands or feet?
Q057 Decreased grip strength	Did you have difficulty opening a jar or bottle because of weakness in your hands?
Q085 Hair loss	Q116. Have you lost any hair? Q457. Have you been upset by how the treatment has affected your hair?
Q091 Hot flush	(R) Have you had hot flushes?
General-Treatment impact	
Q016 Feeling unwell	(R) Q126. Have you felt ill or unwell?
Q018 Treatment side effects	(R) Q168. To what extent have you been troubled with side-effects from your treatment?
Q017 Impact of cancer symptoms	Q46. Modified. How much has your disease and treatment been a burden to you?
Q175 Medicalised lifestyle	NEW 2.0. Did attending hospital visits and treatment interfere with your daily life?
Q019 Health instability caused by treatment and symptoms	NEW2.0. Has your health been unstable as a result of your disease or treatment?
Body image	
Q102 Change in appearance	NEW. Has your appearance changed as a result of your disease or treatment?
Q104 Dissatisfied with body image	SURV100. Have you been dissatisfied with your physical appearance?
Anxiety/depression	
Q106 Depressed mood feeling sad down	Q660. Have you felt that nothing could cheer you up?
Q108 Anxiety	NEW. Have you felt anxious?
Family impact/concerns	
Q152 Worried about family	ELD-37. Have you worried about the future of people who are important to you?
Q153 Parenting worries	SURV100. Have you worried about the impact of your cancer on your children? (If you do not have children, please select N/A)
Q182 Altered partner relationships	Q721. Modified. Has your physical condition or medical treatment altered the relationships with your partner? (N/A)
Q169 Isolation	Q207. Have you felt isolated from those close to you (e.g. family, friends)? AND

	Elderly M. Have you felt able to talk to your family about your illness?
Independence	
Q181 Needing help from family children	NEW2.0. Have you needed help from your family or friends with managing daily life?
Q165 Loss of independence	Q294. Have you worried that you are a burden to other people?
Q166 Dependency on others	Q299. Have you worried about becoming more dependent on others?
Fear/ uncertainty	
Q121 Fear of disease progression	Q587. Modified. Have you been afraid of disease progression? AND Q186. Have you worried about the results of examinations and tests?
Q123 Fear of making symptoms worse	NEW.2.0. Have you worried that your daily activities might worsen your symptoms?
Q109 Anxiety about advanced aspect	Q43. Have you worried about what might happen towards the end of your life?
Q120 Fear of dying	Q460. Have you been worried about dying?
Q157 Unknown prognosis	NEW. Have you found it hard to cope with the uncertain prognosis of your disease?
Q156 Unknown future	SURV100. Have you felt uncertain about the future?
Q159 Future perspective	SURV100. Have you had to limit your life plans or goals? AND SURV100. Has the experience of cancer helped you to distinguish between important and unimportant things in life?
Reproductive	
Q070 Vaginal dryness	Q912. Have you had a dry vagina?
Q073 Decreased sexual activity	BR45-45. Have you been sexually active (with or without sexual intercourse)?
Q074 Decreased sexual enjoyment	(R) Q84. Has sexual activity been enjoyable for you?
Q075 Decreased sexual interest	(R) Q72. Have you been interested in sex?

5.3 Discussion

The main result of the work conducted in Phase II was the successful delivery of a provisional questionnaire for the assessment of quality of life in metastatic breast cancer patients. The questionnaire was developed using a structured approach which prioritised inclusion of patients at the earliest stage. It went through various iterations with the final version consisting of 44 items assessing 40 core issues. Whilst this questionnaire remained provisional at this stage, it provided the core structure and items that would later undergo testing in Phase III and beyond. The success of the questionnaire hopes to bring about better measurement in clinical research as well as aiding clinicians to provide the best support and care to their patients.

This Chapter highlighted the benefit of consulting with experts in the area prior to finalising the questionnaire. This method enabled the identification of potential problems that were resolved prior to Phase III, such as the removal of duplicated items and development of robust novel items. It also showed the challenges of developing an internationally validated questionnaire, particularly during the item selection phase as items were found to have different cultural implications. The use of obtaining consensus via email, as opposed to face to face, in round 1 was a key factor in this work, as the group resided in different countries, across various time zones, managing different workloads, therefore this method supported the collection and evaluation of data from each member at a time that was convenient to them.

The decision to add sore mouth to the questionnaire was a result of the feedback from the experts in Round 2, coupled with the data provided in the updated systematic review. The review data highlighted the prevalence of ‘sore mouth’ within the newly published treatments leading to concerns that this may have been an underestimated issue in the original sample. There was strong support from the experts that this issue should be included prior to the review and thus the decision was taken to include it at this stage as the item will be assessed by patients in Phase III, if found to be problematic or irrelevant it can later be removed.

Patients rated as highly important and relevant a large number of issues related to psychosocial aspects of living with advanced cancer, uncertainty about the future and the impact on family, children and on social aspects of their lives. This resulted in a relative predominance of those issues over the physical side effects of new treatments. These results were discussed at the QLG meetings with concerns raised if this module would be seen as useful for clinical trials of new treatments. These issues have proved

to be relevant and important to patients living with MBC, hence it was felt to be wrong to exclude them from the provisional questionnaire. It could also be argued that if treatments are effective, they should not only improve the physical symptoms of the disease, but also have positive impact on psychosocial and coping aspects of patients' lives. Feedback from the collaborators was extremely useful during this process. It should also be noted that the module for elderly patients has many items on psychological aspect and independence [296]. One proposal to address these concerns could be to recommend the items that are of particular interest to those conducting clinical trials in this area to be administered as a shorter measure (akin to the Trial Outcomes Index TOI of FACIT measures) [90].

A strength of Phase II was the utilisation of the EORTC Item Library. Conducting the review of the library reduced the risk of duplicating the work when developing the items for the module. This saved time and resources pre-existing items were selected that matched the style and format of EORTC measures. Not only did it provide pre-existing items, and their translations, the review highlighted the core issues for which new items were needed enabling me to focus on developing wording for these items, which in turn will be added to the library as the development of the module progresses.

Although it was not required to include patients at this phase in the EORTC guidelines, I feel that this was a missed opportunity within my thesis. I had planned to hold a consultation with a Patient and Public Involvement and Engagement group to discuss the items selected in the final version of the questionnaire. However, due to the time taken to receive feedback from the experts and to finalise the questionnaire there was no time available to conduct this task. The questionnaire will be reviewed in full by patients in Phase III and any problems with items such as their wording or order will be identified at this stage, however a pre-check with a small group of patients at the end of Phase II may have helped identify potential problems earlier.

If time and resources had have permitted, a more structured approach to obtaining feedback and consensus, such as the Delphi method, would have added further strength to this study [297]. The current method used was however beneficial in the generation feedback in an efficient manor, particularly as this was an international project with collaborators located across different time zones.

5.3.1 Conclusion

The successful delivery of Phase II of the module development process resulted in a 44-item questionnaire, capable of assessing a range of QOL related issues relevant and important to metastatic breast cancer patients. Due to unforeseen circumstances, it was not possible to complete Phase III development with the available timeframe of my PhD. Therefore, future work should look to test the provisional questionnaire for its comprehension and depth of coverage with a large, international sample of patients to validate the work conducted in Phases I and II. Further to this, the psychometric properties, and scale structures should be assessed before conducting Phase IV, the final large scale international validation of the questionnaire.

The subsequent chapter presents the internet mediated research study conducted using a qualitative dataset extracted from an online breast cancer forum. Chapter 6 provides background and rational behind this research, as well as outlining the methods used to collect and analyse the data. The results and discussion are presented, with a critique of the method and its merit for use in the development of patient reported outcome measures.

Chapter 6. Online forum review

The objective of the study detailed in this chapter was to provide a complementary methodology to that of the standard questionnaire development procedures, by exploring if different, and/or additional information, can be obtained from the content of an online breast cancer forum about Quality of Life (QOL) in Metastatic Breast Cancer (MBC). This research aimed to summarise the QOL issues people living with MBC report online and determine how they compare to those identified by the methods used in Chapters 3 and 4.

Online forums have been shown to be a valuable source of real-world data [298]. They are capable of providing data in real-time, as well as doing so in an uncensored, and unsolicited manner. This is of particular value for those conducting health-related research, such as, those developing new questionnaires [299]. Forums can be assessed to develop an understanding of the treatments, symptoms and wider patient experiences, as they provide a platform for users to view and discuss a multitude of health-related topics relevant to their condition [300, 301]. Widespread internet access has provided new opportunities for people to communicate, obtain and share health-related information. For example, in the UK, 89% of adults report using the internet daily or almost every day with increasing numbers of the population using the internet to access health-related information [302]. Several online forums have been established by various cancer organisations in the UK, including Macmillan, Cancer Research UK and Breast Cancer Now, to help those affected by cancer ask questions and seek support from individuals in a similar position [303-305]. The findings of this study aimed to further our knowledge of the potential benefit of harnessing online forum data in the methods for developing of quality-of-life measures.

The aims of this research were to:

- Summarise the range of QOL issues (physical and psychosocial) people living with MBC report through a retrospective analysis of data captured on an online breast cancer forum
- Determine how the QOL related issues reported online compare to those reported via traditional research methods (face-to-face interviews)

6.1 Method

6.1.1 Study design

Following the 'practical guide to analysing online forums', published by Smedley and Coulson (2018), a retrospective observational design was adopted [125]. A qualitative, thematic content analysis, was conducted using data extracted from Breast Cancer Now's (BCN) online forum to explore the quality-of-life related issues reported and discussed within the forum. The Generic Choice Model was used as the conceptual framework from which the analysis was underpinned. The same framework was used in the developmental procedures outlined in Chapters 4 and 5. Its inclusion in this chapter facilitated the triangulation of results between the online forum, quantitative Phase I data and the systematic review data.

6.1.2 Data collection

Breast Cancer Now is the UK's largest breast cancer charity and champions research across both primary and secondary or metastatic breast cancer with the goal of saving as many lives as possible. The charity also provides support to those diagnosed with breast cancer, including male and metastatic breast cancer, via their website and online forum. The forum is a dedicated online platform where people affected by breast cancer can go to find information, seek support, and discuss their problems. The forum is written in English and primarily intended for UK use only, however was selected due to its popularity and dedicated sections for those diagnosed with metastatic breast cancer. At the time of writing, the forum has over 64,000 members and was divided into 12 main categories where users can navigate to sections most relevant to them. Pre-existing public message threads relating to MBC posted on 'The Forum' (https://forum.breastcancernow.org) between January 2016 - 2021 were extracted, reviewed, and analysed as part of this research.

6.1.3 Structure of the forum

Table 26. ***Definitions of the terminology associated with the structure of an online forum.***

Term	Definition
Forum	Online services with features that enable members to communicate with each other [306]
Message board (themes)	Message boards are used to categorise the information within the forum, they act as the index page that users can use to navigate the forum.
Threads	Each message board contains a variety of different threads. Threads act as sub-topics whereby users can create threads to discuss issues they are experiencing. The content of the threads relate to the overall theme of the message board in which they are contained [307]
Messages	Each thread contains one or more individual messages written by the forum users.

Definitions of the keywords and phrases associated with the structure of the forum are shown in Table 26. The forum had a hierarchical, tree-like structure, whereby users navigate by selecting the topics relevant to them. At the top level, the forum contains a home page listing various topics or 'message boards' that the user can select. In this case we were interested in the Metastatic Breast Cancer Board. Within this area of the forum, users are presented with second set of message boards that specifically relate to MBC. These boards help facilitate discussions and contain many different conversations which are known as threads. A thread is created when a user wishes to start a discussion about a specific topic and may be in the form of a question, asking for advice or talking about an experience [308]. Other users are then able to read and comment if they too wish to share their thoughts or experiences.

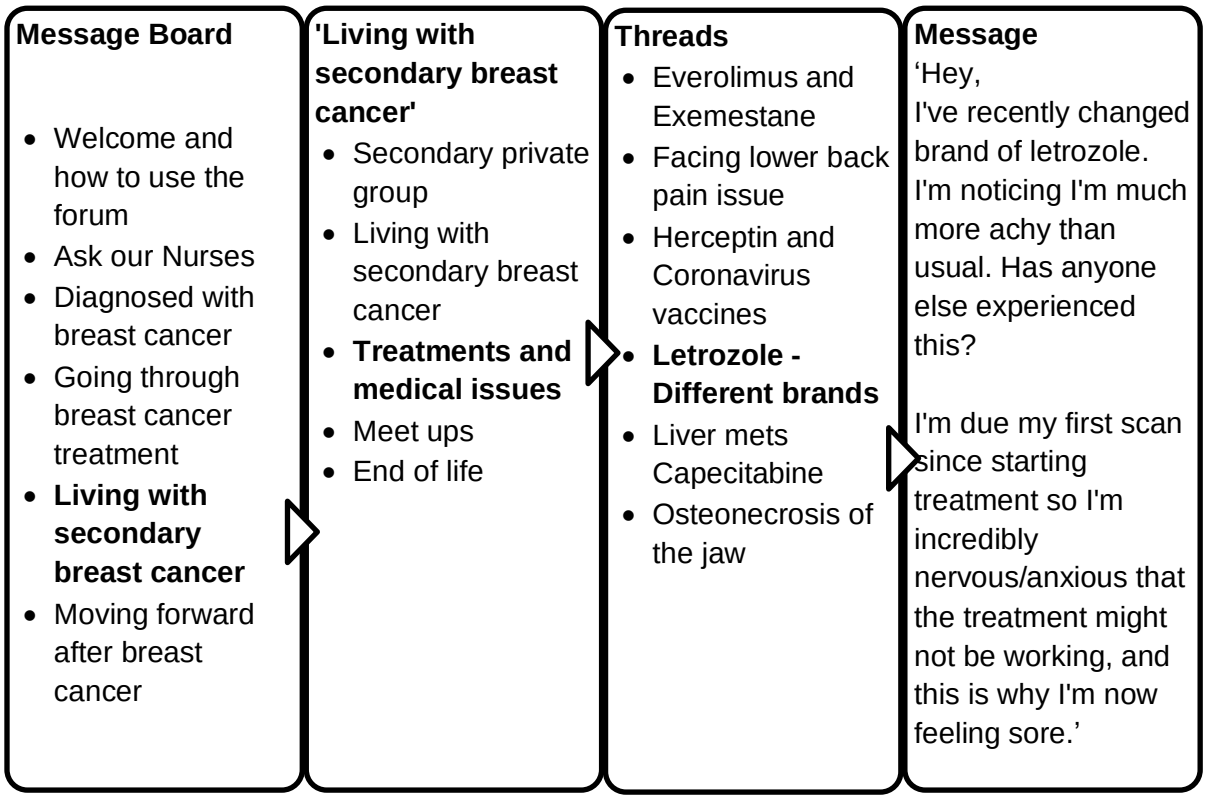


Figure 6. ***Example structure of Breast Cancer Now's online forum.***

6.1.4 Data extraction

Data were extracted from the MBC message board titled 'Treatment and medical issues'.

Different methods of data extraction were considered, such as data mining and the automated export of data from the host. However, with the resources available to me within my PhD, a manual approach to data extraction was adopted. This process involved saving each thread, and its corresponding messages into PDF document. Despite being a very time-consuming method of extracting the data for analysis, it did however preserve of the format of the thread and the messages as they were seen on the website and thus reduced the likelihood of errors occurring when extracting the data.

All PDFs were then subsequently uploaded to NVIVO software for analysis. NVIVO is a digital software package used to organise and analyse qualitative data [309]. The data were entered in the same order it was extracted from the live forum and grouped according to the message board it was extracted from. This included a total of 14 pages each of which containing up to 20 threads. The forum was ordered chronologically with the most active threads appearing on page 1 and so on. The same format applied to the individual messages within the threads, for instance the most recent messages appeared at the top. This format was of particular importance during data analysis, as the narrative

of the messages was of a bottom-up design and thus required the researcher to read from the bottom of the thread to the top.

6.1.5 Inclusion/exclusions

To capture the most relevant information, data was extracted and analysed if published on the forum within the past 5 years. This was to ensure the current issues were identified and provided a more manageable workload as the forum itself contains copious amounts of available data. All data was extracted in January 2021, therefore, a thread was included if it contained messages from January 2016 onwards. Due to the popularity of certain threads, many included messages posted prior to 2016, these messages were not included in the analysis. Threads without replies or threads posted by the moderators were also not included. Data from forum users with early-stage breast cancer were not included in this study.

6.1.6 Participants

The content of naturally occurring, pre-existing posts from the public areas of the online forum were extracted and analysed, and thus, forum users received no instruction or contact from the researcher. The participants were considered as self-selecting, and as the clinical characteristics were unavailable, only data posted within the MBC areas were included as this was the target population being studied.

6.1.7 Analysis

The primary aim of the analysis was to identify the various symptoms and side effects patients living with metastatic breast cancer experience as a result of their disease and/or treatment. Content analysis was conducted to determine the range of physical and psychological quality of life/symptom issues reported across the ‘Treatments and medical issues’ section of the forum. A deductive approach to the analysis was adopted with the issues extracted coded against the conceptual framework, the Generic Choice Model for long term conditions (GCM). Issues relating to physical domains and symptom burden, the Common Terminology Criteria for Adverse Events (CTCAE) criteria was used to sub-categorise the issues further [310]. Each issue was categorised according to the body system in which it impacted, for example, the issue of ‘vomiting’ was coded under gastrointestinal issues. In instances where Users reported their issues but did not specify the location of the problem, for example, ‘I had pain’, the issues were coded under the general domain. Where details were provided, for example ‘I had back pain’

the issues were coded under the body system that was referenced, which in this example would have been musculoskeletal.

The coding to the framework provided an overview of the types of problems being discussed, as well as facilitated the triangulation of the results across the work completed within this thesis. The analysis resulted in a list of issues, categorised by the domain in which they were related, that was compared with findings generated in Chapters 3 and 4.

6.1.8 Ethics

The research procedures followed the British Psychological Society (BPS) guidance for Internet-Mediated Research (IMR) and recommendations published by Smedley and Coulson (2018) on conducting research using online forums. The research was endorsed by Simon Vincent, Director of Research at Breast Cancer Now who gave permission to conduct this research on their forum. The study protocol was submitted to the University's ethics board for review and a favourable opinion was granted by the committee.

6.1.8.1 Ethical considerations

The key ethical considerations for conducting Internet Mediated Research are described below.

Public vs Private data

Online data is considered to be in the public domain if it is realistically accessible to a member of the public [311]. In the case of this study, only data from within public areas of the BCN Forum were extracted and analysed. Data was determined to be in the public domain if users have posted publicly in open message boards/threads as this data was accessible to anyone with access to the internet. Private or closed message threads were not accessed as they are password protected and not considered to be within the public domain. Breast Cancer Now forum users have the option to post publicly or privately and BCN provide users with guidance on who has access the information they share in these threads.

Consent

According to the guidelines published by British Psychological Society (BPS) for Internet Mediated Research (IMR), valid consent should be obtained where it cannot be

reasonably argued that online data can be considered ‘in the public domain’ [312]. As mentioned above, data published on public areas/threads of the forum can be considered to be within the public domain. As private threads will not to be included in this study, consent from the Forums users was not sought. Breast Cancer Now are the owner/licensee of all intellectual property rights and materials published on the site, therefore, approval to access and use the forum for research purposes was obtained from their Director of Research.

Confidentiality

Careful consideration was given to the issue of maintaining confidentiality and anonymity. As a result of using publicly available data, several procedures were implemented to maintain the anonymity of the forum users and thus reducing the risk of forum users being identified in any research outputs. The issue of traceability exists when conducting IMR using online forums as data can be reverse searched and traced back to the source, i.e. googling quotes to identify the author. To mitigate this risk, direct quotes were not included and any quotes used within research outputs were searched in a search engine to check for the potential traceability of the quote. Further to this, usernames were pseudonymised within research outputs, using a random generator, to ensure individual users could not be identified.

The level of personal data available for individual users on the Breast Cancer Now forum was limited and included usernames, date of membership and the messages posted. BCN advised users not to include personal details (full name, email or address) when creating their Usernames, as well as not to post any personal information within the message threads. Forum moderators were in place to remove messages that contain personal information. Any personal information within messages not removed by forum moderators was redacted from data extracted during this study and was not used in any research outputs. Other information about the User that was publicly available was the date of registration.

Information collected during this project was treated in the strictest of confidence. Data was exported and stored within a restricted area on University of Leeds servers (M and N drives, One Drive). Study folders were protected with access limited to members of the direct research team. No personal data, such as names, date of birth or contact details or clinical information was collected in this study. Such data remained confidential between Breast Cancer Now and the user.

6.2 Results

A total of 247 threads were included in the analysis, which resulted in the inclusion of 6548 individual messages. Each of these were analysed and coded in accordance with the data analysis plan. The results yielded 1061 individual codes being assigned across the framework, spanning multiple domains, including both physical and psychosocial. Table 27 provides an overview of the conceptual framework and the number of times a code was assigned to each domain; each domain is highlighted in bold in order of most to least common. Subcategories for symptom burden are also shown in accordance with the CTCAE criteria.

Table 27. ***An overview of the conceptual framework ordered from most to least commonly referenced within the forum.***

Theme	Total number of references
Symptom Burden	784
General disorders	286
Musculoskeletal	121
Gastrointestinal	105
Skin	92
Nervous system	65
Blood and lymphatic	35
Cardiac and vascular	35
Respiratory	22
Psychiatric	16
Reproductive system	5
Immune system	2
Psychological experience	188
Clinical services	38
Support Pathways	22
Work, Finance and Benefits	16
Independent Living	13

Bold items represent the six domains from the Generic Choice Model.

Unsurprisingly, symptom related issues were the most commonly discussed issues within this section of the forum. However, despite this area being targeted towards 'Treatment and medical issues', psychological issues such as anxiety and depression were commonly referenced throughout. The remaining domains made up a smaller percentage of the forum messages, which was perhaps to be expected as they may not have been considered within this area of the forum. Nevertheless, they highlight the wide-reaching impact MBC, and its treatment has on the individuals.

6.2.1 Symptom Burden

Issues relating to symptom burden accounted for the majority of codes indicating a high prevalence of discussion among the forum users. Within this domain, issues were grouped according to the CTCAE criteria to further define the types of issues being discussed. The most common types of issues were related to general disorders, followed by musculoskeletal and gastrointestinal. Skin related problems were the fourth most common type of issues with the remaining body systems being less frequently discussed within the forum. The most common issues within the symptom burden domain are presented below Table 28.

Table 28. ***The most common issues relating to 'Symptom burden' categorised by CTCAE domain.***

CTCAE Domain	N
General disorders	
Fatigue Tiredness	109
Sore mouth	22
General Pain	19
Mouth Ulcers	18
Jaw related issues	16
Weight and appetite	14
Infections	12
Tooth related issues	11
Flu-like symptoms	11
Oedema	8
Eyes (Dry, watery)	7
Injection site or treatment reaction	6
Throat related issues	6
Dry mouth	6
Tinnitus	5
Injection site pain	5
General - Other	4
Nose bleeds	4
Urinary issues	3
Musculoskeletal	
Joint & Bone aches, pains & stiffness	66
Back pain	27
Hands and Feet issues	7
Muscle weakness	6
Musculoskeletal pain (General)	6
Cramp	5
Muscle aches, Pains & Stiffness	4
Gastrointestinal	
Nausea	39
Diarrhoea	24

Stomach pain	10
Vomiting	10
Constipation	7
Bloating	6
General gastro issues	5
Indigestion, acid reflux	4
Skin	
Hair loss	29
Hair thinning	14
Skin - Other	13
Nail problems	10
Rash	8
Itchy Skin	8
Dry Skin	5
Redness	5
Nervous system	
Numbness, tingling, burning	32
Headaches	14
Dizziness, balance, cognition	11
Change in taste	8
Blood and lymphatic	
Blood - Low counts	24
Clots	10
Lymphoedema	1
Cardiac and vascular	
Hot flushes + Sweats	25
Cardiac events	7
Vein issues	3
Respiratory	
Shortness of breath	14
Cough	4
Respiratory - Other	4
Psychiatric	
Sleep	16
Reproductive system	
Reproductive related issues (e.g. vaginal dryness)	5
Immune system	
Immune system related issues	2

6.2.1.1 General disorders

Issues categorised within the general disorders had the highest number of codes assigned and included issues relating to fatigue and tiredness, ear, nose, and throat related issues as well as issues relating to generalised pain. A total of 286 codes were assigned within this category. Fatigue/tiredness was the most frequently mentioned issue within this category with 109 instances coded. User:4474 explored their feeling of tiredness, posting they '*Feel a bit tired but that could be a) because of the current chemo, b) because of last year's chemo, c) because of the radiation earlier this year or d) all of the above.*'. Highlighting not only that tiredness was an issue for them, but also their desire to understand or make sense of the problem. Other users reported fatigue as being an immediate side effect of treatment and feeling in a state of '*general zombie-ness – User:4517'* lasting up to 4 days a week.

Ear, Nose and Throat (ENT) related problems were also found to be prevalent within the forum. Users reported having experienced sore mouths, mouth ulcers and osteonecrosis whilst receiving treatment for MBC. In most cases, sore mouth caused pain, difficulty eating and infections. In extreme cases, it was described as having had the '*skin stripped off, exposing the never endings of their tongue – User:4251'*. ENT related issues also included dry mouth and nose bleeds, however these were less common.

General Pain was the third most common issue within this category. Though many of the users specified the pain they were experiencing, this code existed for the times when there was limited indication of what or where the pain was being experienced. As a result, general reports of pain were coded as such. An example included one User:4521 reported having 'some aches and pain' but overall felt okay physically. User:4369 was receiving Paclitaxel and reported experiencing 'aches and pains' as well as numerous other side effects. Pain was a common problem that was experienced by many Users, with specific pain such as back pain, coded under the body system in which they impact.

6.2.1.2 Musculoskeletal

Within the musculoskeletal subcategory, a total of 121 codes were assigned to problems relating to the joints, bones, and muscles. The majority of codes were linked to pain, specifically back pain, as well as more general joint/bone pains and some muscle pain and weakness. Back pain commonly discussed as a result of metastasis to the spine both pre and post diagnosis of metastatic disease. Users reported experiencing 'dreadful backache' prior to their diagnosis but have since seen improvement, whereas other Users reported chronic back pain that impacts their ability to maintain employment.

Other, more general issues with bone and joint pain were frequently discussed. Joint aches and pains were very common with some Users specifying that their issues were located in the hips or legs. These types of issues were shown to impact on the Users daily life with many reporting difficulties with walking and reduced mobility in their arms due to pain, however the level of pain varied from User to User. Muscular related problems were less prevalent within the forum when compared with skeletal issues, however, were reported by a small number of Users and included muscle aches, pains, stiffness, and weakness. When considering the overall prevalence of 'Pain', it was referenced 122 times making it a leading issue identified across the forum.

6.2.1.3 Gastrointestinal

Eight categories emerged within gastrointestinal system. Nausea was by far the most common issue within this domain. One user reported suffering from 'intense nausea', however most users did not specify the degree in which they were impacted. The sharing of information relating to the management of this side effect was common, users often shared advice or commented on how they managed this side effect. For example, one user reported they were 'trying to eat small amounts but often enough' to combat the effect of nausea whereas other shared details about the anti-emetics they were using 'I've resorted to metoclopramide for my nausea'.

References of diarrhoea were mixed, with some users reporting having 'dreadful' or 'severe' bouts, one of which led to hospitalisation '*Ended up at A&E to be hooked up to fluids. I just about managed to stop the diarrhoea using codeine tablets - User:4398*'. Those reporting more negatively were posting within the capecitabine message thread, '*I have had two cycles of cape but had to stop halfway due to severe diarrhoea - User:4129*'. Users on other treatments such as abemaciclib and fulvestrant or epirubicin reported a lesser impact, finding diarrhoea to be a manageable side effect. However, overall, it appears to be a side effect that impacts individuals differently irrespective of the treatment.

Stomach pains and vomiting were each referenced 10 times. Stomach pains appeared to be a side effect of treatment, however for one user it was a sign of progression, following '*horrendous stomach pain*', multiple tumours were found within their small intestine.

6.2.1.4 Skin

Skin related issues were also common with 92 codes. Hair loss, as well as hair thinning, were the leading issues within this category. Some Users reported their hair fell out slowly over the duration of their treatments, whereas others reported the rapid and somewhat distressing way it was lost. User:4474 talked about how their hair ‘came out in huge handfuls’ every time they washed and/or brushed it, and this occurred after the first cycle’. However, not all cases were as extreme, with several Users reporting their hair had thinned, this was particularly the case in threads related to Target therapy such as palbociclib and ribociclib.

6.2.1.5 Symptom burden - other

Whilst all issues experienced by the users are important, the remaining issues were discussed less frequently within the forum. Neuropathy was of a particular concern to users with 32 references. This included problems with numbness, tingling and burning sensations in their extremities. Menopausal issues included hot flushes and sweats were also commonly discussed across the forum (25). Other key issues included the impact of treatment on blood counts (24), as well as issues with sleep (16) and shortness of breath (14).

6.2.2 Psychological experience

Issues relating to psychological experience resulted a total of 188 codes being assigned to this domain of the Generic Choice Model. As with the physical symptoms, the psychological issues were further subcategorised to provide an overview of the types of issues being discussed within the forum Table 29. The number of codes for psychological issues were significantly lower that symptom related issues, however, the section of the forum analysed was focused on ‘treatments medical issues’ so was to be expected. The number of codes was however significantly higher than in the other domains of the GCM.

Table 29. ***The most common issues categorised within the psychological experience domain.***

Issue	N
Anxiety - Medical	27
Fear	26
Treatment related fear	18
Shock - Diagnosis	17
Difficulty coping	12
Uncertainty	11
Shock - Progression	10
Depressed mood/feeling sad	10
Anxiety - Progression	10
Worries	9
Anxiety - Side effects	8
Mood Disturbance	7
Psychological - Other	5
Difficulty thinking positively	4
Stress	3
Fear of unknown	3
Family concerns	2
Depression	2
Anxiety - General	2
Shock - Treatment	2

6.2.2.1 Anxiety

Anxiety existed across multiple areas and domains with the three most cited areas being medical anxiety followed by anxiety about disease progression and treatment side effects. Medical anxiety related to undergoing medical procedures, starting new treatments and waiting for, or receiving results. Scan related anxiety or 'Scanxiety' as it is often referred was common, with many Users reported having experienced anxiety when waiting for their scan results, '*Scan time is so full of anxiety (scanxiety) – User:4066'*. This type of anxiety was also seen in Users receiving less frequent scans, in that the anxiety of not being scanned was also an issue with one User reporting their break of 15months without a scan cased them to experience anxiety. Similar findings were seen in those having a break in treatment whereby their lack of active treatment during a three week break also produced feelings of anxiety.

Anxiety surrounding disease progression manifested in different ways across the users. For some, the anxiety existed as a direct result of a physical sign of progression, for example, users who felt pain or discomfort in their bones were anxious that the disease had progressed '*Started to get rib pain with no history of failing/injury…worried it's the cancer back – User:4204*'. For others, anxiety was a result of 'what if', for example, one

user was reluctant to take pain relief as they felt this could 'mask something' that they needed to be aware of, and thus signs of progression being missed.

6.2.2.2 Fear

For Users of the forum, the combined psychological experience most referenced was fear. Fear was categorised into general, and treatment related fear. General fear consisted of issue relating to the future and the fear of the unknown as well as feeling afraid and scared in the current moment. One person found themselves to be uncharacteristically afraid stating '*I feel absolutely terrified at the moment and I'm known for being calm – user:4023'*, whereas others reported they feared what the future had in store for them. Fears were shown to impact the wider psychological state of the users whereby they were 'struggling to stay positive' as they were scared.

Another source of fear stemmed from treatments. For many this was a fear of having to stop treatment and/or running out of treatment options. Despite the clearly distressing nature of this topic, Users were on hand to acknowledge this fear as well as to offer reassurance. In response to one User stating, '*they were scared that they were at the end of the line – User:4499'*, User:4113 responded with supportive comments, 'it is one of our fears that we have run out of options, but it sounds like there are new drugs being trialled right now for ladies such as ourselves'. These results show the power that fear has among women living with metastatic breast cancer.

6.2.2.3 Shock (Diagnosis)

Shock was a common issue experienced by the forum users and was categorised into three subthemes, including shock relating to their diagnosis, shock around disease progression and shock around treatments. There were 17 instances of users discussing the shock of receiving their diagnosis of metastatic disease. For many it was not something that they had anticipated as they had previously been successfully treated. For others, the shock came when they were informed of disease progression. These users expressed a level of comfort they had developed as a result of a long and successful management of the disease and thus the resulting news of progression came as a great shock to them. There were two counts of treatment related shock which included shock of having no further treatments available to them.

6.2.2.4 Psychological - Other

Other notable psychological problems identified included, difficulties coping with the illness and/or treatment (12), finding it difficult living with the uncertainty (11) and feeling sad or in a depressed mood (10). The remaining psychological issues were reported fewer than ten times within the forum and can be found in Table 29.

6.2.3 Generic Choice Model - Other

The remaining domains of the Generic Choice Model (GCM) saw a fewer number of issues being identified (Table 30). Clinical services and support pathways each had four issues assigned. Lack of support/trust in HCP and poor communication with HCP were referenced 15 and 13 times respectively. Support pathways saw issues relating to the impact it had on their family life (8) and the reduced levels of social support they have received (6). Reduced ability to work was the most common issue relating to work, finance and benefits (12). The reduced ability to participate in leisure activities and the loss of normality and independence were the issues associated with independent living domain. Although these issues are less common, the results are in line with the issues included in Phase I of the questionnaire development.

Table 30. ***The most common issues identified within the Clinical service, Support pathways, Work and independent living domains of the GCM.***

GCM Domains	N
Clinical services	
Lack of support/trust - HCP	15
Poor communication - HCP	13
Stopping/Changing treatments	5
Reduced treatment options	5
Support Pathways	
Impact on family life	8
Reduced social support	6
Lack of understanding	5
Impact on social activities	3
Work, Finance and Benefits	
Reduced ability to work	12
Medicalised lifestyle	3
Financial difficulties	1
Independent Living	
Impact on hobbies / leisure	6
Loss of normality	5
Loss of independence	2

6.2.4 Triangulation of results

In addition to identifying the issues reported with the online forum, the objective of this study was to compare the findings with those of the systematic review and the Phase I data. This was achieved via the triangulation of the three datasets to explore the similarities and differences between the type, and frequency of the issues identified by each method. The Generic Choice Model was the conceptual framework used across each of the datasets and facilitated the triangulation of the results. Table 31 shows the total count of issues identified for each data set, categorised by the conceptual framework.

Table 31. ***Comparison of the number of issues stratified against the Generic Choice Model across the online forum, Phase I and systematic review datasets.***

Generic Choice Model Domain	Online forum data (%)	Phase I data	Systematic review data
N	92 (100)	185 (100)	305 (100)
Symptom Burden	58 (63)	93 (50)	161 (53)
Psychological experience	20 (22)	68 (37)	91 (30)
Support Pathways	4 (4)	10 (5)	29 (10)
Clinical services	4 (4)	2 (1)	5 (2)
Work, Finance and Benefits	3 (3)	6 (3)	6 (2)
Independent Living	3 (3)	6 (3)	11 (4)

Results indicated consistent findings and trends in the types of issues identified across the datasets, whereby physical symptoms were most common followed by psychological issues. The online forum data saw a higher proportion of physical issues compared to the Phase I and systematic review data. This may be due to the nature of the forum and the analysis of only the 'Treatments and medical issues' section. Higher proportion of psychological issues in Phase I data suggests these types of issues are important and that perhaps patients find it difficult to spontaneously generate these types of issues. Issues related to the patients support pathways were more prevalent with the systematic review data with double the number of issues being found compared with the online forum and Phase I data, likely due to the inclusion of psychological intervention studies.

Phase I data were different in their inclusion of wider issues beyond physical symptoms, namely psychological/existential (worries, fear, family impact) and daily/physical activities. Both online forum and systematic review data provides good support for including wider psychological issues as 22% and 30% of the issues in Table 31 were classified as psychological. In addition, qualitative data from the online forum supports the importance of those issues and justifies their inclusion in the MBC module.

When exploring the issues at an individual level, similarities and differences were found across the three datasets. Table 32 highlights the top 15 issues reported across the online forum, Phase I and systematic review data. For the online forum and systematic review, the top issues were determined by their frequency, for instance, the higher the rank, the more frequent the issue was reported. The Phase I data is ranked by importance, in that the higher the rank, the more important the issue was to the patient.

Table 32. The top 15 issues* identified across the Online Forum, Phase I and Systematic review.

Rank	OF - Highest frequency	Phase I - Most important	SR - Highest frequency
1	Fatigue Tiredness	Strenuous Activities	Fatigue
2	Joint & Bone aches, pains & stiffness	Hair loss	Nausea
3	Nausea	Fear of disease progression	Diarrhoea
4	Numbness, tingling, burning	Worried about family	Vomiting
5	Hair loss	Treatment side effects	Alopecia
6	Anxiety - Medical	Worries about the future	Pain
7	Back pain	Worrying	Stomatitis
8	Fear	Fear leaving family behind	Constipation
9	Hot flushes + Sweats	Pain	Asthenia
10	Diarrhoea	Fatigue	Arthralgia
11	Sore mouth	Reduced daily activities	Headache
12	General Pain	Long term health concerns	Rash
13	Treatment related fear	Feeling weak	Cough
14	Mouth Ulcers	Difficulty walking long distances	Dyspnoea
15	Shock - Diagnosis	Impact on family life	Hand–foot syndrome

OF, Online Forum; SR, Systematic Review. *Issues relating to non-self-reporting issues i.e. anaemia and neutropenia were excluded from this table. Individual colours are arbitrary, used to indicate a shared issue across the datasets. Issues in black were not seen in the top 15 issues presented in the other included datasets.

The top issues across each dataset were shown to differ in the types of issues they contained. Issues relating to both symptom burden and psychological experience were found to be important to patients in the Phase I data. Eight issues were categorised as symptom burden, six as psychological and one as relating to support pathways. This pattern in the types of issues included was not seen in the remaining datasets. The higher proportion of psychological issues in Phase I data may indicate that patients find those types of problems difficult to spontaneously generate, or that they find it easier to talk about physical symptoms.

In the online forum and systematic review data, physical symptoms were more frequent, i.e. those categorised as symptom burden. The online forum data consisted of 11

physical symptoms and four psychological issues, whereas the most frequently reported issues identified by the systematic review contained only symptom burden related issues. With regards to the individual issues, comparing the three datasets using colour to indicate a match, the results showed the online forum data to be the most comprehensive of the three sets of data. Twelve of the 15 issues in the online forum list were also found in at least one of the other datasets, indicating that online forums provide comprehensive coverage of the issues women with MBC experience. The three issues not included within the other datasets included those related to neuropathy, the menopause and shock.

The issues related to physical and daily activities in Phase I do not appear directly in the other sources. This could be related to the coding of the issue, as the Generic Choice Model does not have a separate category for physical functioning and instead those problems may be closest to the domain of Independent living. With regards to the module, reduced daily activities, long walks and strenuous activities are covered by the core questionnaire (EORTC QLQ-C30), and will therefore be included in the assessment anyway.

When comparing the issue lists, three key issues were observed. These included fatigue, pain and hair loss. Fatigue was ranked as the most commonly discussed and reported issue by both the online forum and systematic review and was ranked as the tenth most important issue by patients in the Phase I data. General pain was a common issue across each dataset with the addition of back pain being ranked highly within the online forum data. Hair loss was ranked as the second most important issue to patients in Phase I and was ranked fifth in both the online forum and systematic review data. These three issues offer a thread in which all three sets of data are connected and provided support for the use of online forum data in the generation and identification of the issues experienced by MBC patients.

Lastly, I looked at whether the physical symptoms frequently appearing in the online forum would be covered by the new provisional MBC module. Almost all of them are included, except “treatment related fear” (although items on fear of the future, but not specific to treatment are included) and “Shock at diagnosis”. The high frequency in which shock of diagnosis was reported within the forum is an important finding in itself as it perhaps indicates a lack awareness that their breast cancer could return. However, its omission in the module is acceptable, as this is an acute issue at a specific time point within the illness trajectory and may not be conducive to being assessed over time.

6.3 Discussion

This study utilised a novel source of data to investigate the quality-of-life related issues spontaneously discussed by metastatic breast cancer patients and attempted to compare its findings with traditional sources of data. The results of the study were important in providing a new insight into the issues and problems women living with MBC experience as a result of their cancer and/or treatment. The research findings add to that of the scientific research conducted as part of this thesis, as well as the wider scientific community. The results supported the need to include physical problems in the module, as well as highlighted the importance of the inclusion of wider psychological issues, which were frequently discussed even in the section on Treatment and medical issues.

The modern patient has become more self-sufficient, taking greater control of their care, particularly with regards to self-help and self-management. Online forums have been shown to facilitate this by providing a platform from which patients can communicate in an anonymised space with fellow individuals sharing their experience. This study has shown the value, and potential, online forums have within the realm of health-related research by highlighting the application of the large quantity of real-world data available.

The results provided evidence that patients living with and being treated for metastatic breast cancer experience a wide array of issues which impact their quality of life. The issues identified were not limited to the symptoms and side effects associated with their treatment and/or disease but also spanned psychosocial domains. The identification of issues experienced by patients is a critical step in the development of patient reported outcome measures (PROMs) and the data extracted from the forum has been shown to be an effective method for generating a comprehensive list of QOL related issues. This finding highlights the potential inclusion of this method within the future development of PROMs [298, 313], specifically as an additional method of data collection when developing PROMs for rarer cancers.

Online forum research has recently shown to be a useful approach for the collection and pharmacovigilance of adverse event data in rare cancers, where levels of available data are limited [298]. Within the development of PROMs for rarer cancers, similar challenges surrounding the paucity of available data exist, and therefore the application, and integration of the online forum review methodology within the early stages of questionnaire development, may facilitate the identification of a more issues and/or adverse events that these patients experience. Further to this, if conducted in parallel with a traditional review of the literature, it may help significantly improve the range of

data that is collected. The online forum data could then be cross checked against that of the literature, with any new issues or adverse events being included and analysed in the Phase I interviews.

Overall, the application of this methodology in the generation and identification of issues has wide reaching benefits during the initial phases of questionnaire development. Physical issues relating to symptom burden were the most frequently discussed issues and included items such as fatigue, joint and bone related aches and pains, nausea, and neuropathy. This was largely expected as the forum message board analysed within this study was focused on the treatment and medical issues associated with MBC. Interestingly, despite the strong focus on physical symptoms and side effects within this section of the forum, many psychological issues were also identified. This suggests patients may not see their issues as singular events that occur in isolation but instead, view them in a holistic manner whereby physical symptoms also have a psychological impact. This is important to consider as often the psychological impact on the patient may live on with the patients beyond that of the physical issue and is overlooked during treatment.

Previous research has claimed online forums offer an advantage of traditional research methods such as interviews and questionnaires as the provided a greater insight into the patient's attitudes and perceptions of their condition [314]. To assess this claim, triangulation analysis of the data collected throughout this thesis was conducted. The results looked at the overall comparison of the types of issues, as well as the most common issues, identified across the different datasets. Overall, results were consistent across the datasets with regards to the types of issues reported, however the online forum data saw a higher proportion of physical issues compared to the other datasets. This may be due to the nature in which the forum is structured. With designated threads for the discussion of treatment and medical issues, the discussion of such topics is focused, allowing users to engage in conversation about more of the issues they experience.

Whilst being beyond the scope of this study, the ways in which Users interacted and utilised the forum was noted throughout the analysis. Users may have found some relief in discussing the issues they were experiencing; however, it was clear from the review that this was not the only function of the forum. Some turned to the forum for advice, and others used the forum as a platform to share their knowledge and experience to help those going through a shared experience.

The findings from this study provided valuable information about the quality-of-life related issues experienced as a result of living with and being treated for metastatic breast cancer. The results fed into the wider context of the thesis with regards to using novel methods to support the traditional methods used throughout the development of the questionnaire. The results also supported the content chosen for the MBC module. A strength of the study was the ability to draw on such a large quantity of real-world data, which enabled the exploration of a wide range of themes and topics relevant to this patient group.

The scale of the available data for analysis can largely be seen as a positive of conducting research into online forums however the large quantities of data posed challenges in both the management and analysis in my thesis. The manual process was very time consuming thus limiting the number of message boards included in the analysis. Whilst this method yielded interesting findings, and facilitated the analysis of large quantities of qualitative data, any continuation or development of this work should strongly consider the use of artificial intelligence or similar methods to facilitate the analysis of such vast quantities of data [298].

A common limitation of this form of research is the reduced ability to define the included sample. Great care was taken in the planning of this study to ensure that the sample was controlled and limited to only those diagnosed with MBC. The selection of the BCN forum played a part in this as its structure provides a designated space for those with MBC to communicate. Any posts or comments made by primary breast cancer users were not included in the analysis. The reduced ability to define the sample increases the potential risk of bias. This limits the scope of the method and its current application, to that of a supportive or supplementary method within the questionnaire development process, as traditional sources of primary data such as that published in journal articles and collected via interviews remain the gold standard approach as they do not suffer the same limitations [315]. The role of the online forum method does however show promise within this field in its ability to replicate similar data to that obtained via interviews and the literature.

Regarding the overall integration of this work within the thesis, the timing in which this review took place limited the impact it had on the development of the module. On reflection, if this work had been completed prior to the Phase I interviews, it would have provided an additional strength to the work and the module and issues could have been better integrated. This however was not possible due to the wider project demands and the time pressure associated with conducting the Phase I interviews. This work was still

of value as it provided supportive and confirmatory evidence for the issue included in the module. The depth of information available within the forum goes beyond what was utilised in this research study. The content analysis determined the types of issues users experienced and facilitated achieving the aims of this study, there is scope to gather more in-depth information about specific treatments to identify gaps or disparity between the known issues reported within the clinical literature and those being discussed on the forum. For example, this could be of importance when new drug treatments have become available and limited clinical study data is available.

Further to this, future work in this area should investigate the ways in which people interact and use the forum. Whilst coding the data, themes began to emerge regarding the 'type of forum user' interacting with the site. The needs of the user appeared to differ, with those at the start of their metastatic journey using the forum in different ways compared to those who had been living with metastatic disease for longer. This is important as more and more patients turn to the internet for health-related information and support, further research could help to improve and validate the information available, and ensure online forums continue to be a valuable source for patients.

6.3.1 Conclusion

Online forums provide a valuable source of real-world data relating to the quality-of-life related issues experience by those living with MBC, that can be used to support that of which is presented in the scientific literature. The identification of a comprehensive list of issues provides evidence that online forums not only offer a novel source of data but also may play a role in the future of health-related research, in particular, within the early development phases of patient reported outcome measures.

Chapter 7. Discussion

The overall aim of this PhD was to further our understanding the quality-of-life related issues women living with, and being treated for, metastatic breast cancer experience. The objective was to use this knowledge to deliver an international tool for measuring the QOL of these patients. It was hypothesised that the heterogeneity and prolonged treatments associated with MBC would result in a range of treatment and disease related symptoms and side effects, as well as having a wider psychological and social impact on the patient's life. This final Chapter presents the overall discussion and conclusions of the thesis, highlighting the key findings as well as the implications of the work. Following this, the strengths, limitations and future directions of the work is discussed and closes with a reflective account of my PhD journey and the final conclusions of the project.

7.1 Key findings

Five research questions were outlined in Chapter 1. The key findings from the work completed in the thesis are presented below with reference to the research questions they addressed.

Firstly, the thesis looked to determine the issues patients with MBC experience as a result of their disease and/or treatment as indicated within the available MBC literature. Chapter 3, the systematic review, identified 305 issues spanning multiple domains. Overall, physical symptoms were most prevalent, specifically those relating to the gastrointestinal system, for example nausea, diarrhoea and vomiting. A number of psychosocial issues, such as, fear of progression, anxiety and depression, difficulty sleeping and issues relating to body image were also reported, however these issues were more commonly reported in non-CTIMP studies. Further to this, the review highlighted multiple measurement tools used in the assessment of QOL in this patient group. The most frequently used measure was the EORTC QLQ-C30, and no specific MBC measure was identified across the literature.

Secondly, the research question relating to the perceptions and significance placed on these issues by patients and Healthcare Professionals (HCPs) were addressed in Chapter 4 (Phase I). In this Chapter, Phase I built on the findings of the systematic review and provided new data that highlighted the most relevant and important issues from the perspective of the patients and HCPs. For patients, issues related to hair loss and treatment side effects were among those rated highly for their importance. Worries and fears surrounding disease progression, the future and their families were also found to

be a priority to patients based on their relative importance scores. These findings were reflective of the wider literature and encompassed the QOL related issues across the various phases of the disease trajectory [70]. Analysis of Phase I data resulted in a total of 44 core issues selected for inclusion in the provisional questionnaire. In addition to the main results of this phase, evidence supporting the use of the EORTC QLQ-C30 within MBC was provided with patients rating its included items with high relevance and priority.

Thirdly, the thesis sort to take the steps towards delivering better measurement of QOL in this patient group. The lack of a MBC-specific questionnaire was identified across the literature (Chapter 3) and the prioritisation of the more relevant and import issues was conducted in Chapter 4. Chapter 5 built on this further with the development of a provisional questionnaire consisting of 44 items that assessed 40 core issues. Upon its completion, this MBC-specific questionnaire module is to be used in combination with the EORTC QLQ-C30 to provide a more inclusive assessment of the issues these women experience.

Finally, this thesis looked at how alternative data from an online forum could be integrated into the process for developing health-related questionnaires. Chapter 6 supported the work conducted in previous chapters and was used to enrich the data by identifying the most common QOL related issues experienced. The data were compared with that collected in the systematic review and Phase I interviews to determine whether differences existed across the three datasets. This was an important question as the reporting of symptoms on a platform where patients freely able to discuss their symptoms and side effects with 'peers', opposed to clinical or research personnel, may have yielded different results. The findings of the review found physical symptoms (e.g. fatigue) to be the most commonly discussed withing the forum. This was followed by psychological experiences, such as anxiety and fear, supporting previous findings of the systematic review and interview study. The triangulation analysis provided complementary data for the issues included in the provisional questionnaire, as well as highlighting a greater number of psychological issues were ranked highly in the Phase I data, compared to the review data. These findings suggest that online forums can provide high value data when assessing QOL in MBC and thus are a viable methodology to consider in the development of PROMs.

A key deliverable from this thesis was the development of a 44-item disease-specific questionnaire for assessing QOL in MBC. The need for a tool to better assess QOL in this patient group has been documented [5, 25] and supported by previous research, including the findings of the systematic review presented in Chapter 3. The lack of a disease specific measure results in the reliance of generic, or general breast cancer

questionnaires to assess QOL of MBC patients. The consequence of which may result in a less sensitive assessment due to the omission of the specific issues faced by those living with advanced disease [156, 268]. This thesis addressed this issue by developing a new questionnaire that contains the most relevant and important issues to those with metastatic disease and aims to deliver an improved assessment of QOL in this patients group.

The development of the questionnaire would not have been possible without the successful delivery and management of the wider EORTC Quality of life group project. I was successful in coordinating the recruitment of 187 patients and 41 HCPs from multiple countries around the world. The recruitment figures exceeded the targets outlined prior to the study, which indicates the drive and desire of the collaborating sites to promote this much needed research for this patient group. My ability to coordinate this large scale international project was an achievement to be proud off, as it was a very complex and challenging task to have undertaken as part of my PhD. However, having overcome the obstacles put before me, I have been left with a wealth of experience and a series of strong professional relationships with new colleagues from around the world. This is something that I feel was invaluable throughout my PhD and something that I hope to continue to build upon in the future.

In the process of developing the new questionnaire, this project provided evidence not only of the types of issues experienced but also of the patient priorities towards QOL. Much of the previous evidence has reported symptoms and side effects, which has provided an overview of the most common issues experienced [48, 316], however few have expanded this knowledge to determine what the issues mean to the patient [317]. Although it is imperative to resolve these types of issues as they arise, having a better understanding of what is important to the patient, which in this case are the psychological issues associated with living with, and being treated for MBC, may help shape consultations and result in a more patient centred approach to their care. The results of this thesis hope to inform those providing treatment and care to those with MBC of the relative importance patients place on the wider psychological issues impacting their QOL.

7.2 Strengths and limitations

A strength of this thesis was the large and diverse multi-cultural sample from which Phase I data was collected. Having a large sample reduces the margin of error when reporting the results and allows for greater generalisations to be made about the data [318]. The inclusion of a smaller sample may have resulted in the development of a less

representative questionnaire due to higher variability, and potential for bias within the data [319]. A sampling matrix was designed and implemented within this research to mitigate these limitations by facilitating the inclusion not only of a large sample but also a sample representative of the target population. The multi-cultural nature of the sample provided further strength to the study.

The inclusion of patients from a range of cultures was of particular importance in this thesis as the resulting questionnaire was to be used on an international scale and thus must be shown to have high content equivalence, whereby the issues addressed by each item is relevant across each culture [320]. The sample included participants from a range of nations, languages and cultures to capture the relevant data and improve the cross-cultural validity of the study. The inclusion of non-European centres in Phase I was not a requirement of the EORTC module guidelines however, I felt it important that at least one non-European centre be included as early as possible in the development process. This was to ensure I captured data from a range of different cultures and languages and not just limit this to a European demographic. I was able to include two non-European countries, which included three centres in Japan and one centre in Jordan, both of which were able to provide important data used in the development of the module. Further testing of the questionnaire in other countries is required to determine its performance and validity, which is to be conducted independently of this thesis.

Beyond the benefits seen in Phase I and data collection, the addition of non-European sites provided important feedback when selecting items for inclusion in the questionnaire. The feedback provided by the centre in Jordan facilitated an interesting and important discussion regarding the items relating to sexual activity and whether or not it was acceptable to include these within Arabic nations. Identifying issues such as this within the early phase of the development allows for their resolution prior to the finalisation of the questionnaire, when it is more difficult to make changes. This is an issue recognised by the EORTC who have since updated the module guidelines to reflect this.

The value of working as part of a multidisciplinary has been widely demonstrated in the clinical care of individuals with cancer, with studies showing survival benefits of patients when this method of working is adopted [321, 322]. Within research, the benefit of this approach has been displayed in this thesis as it provided expertise in different areas that could be called upon and utilised over the course of the project. The discussions that occurred during the development phases, particularly during the issue selection and the item generation phase, were essential to ensure a high quality questionnaire was developed. For instance, coming from a non-clinical background, the ability to be able to

learn and gain knowledge from clinicians leading their field in their respective countries was invaluable. Further to this, having experienced academics with expertise in questionnaire design and other methodological expertise was of particular benefit when selecting the issues and items for inclusion.

The thesis successfully integrated a mix of methodologies to achieve its aims in expanding the knowledge of QOL in MBC and providing a tool with the potential to better measure the QOL of women living with and being treated for metastatic breast cancer. The inclusion of the conceptual framework throughout the thesis enabled the triangulation of results and the integration of methodologies that enriched the data collected throughout thesis, facilitating the development of a comprehensive and robust provisional questionnaire.

A strength of this thesis was the application of novel methods to enhance existing methodological frameworks used in the development of PROMs. For example, the introduction of the Investigator Brochure (IB) review and online forum analyses highlighted how new methods can be integrated into the development process. The IB review proved to be a highly effective and efficient way of synthesising data relating to the physical symptoms and side effects associated with current treatments and offers an alternative approach to collecting this type of data. Traditionally, systematic reviews of the literature are conducted to identify and extract similar data from Phase III randomised clinical trials and whilst this approach is considered the gold standard for synthesising data, the needs of questionnaire development may in fact be better suited to that of IB reviews. A limitation of the IB methodology is the less comprehensive approach which may result in missing issues, however with the inclusion of patient interviews, it could be argued that these potentially missing issues would be identified at this point in the development process.

Further to this, the work conducted on the online forum provided a promising insight into how new and alternative sources of data can be collected, analysed and integrated into the development methodology of PROMs. This methodology provided support for the use of real-world data, in the form of online forums, in the generation and analysis of data to identify the quality of life related issues women with MBC experience as a result of their treatment and/or disease [299]. Its application, coupled with ongoing research in the area to improve and automate the methodological processes, may prove to be a vital approach in the development of future questionnaires, particularly those developed for rarer cancers and/or diseases.

7.2.1 Limitations

The collection of socio-demographic information was kept to a minimum in this study as they were not intended to be included in the analysis, instead they were used to describe the sample. A limitation of this minimalistic approach was the omission of data pertaining to the ethnicity of the sample. While not specifically relevant to the aims of the research, it is acknowledged its inclusion would have aided in providing additional context to the included sample. This is something that should be addressed in future phases. Further to this, additional information with regards to the clinical characteristics of the patients could have provided a more detailed description of the included sample. It is recommended that in future phases, a more detailed clinical demographics form should be used, for example, with the inclusion of the molecular subtypes of the tumours and more details on the treatments.

The systematic review covered a multitude of papers, including CTIMP and Non-CTIMP studies which provided great strength to the review in regards to its comprehensive coverage of the literature. A drawback of this approach was that time and resources invested was also high, and with the time pressures of the overall project, the review was not published at the time of completion. Having completed the review, focus was then on starting the Phase I interviews. As a result, the publication of the review was delayed which ultimately proved to be problematic when it came to publishing a manuscript at a later date. The search became 'out of date' quicker than expected as the last 3 year witnessed a large number of new drug treatments for MBC entering clinical practice.

In the time between conducting the search and writing the publication, many new clinical trials were published on these newly available treatments. As previously discussed, the impact of this influx of new research was of concern to the development of the module, in that new treatments may have new side effects associated with them. In the thesis, this was mitigated with an update to the investigator brochures to include the most up-to-date information from the available treatments and an update to the systematic review to include the new CTIMP trials published within that timeframe. Results indicated that 'sore mouth' was a potential issue of concern and was subsequently added to the module to be assessed in Phase III. With regards to the publication of the review, it was determined that a full update to the search was required to ensure all new evidence was included. Plans are in place to complete this updated manuscript following the submission of the thesis, the CTIMP search has been updated and the papers screened. The next steps are to extract the data and update the results of the main systematic review.

Patient interviews with subsequent descriptive quantitative analysis were useful in allowing patients to have their say on the issues they experienced and enabled me to ensure the list of issues included in the issue list survey was comprehensive. This approach was taken for consistency as there was no opportunity, financially or available resources, to transcribe the interviews conducted in the other languages. Whilst this achieved the objectives outlined in Phase I, I feel that there was an opportunity to have explored this data further with transcribing of the interviews and a more detailed thematic analysis within my PhD. Had the interviews been transcribed this may have provided greater scope for the data to be analysed further. This is an idea that could be developed further following my PhD. However, despite this limitation, the benefit was that I was able to focus my time and resources on completing the online forum work, which proved to offer interesting and beneficial results.

It was planned that phases I-III would be completed as part of this project, however due to delays caused by the COVID-19 pandemic, it was not feasible to complete the third phase. Despite these delays, I was able to deliver Phases I-II of the project. Phase III is to be completed by the study team. The protocol for Phase III has been approved as it was part of the original submission process and will be updated with the new EORTC module development guidelines.

Whilst the online forum provided interesting data, the methodological approach to extracting and coding the data limited the scope of the study. The manual approach limited the number of forum threads that could be analysed which may have not been as inclusive of all issues. Future work should strongly consider the use of automated processes for extracting data from the forum, this may include the use of artificial intelligence or data mining techniques [125, 323]. The wealth of information available within online forums offers a huge potential for future health research and methods for collecting and extracting this type of data should continue to be developed.

7.3 Implications

Whilst the inclusion of PROMs in clinical research is well established, the choice of measure used can vary [93, 324], with researchers considering the strengths and limitations of their choice. However, research has shown that the selection can also depend on lessor reasons, such as geographical location, for example, trials designed in the USA are more likely to select the FACT-G, compared to European trials that used the EORTC QLQ-C30 [156]. It is important to select measures on empirical evidence, of which, the results of Phase I (Chapter 4) provide support for the use of the EORTC QLQ-

C30 and its inclusion due to the fact its items were shown to score highly for their relevance and importance to this patient group. This finding is of importance to those designing future clinical trials as the inclusion of QOL as study endpoints, as the selection of the right measures is essential for the collection of valid and impactful data. Knowing this, the choice the EORTC QLQ-C30 coupled with the newly developed MBC specific measure is likely to provide robust QOL assessment in this patient group. Further research would be needed to compare the new EORTC measures with other measures such as the FACT-G and FACT-B. This may help to standardise the research, making comparisons between studies easier.

Data obtained by the MBC-specific questionnaire will provide key information for regulators looking to implement new treatments for MBC, the results of which may also impact labelling claims of new drugs. This is of importance within the metastatic setting due to the fact new treatments for breast cancer often begin testing with these patients [325, 326]. Therefore, a detailed understanding of the wider effects the new drugs have on QOL is a critical component of the decision making for the rollout and administration of the treatments.

The impact of my research may also prove beneficial within clinical practice as well as clinical research. Having highlighted the importance of psychological issues to the patients, additional support within the clinical environment may be of use in this patient group. The significance of the high number of psychological issues perhaps indicates a shift in priorities as patient begin to come to terms with their own mortality and what this means for the wider aspects of their life, such as their family and friends. Whilst the delivery of interventions to deal with these problems may be challenging to implement during the current climate with additional pressures continually added to clinical practice, a greater awareness and understanding of the challenges these women face is not something that should be ignored.

Often the priority to the clinician or healthcare team is the preservation of life, with a focus on the treatment of physical symptoms and side effects in order to support the patient to live longer and more comfortably. Within the metastatic setting, a shift towards a more holistic approach to treatment is recommended to ensure the wider needs of the patient are met, particularly as MBC patients often report feeling forgotten and/or left behind [70]. This current research highlights the broad range of issues that go beyond the physical issues and symptom burden and therefore, if we are to better support MBC patients through their journey, a wider view of the issues is needed. This is a challenging aspect to manage and would likely call on third sector organisations to help bridge this

gap, but ultimately this problem will continue to grow and the provisions for support should be embedded within clinical practice. The development of the MBC-specific questionnaire may aid healthcare professionals to better identify the areas in which the patient needs greater support, this could be either the physical side effects of treatment and/or psychological burden of living with an treatable, yet incurable disease.

Further to this, findings from this thesis may also facilitate the development and implementation of interventions that aim to improve the quality of life of these patients. This is essential for the provision of evidence based tools which clinicians and supporting healthcare professionals have at their disposal in order to limit the psychological burden experienced by this patient group. Such interventions currently include the use of Mindfulness, supportive-expressive group therapy and digital support solutions and are expected to continue to grow as more is learned and understood within this area [327-329].

During this research, several areas of interest were noted including the effect of age and culture on the types and priorities of the issues. Future work could use the data collected in Phase I to further explore this to determine whether differences exist across the various cultures. Feedback during the Phase II expert rounds highlighted potential differences existing within the issues, particularly those relating to sex.

Alternatively, future work could focus on the differences between patient and HCP data from Phase I. In this thesis patient and HCP data was used in combination to determine the most relevant and important issues, and in making these decisions, priority was given to the patient data, and supported by the HCP. An observation from this work revealed that HCP were far less selective of relevant issues compared with patients. This is something that could be investigated further to identify whether differences also exist within how each group views the importance of the issues. Identifying potential disparities in what issues patients and HCP deem to be important could provide valuable information, as conflicting views/opinions may hinder the effectiveness of consultations whereby patients issues have been dismissed or not acknowledged. A better understanding and alignment of what both parties want to prioritise may lead to a more patient centred approach.

Plans are in place to continue this work beyond that discussed within my thesis. The priority is the completion of Phase III of the development process, resulting in a provisional questionnaire that can be utilised within research. Beyond this, work should look to complete the international validation of the module (Phase IV). The importance of this work is critical as the scope for the questionnaire is wide reaching, especially with

the drive for the routine collection of PROMs in clinical practice and the increase uptake of QOL as study endpoints in clinical research.

7.4 Reflective account

The management of a large, international, multi-centred project was a significant part of my role as the study coordinator. As my PhD was largely dependent on the successful delivery of the wider EORTC Quality of life group project, there was pressure to ensure this target was achieved. Whilst now I can look back and appreciate the magnitude of the task, at the time, the significance of it all was perhaps somewhat underestimated, specifically the time and effort that goes into setting up a project of this nature.

My initial role was to identify and establish a group of collaborators, from multiple countries, to take part in the project. This involved utilising the EORTC network to approach centres that had expressed an interest in participating in the project prior to the funding being awarded. Over 57 sites from across 20 countries expressed interest in collaborating on this project. To ensure a representative sample of languages and cultures I selected sites from the UK, Italy, France, Poland, Japan, Germany, the Netherlands, Brazil and Japan. Unfortunately, Brazil were unable to participate due to the pressures and demands the COVID-19 pandemic put on their healthcare system. Brazil were later replaced with a centre in Jordan.

Following this, I was tasked with completing the necessary research governance procedures, for establishing a research project of this nature. These tasks included the development of the study protocol and supporting documents including consent forms, participant information sheets, socio-demographic and clinical data forms, as well as interview guides and project advertisement materials. The development of these materials was challenging as the documents were to be shared and submitted across multiple countries each of which had different research governance standards. This resulted in me developing two versions of each document, the first being documents specific to the UK and the second being a generic version for use in the other countries. This created a lot of work that on reflection could have been reduced, if I had delegated the adaption of the study materials to the individual centres, however at the time, the emphasis was to encourage collaborators to join by minimising the amount of work they had to do.

The next step was submitting the project for review by the Research Ethics Committee (REC). All study documents were submitted, and I attended the REC meeting to discuss the project in person, and answer any questions or queries they had. This was an

excellent opportunity for me as it gave me a great insight into the procedures involved in conducting research involving cancer patients in the UK and whilst the overall process was extremely time consuming, the feedback from the committee enabled me to ensure my research had been well planned and would be executed in a way that did not negatively impact my participants or those involved. Having obtained the favourable opinion from the REC after minor alterations, study documents were sent to the collaborating sites where they were to be submitted to the relevant governance bodies for approval. During this time, I had several key responsibilities, the first being to seek local approval from the NHS site involved. As with the REC approval, obtaining local approval was also a long and slow process. The knowledge gained from undertaking these activities has enabled me to better understand the policies and procedures in place at the NHS trust, as well as how to best navigate this to ensure my research is not forgotten or deprioritised. A positive of the time spend waiting for approvals was that I was able to attend and complete various types of training and to work on the systematic review.

The second key responsibility I had at this stage was to manage the collaborating sites and to facilitate their obtaining of the required approvals. This involved sending additional letters from the sponsor and arranging contracts for the centres that required them. As study coordinator, I liaised between the two parties involved with the contract and provided key information regarding the type and amount of data collected as well as the payment fee the site would receive on study completion. The variability within the research governance procedures across the different countries was something I had not previously considered, however having been in the position to experience this first hand I have developed a wealth of knowledge surrounding these differences as well as a better understanding of how to have better managed this at the time. Specifically, I learnt that during this process, maintaining communication with the centres is critical in order to keep driving the project forward. Centres often failed to provide timely updates of their progress to me which resulted in delays in the approval process.

Having successfully set up centres in seven of the eight counties included, I was pleased with my achievement, especially considering the COVID-19 pandemic hit at a critical phase of the study. Overall, the process of obtaining the required approvals and activation of all centres took well over two years to complete, with Phase I recruitment taking 20 months from the first to the last patient entered onto the study. Fortunately, I had received all approvals for my study to commence in the weeks before the first national lockdown. However, for many of the countries involved this was not the case and the effect of the pandemic caused severe delays in obtaining ethical approvals and

recruiting participants. An example of this was the seen in the UK where there was a complete shutdown of all non-essential research within the trust as a result of the first UK lockdown. I was therefore unable to recruit any patients for six months, after which I received priority approval to continue my research. I was amongst the first researchers in the hospital to start patient recruitment in clinics during the pandemic and received training on how to conduct research activities during this time.

The effect of COVID however was seen well beyond the end of the first lockdown, with tighter procedures remaining in place within the hospital including limitations of patient contact as well as a full protocol for the safeguarding of staff and patients with regards to wearing personal protective equipment (PPE). This was challenging as it placed several barriers between myself and the patients and was particularly difficult when approaching and interviewing patients face to face. Barriers included physical barriers from the PPE and social distancing measures as well as barriers created by fear of exposure to the virus with patients not wanting to spend extra time in a clinical environment. Further difficulties were faced when new restrictions were put in place during the November/December 2020 and January 2021 lockdowns. I feel that the achievement of successfully recruiting and interviewing patients during this time and having to adapt to fit the changing clinical environment was something, that with the help of my supervisors, I was able to succeed in.

Finally, my role in data collection, management and analysis was key in the delivery of this project. I was responsible for coordinating recruitment across the multiple sites in the various countries. This required strong communication between the sites to ensure that patients were recruited in line with the sampling matrix. In the early stages of recruitment, when centres had fewer restrictions over the types of patients recruited, communication was less frequent. Centres provided group updates on their recruitment figures from which I updated the sampling matrix. This however changed as recruitment progressed as closer attention was needed to ensure a balanced sample was obtained. I therefore developed individual sampling matrices for each centre to increase the efficiency in which recruitment numbers were communicated. These were shared documents that could be viewed by each centre within that country and thus allowed each collaborator to see which type of patient needed to be recruited. This worked well in the countries with multiple centres, for example Japan and the UK.

Overall, the skills I have gained from coordinating this project go beyond that of what I originally anticipated prior to undertaking my PhD and has provided me with the tools to move forward as a researcher. I discovered that communication is key. Without this,

projects of this nature would be near impossible to complete. Challenges in maintaining communication related to my limited experience as a study coordinator and well as the variable experience of the collaborators. Those with experience in completing similar research were more engaged and required less management than those new to this type of research.

Over the course of my PhD I have had the opportunity to present my work to leading experts in the field at multiple international events. As study coordinator, I attended the EORTCs bi-annual meetings where I presented project updates to key stakeholders, including members of the EORTC Quality of Life Group, collaborators and members of the EORTC Breast group. The aims of the meetings were to bring collaborators together from around the world to discuss ongoing projects and facilitate the exchange of ideas and knowledge to achieve best possible project results. The meetings provided an excellent opportunity for me to grow my professional network and develop a wider understanding of the EORTC organisation including the work conducted across various cancer sites.

Attending and being part of these meetings helped to develop my interpersonal skills, for example, having the confidence to engage in discussions with individuals from a range of different professional backgrounds, as well as presenting my research both face to face and virtually. The overall importance of these meetings was highlighted after the COVID-19 period whereby the meetings had to be virtual. Due to this limitation, I had lost a lot of the intangible aspects, such as the informal chats with other researchers that made the meetings so beneficial. The wealth of knowledge available at the meetings was invaluable to me as an early career researcher, and was made accessible as the more experienced members were keen on sharing their knowledge and experience with me to enable me to progress and develop as a researcher.

7.4.1 Epistemology

Researchers make choices based on philosophical assumptions which ultimately guide their project. Within the realm of health-related research, a positivist approach to research is often taken. Positivism assumes that reality is objective, ordered, and governed by natural laws that can be realised through experience. Methodologies of a positivist approach include randomised control trials, experiments, and the use of structured questionnaires. Alternatively, researchers may take an interpretative standpoint whereby reality is considered socially constructed and internally experienced through interactions and interpretations [130]. Methodologies associated with this

approach include interviews, observations and focus groups. The third approach is known as pragmatism, which is a more flexible world view that recognises there are many different ways of interpreting the world and that no single viewpoint can provide an encompassing view of the world [330]. Pragmatic methods include mixed methods or multiple methods research, where a researcher utilises a combination of methods to advances a specific research question in the best possible manner.

The wider EORTC Quality of life group project was guided by an accepted methodology in questionnaire development which took a largely structured positivist approach, I decided to use a pragmatic approach including mixed-methodology. Ultimately, the aims and questions I posed to answer within my thesis required an approach that was not limited by its philosophical underpinnings. Pragmatism provided me with this as I was able to take advantage of multiple philosophical systems whilst being grounded in the knowledge and understanding of limitations associated with both positivism and interpretivism [331].

The impact of COVID has been touched upon throughout the thesis and further information can be found in the COVID impact statement. However, on a personal note, the impact COVID had was very significant. The loss of physical contact with the research team and my supervisors was impactful, it was difficult to find the motivation to keep going during the strict first lockdown. Further to this, not having a dedicated work space or equipment within my home added to this challenge.

7.5 Conclusion

This thesis has provided important steps in addressing a crucial gap within the realm of assessing QOL in MBC. It has detailed not only the various types of issues these women experience, but also determined the attitudes towards the issues to produce a core set of issues women with metastatic breast cancer deem to be relevant and important. The thesis took this data forward and delivered a provisional questionnaire for assessing quality of life in this patient group, from which future research can build upon in order to finalise, validate and disseminate the questionnaire. Ultimately, better measurement of QOL of patients with MBC will lead to better supportive treatments and patient-centred care.

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Appendices

9.1.1 International centres and collaborators.

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Dr Omar Shamieh - King Hussein Cancer Center, Jordan

9.1.2 Systematic review search strategy terms

Domain	Search terms
Metastatic Breast Cancer	Breast Neoplasms (MeSH) Neoplasm Metastasis (MeSH) Metastatic Secondary Advanced Metastasis Stage 4 or four or IV Breast (cancer or neoplasm or carcinoma or malignancy or tumour)
Adverse Event	Adverse (effect or reaction or event or outcome) Side effect Undesirable effect Treatment emergent adverse event Tolerability or toxicity
Study Design	Randomized controlled trial Controlled clinical trial Exclude animal studies
Quality of Life	Quality of Life (MeSH) QOL or HRQL Psychosocial (effect or wellbeing or factor or issue) Social (effect or wellbeing or factors or issue) Psychological (effect or wellbeing or factors or issue) Emotional (effect or wellbeing or factors or issue)
Outcome	Patient Reported Outcome Measures (MeSH) Patient based outcome PROM or PROMS Health Status/ Self Report/ Symptom (reporting or burden) Symptom Assessment/ Surveys and Questionnaires"/ Interview
Limit	Date: 2000 - 2019

9.1.3 Risk of Bias review table: MMAT

Qualitative studies								
Author/Year	Search	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	1.1. Is the qualitative approach appropriate to answer the research question?	1.2. Are the qualitative data collection methods adequate to address the research question?	1.3. Are the findings adequately derived from the data?	1.4. Is the interpretation of results sufficiently substantiated by data?	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation ?
Chen (2014)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Krigel (2014)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lee Mortensen (2018)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lewis (2015)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Luoma (2004)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McClelland (2005)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McClelland (2016)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mosher (2018)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Vilhauer (2008)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quantitative - RCT								
Author/Year	Search	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	2.1. Is randomization appropriately performed?	2.2. Are the groups comparable at baseline?	2.3. Are there complete outcome data?	2.4. Are outcome assessors blinded to the intervention provided?	2.5 Did the participants adhere to the assigned intervention?
Alba (2004)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Albain (2008)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
André (2014)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baselga 2012	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Beaver (2012)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blackwell (2010)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Burris (2013)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Campone (2013*)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cassier (2008)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chia (2008)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conte (2004)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cortes (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Di Leo (2010)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ejlertsen (2004)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Falandry (2009)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Fountzilas (2004)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Gligorov (2014)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Guan (2013)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Hagiwara (2018)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Harbeck (2016)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Harbeck (2016*)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Harvey (2006)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Hopwood (2008)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hortobagyi (2016)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Inoue (2010)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Janni (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jones (2005)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Kaufman (2000)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Kaufman (2009)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Keller (2004)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Krop (2014)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Langley (2005)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Lück (2013)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Miller (2005)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Miller (2007)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes

O'Shaughnessy (2002)	CTIMP	Yes	Yes	No	Yes	Yes	No	Yes
O'Shaughnessy (2018)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Osoba (2002)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Pallis (2012)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Paridaens (2000)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Park (2013)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Park (2015)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Park (2019)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Parnes (2003)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Perez (2015)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Robert (2011)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Rugo (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Rugo (2019)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Schmid (2005)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Schröder (2011)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Slamon (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smorenburg (2014)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Sparano (2010)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Trédan (2016)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Tripathy (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Urruticoechea (2017)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Wu (2011)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Yamamoto (2017)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Zhang (2017)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Zhou (2009)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Zielinski (2005)	CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Aranda (2006)	Non-CTIMP	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Bordeleau (2003)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Goodwin (2001)	Non-CTIMP	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes
Hanser (2006)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Kissane (2007)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Low (2010)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
				Quantitative - Non RCT				
Author/Year	Search	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	3.1. Are the participants representative of the target population?	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	3.3. Are there complete outcome data?	3.4. Are the confounders accounted for in the design and analysis?	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?
Campone (2013)	CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Cella (2011)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Iwata (2017)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Krop (2015)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Liu (2006)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Sherrill (2010)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Verma (2012)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Verma (2018)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Amado (2006)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Brems-Eskildsen (2019)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Ecclestone (2016)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Karamouzis (2007)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Koopman (2002)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Muller (2014)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Muller (2018)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Shin (2016)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Walker (2011)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Walker (2013)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
Walker (2014)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	No	Yes
				Quantitative - Descriptive				

Author/Year	Search	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	4.1. Is the sampling strategy relevant to address the research question?	4.2. Is the sample representative of the target population?	4.3. Are the measurements appropriate?	4.4. Is the risk of nonresponse bias low?	4.5. Is the statistical analysis appropriate to answer the research question?
De Luca (2019)	CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Aranda (2005)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Brufsky (2017)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Marschner (2018)	Non-CTIMP	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Yes
McClelland (2015)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reed (2012)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tometich (2018)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
				Mixed Methods Studies				
Author/Year	Search	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?	5.2. Are the different components of the study effectively integrated to answer the research question?	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?
ten Tusscher (2019)	Non-CTIMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes

9.1.4 Investigator Brochure Review: Adverse Events of thavailable treatments

Drug	Issues/Adverse Events (common & very common)
Targeted Therapy	
Everolimus	Infections, Anaemia, Thrombocytopenia, Neutropenia, Leukopenia, Lymphopenia, Decreased appetite, Hyperglycaemia, Hypercholesterolaemia, Hypertriglyceridaemia, Hypophosphataemia, Diabetes mellitus, Hyperlipidaemia, Hypokalaemia, Dehydration, Hypocalcaemia, Insomnia, Dysgeusia, Headache, Eyelid oedema, Haemorrhage, Hypertension, Pneumonitis, Epistaxis, Cough, Dyspnoea, Stomatitis, Diarrhoea, Nausea, Vomiting, Dry mouth, Abdominal pain, Mucosal inflammation, Oral pain, Dyspepsia, Dysphagia, Aspartate aminotransferase increased (liver damage), Alanine aminotransferase increased, Rash, Pruritus, Dry skin, Nail disorders, Mild alopecia, acne, erythema, onychoclasis, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, skin lesion, Arthralgia (joint pain), Proteinuria, blood creatinine increased, renal failure, Menstruation irregular, Fatigue, Asthenia, Oedema peripheral, Pyrexia (fever), Weight decreased.
Palbociclib	Infections, Neutropenia, Leukopenia, Anaemia, Thrombocytopenia, Febrile neutropenia, Lacrimation, increased, Dry eye, Epistaxis, Stomatitis, Nausea, Diarrhoea, Vomiting, Rash, Alopecia, Dry skin, Fatigue, Asthenia, Pyrexia, AST Increased.
Trastuzumab	Infection, Nasopharyngitis, Neutropenic sepsis, Cystitis, Herpes zoster, Influenza, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Cellulitis, Pharyngitis, Febrile neutropenia, Anaemia, Neutropenia, White blood cell count decreased/leukopenia, Thrombocytopenia, Hypersensitivity, Weight decreased/Weight loss, Insomnia, Thinking abnormal, Tremor, Paraesthesia, Dysgeusia, Peripheral neuropathy, Hypertonia, Conjunctivitis, Lacrimation increased, Dry eye, Blood pressure decreased, Blood pressure increased, Heart beat irregular, Palpitation, Cardiac flutter, Ejection fraction decreased*, Cardiac failure (congestive), Supraventricular tachyarrhythmia, Cardiomyopathy, Hot flush, Hypotension, Vasodilatation, Wheezing, Dyspnoea, Cough, Epistaxis, Rhinorrhoea, Pneumonia, Asthma, Lung disorder, Diarrhoea, Vomiting, Nausea, Lip, swelling, Constipation, Haemorrhoids, Dry mouth, Erythema, Rash, Nail disorder, Palmar-plantar syndrome, Acne, Dry skin, Ecchymosis, Hyperhydrosis, Maculopapular rash, Pruritus, Onychoclasis, Dermatitis, Arthralgia, Muscle tightness, Myalgia, Arthritis, Back pain, Bone pain, Muscle spasms, Neck pain, Pain in extremity, Asthenia, Chest pain, Chills, Fatigue, Influenza-like symptoms, Infusion, related reaction, Pain, Pyrexia, Mucosal inflammation, Peripheral oedema, Malaise, Oedema.

Pertuzumab	Nasopharyngitis, Paronychia, Upper respiratory tract infection, Febrile neutropenia*, Neutropenia, Leucopenia, Anaemia, Infusion reaction, Hypersensitivity, Drug hypersensitivity, Decreased appetite, Insomnia, Neuropathy peripheral, Headache, Dysgeusia, Peripheral sensory neuropathy, Dizziness, Paraesthesia, Hot flush, Cough, Epistaxis, Dyspnoea, Diarrhoea, Vomiting, Stomatitis, Nausea, Constipation, Dyspepsia, Abdominal pain, Alopecia, Rash, Nail disorder, Pruritus, Dry skin, Myalgia, Arthralgia, Pain in extremity, Mucosal inflammation, Oedema peripheral, Pyrexia, Fatigue, Asthenia, Chills, Pain, Oedema.
Kadcyla	Urinary tract infection, Thrombocytopenia, Anaemia, Neutropenia, Leucopoenia, Hypokalaemia, Insomnia, Neuropathy peripheral, Headache, Dizziness, Memory impairment, Epistaxis, Cough, Dyspnoea, Stomatitis, Diarrhoea, Vomiting, Nausea, Constipation, Dry mouth, Abdominal pain, Dyspepsia, Alopecia, Nail disorder, Palmar-plantar erythrodysaesthesia syndrome, Urticaria, Musculoskeletal pain, Arthralgia, Myalgia, Fatigue, Pyrexia, Asthenia, Chills, Peripheral oedema.
Lapatinib	Anorexia, Insomnia, Headache, Hot flush, Epistaxis, cough, dyspnoea, Diarrhoea, nausea, vomiting, stomatitis, constipation, abdominal pain, Constipation, Rash, dry skin, palmar-plantar erythrodysaesthesia, alopecia, pruritus, Nail disorders including paronychia, Pain in extremity, back pain, mucosal inflammation, asthenia.
Denosumab	Hypocalcaemia, Hypophosphataemia, Dyspnoea, Diarrhoea, Tooth extraction, Hyperhidrosis, Musculoskeletal pain, Osteonecrosis of the jaw.
Bevacizumab	Sepsis, Abscess, Cellulitis, Infection, Urinary tract infection, Febrile neutropenia, Leucopenia, Neutropeniab, Thrombo-cytopenia, Anaemia,, Lymphopenia, Hypersensitivity, infusion reactions, Anorexia, Hypomagnesaemia, Hyponatraemia, Dehydration, Peripheral sensory neuropathyb, Dysarthria, Headache, Dysguesia, Cerebrovascular accident, Syncope, Somnolence, Eye disorder, Lacrimation increased, Congestive heart failureb, Supraventricular tachycardia, Hypertensionb, Thrombo-embolism (venous), Thrombo-embolism (arterial), Haemorrhageb,Deep vein thrombosis, Dyspnoea, Rhinitis, Epistaxis, Cough, Pulmonary haemorrhage/ Haemoptysisb, Pulmonary embolism, Hypoxia, Dysphonia, Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea,, Vomiting, Abdominal pain, Gastrointestinal perforationb, Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulaed,e, Gastrointestinal Disorder, Proctalgia, Wound healing complicationsb, Exfoliative dermatitis, Dry skin, Skin discoloration, Palmar-plantar erythro-dysaesthesia syndrome, Arthralgia, Myalgia, Fistulab, Muscular weakness, Back pain, Proteinuriab, Ovarian failure, Pelvic Pain, Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation, Weight decreased, Lethargy.
Ribociclib	Infections, Neutropenia, leukopenia, anaemia, Lymphopenia, febrile neutropenia, Decreased appetite, Hypocalcaemia, hypokalaemia, hypophosphataemia, Headache, dizziness, Vertigo, Lacrimation increased, dry eye, Dyspnoea, cough, Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain, Dysgeusia, Alopecia, rash, pruritus, Erythema, dry skin, vitiligo, Back pain, Fatigue, peripheral oedema, asthenia, pyrexia, Dry mouth, oropharyngeal pain.
Hormone Therapy	

Tamoxifen	Anaemia, Hypersensitivity reactions, Fluid retention, Ischaemic cerebrovascular events, Headache, Light-headedness, Sensory disturbances , Cataracts, Retinopathy, Hot flushes, Thrombo-embolic events, Thrombo-embolic events , Changes in liver enzyme, Fatty liver, Skin rash, Alopecia, Leg cramp, Myalgia, Vaginal bleeding, Vaginal discharge, Pruritus vulvae, Endometrial changes, Fatigue, Tumour pain.
Faslodex	Urinary tract infections, Reduced platelet count, Hypersensitivity reactions, Anorexia, Headache, Hot flushes, Venous thromboembolism, Nausea, Vomiting, Diarrhoea, Elevated hepatic enzymes, Elevated bilirubin, Rash, Joint and musculoskeletal pain, Back pain, Vaginal haemorrhage, Asthenia, Injection site reactions, Neuropathy peripheral, Sciatica.
Anastrozole (Arimidex)	Anorexia, Hypercholesterolaemia, Headache, Somnolence, Carpal Tunnel Syndrome, Hot flushes, Nausea, Diarrhoea, Vomiting, Rash, Hair thinning (alopecia), Allergic reactions, Arthralgia/joint stiffness, Arthritis, Osteoporosis, Bone pain, Vaginal dryness, Vaginal bleeding, Asthenia.
Letrozole (Femara)	Hypercholesterolaemia, Decreased appetite, Increased appetite, Depression, Headache, Dizziness, Palpitations, Hot flushes, Hypertension, Nausea, Dyspepsia, Constipation, Abdominal pain, Diarrhoea, Vomiting, Hyperhidrosis, Alopecia, Rash , Dry skin, Arthralgia, Myalgia, Bone pain, Osteoporosis, Bone fractures, Arthritis, Vaginal haemorrhage, Fatigue , Peripheral oedema, Chest pain, Weight increased.
Exemestane (Aromasin)	Leucopenia, Thrombocytopenia, Anorexia, Depression, Insomnia, Headache, Dizziness, Carpal tunnel syndrome, Paraesthesia, Hot flushes, Abdominal pain, Nausea, Vomiting, Diarrhoea, Constipation, Dyspepsia, Hepatic enzyme increased, Blood bilirubin increased, Blood alkaline phosphatase increased, Increased sweating, Alopecia, Rash, Urticarial, Pruritus, Joint and musculoskeletal pain, Fracture, Osteoporosis, Pain, Fatigue, Oedema peripheral, Asthenia.
Goserelin (Zoladex)	Libido decreased, Mood changes, Depression, Paraesthesia, Headache, Hot flush, Blood pressure abnormal, Hyperhidrosis, Acne, Rash, Alopecia, Arthralgia, Vulvovaginal dryness, Breast enlargement, Injection site reaction, Tumour flare, Tumour pain , Bone density decreased , Weight increased.
Megestrol acetate	Adrenal insufficiency, Cushingoid, Cushing's syndrome, Diabetes mellitus, Glucose tolerance impaired, Hyperglycaemia, Increased appetite, Mood altered, Carpal tunnel syndrome, Lethargy, Cardiac failure, Thrombophlebitis, Pulmonary embolism, Hypertension, Hot flush, Dyspnoea, Constipation, Nausea, Vomiting, Diarrhoea, Flatulence, Rash, Alopecia, Pollakiuria, Menorrhagia, Asthenia, Pain, Oedema, Weight increased, Tumour flare.
Chemotherapy	

Carboplatin	Infections, Thrombocytopenia, Neutropenia, Leukopenia, Anaemia, Haemorrhage, Hypersensitivity, anaphylactoid type reaction, Neuropathy peripheral, Paraesthesia, Decrease of osteotendinous reflexes, Sensory disturbance, Dysgeusia, Visual disturbance, Ototoxicity, Cardiovascular disorder, Respiratory disorder, Interstitial lung disease, Bronchospasm, Vomiting, Nausea, Abdominal pain, Diarrhoea, Constipation, Mucous membrane disorder, Alopecia, Skin disorder, Musculoskeletal disorder, Urogenital disorder, Asthenia, Creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased, Blood bilirubin increased, blood creatinine increased, blood uric acid increased.
Cisplatin	Sepsis, Bone marrow failure, Thrombocytopenia, Leukopenia, Anaemia, Hyponatraemia, Arrhythmia, Bradycardia, Tachycardia, Phlebitis at injection site, Dyspnoea, Pneumonia, Respiratory failure, Hyperuricaemia.
Doxorubicin	Sepsis, Septicaemia, Bone-marrow suppression, leucopenia, Neutropenia, Anorexia, Cardiomyopathy, Nausea, Vomiting, Mucositis/stomatitis, Diarrhoea, Alopecia, Chemical cystitis.
Epirubicin	Infection, Leukopenia, Granulocytopenia, Neutropenia, Anaemia, Febrile neutropenia, Anorexia, Dehydration, Hot flashes, Mucositis, Oesophagitis, Stomatitis, Vomiting, Diarrhoea, Nausea, Alopecia, Red coloration of urine, Infusion site erythema, Chemical cystitis, Haemorrhagic.
Capecitabine	Herpes viral infection, Nasopharyngitis, Lower respiratory tract , Neutropenia, Anaemia, Anorexia, Dehydration, Weight decreased, Insomnia, Depression, Headache, Lethargy, Dizziness, Parasthesia, Dysgeusia, Lacrimation increased, Conjunctivitis, Eye irritation, Thrombophlebitis, Dyspnoea, Epistaxis, Cough, Rhinorrhoea, Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain, Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth, Palmar-plantar , Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Dermatitis, Nail disorder, Pain in extremity, Back pain, Arthralgia, Fatigue, Asthenia, Pyrexia, Oedema peripheral, Malaise, Chest pain.
Gemcitabine	Leukopenia , Thrombocytopenia, Anaemia, Febrile neutropenia, Anorexia, Headache, Insomnia, Somnolence, Dyspnoea , Cough, Rhinitis, Vomiting, Nausea, Diarrhoea, Stomatitis and ulceration of the Mouth, Constipation, Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, Increased bilirubin, Allergic skin rash frequently associated with pruritus, Alopecia, Itching, Sweating, Back pain, Myalgia, Haematuria, Mild proteinuria, Influenza-like symptoms, Oedema/peripheral oedema, Fever, Asthenia, Chills.
Fluorouracil	Infections , Leukopenia, Myelosuppression, Neutropenia, Granulocytopenia, Thrombocytopenia, Anaemia, Pancytopenia, Immunosuppression, Conjunctivitis, Chest pain, Tachycardia, Angina pectoris, Diarrhoea, Nausea, Vomiting, Mucositis, Stomatitis, Alopecia, Palmar-plantar, Fever, Fatigue.

Methotrexate	Herpes zoster, Leukocytopenia, Thrombo-cytopenia , Anaemia, Headache, Fatigue, Drowsiness, Interstitial alveolitis / pneumonitis , Dry, irritating cough, Shortness of breath, Dyspnoea, Chest pain, Fever, Loss of appetite, Nausea, Vomiting, Abdominal pain, Inflammation and ulcerations of the mucous membrane of mouth and throat, Stomatitis, Dyspepsia, Diarrhoea , Increase in liver-related enzymes , Exanthema, Erythema, Itching.
Docetaxel	Infections , Sepsis , Pneumonia, Neutropenia , Anaemia , Febrile neutropenia, Thrombocytopenia , Hypersensitivity, Anorexia, Peripheral sensory neuropathy, Peripheral motor neuropathy , Dysgeusia , Arrhythmia , Hypotension, Hypertension, Haemorrhage, Dyspnoea , Stomatitis , Diarrhoea, Nausea, Vomiting, Constipation , Abdominal pain , Gastrointestinal haemorrhage, Alopecia, Skin reaction, Nail disorders, Myalgia, Arthralgia, Fluid retention, Asthenia , Pain, Infusion site reaction, Non-cardiac chest pain.
Eribulin	Urinary tract infection, Pneumonia, Oral candidiasis, Oral herpes, Upper respiratory tract infection, Nasopharyngitis, Rhinitis, Herpes zoster, Neutropenia, Leukopenia, Anaemia, Lymphopenia, Febrile neutropenia, Thrombocytopenia, Decreased appetite, Hypokalaemia, Hypomagnesaemia, Dehydration, Hyperglycaemia, Hypophosphataemia, Insomnia, Depression, Peripheral neuropathy, Headache, Dysgeusia, Dizziness, Hypoaesthesia, Lethargy, Neurotoxicity, Lacrimation increased, Conjunctivitis, Vertigo, Tinnitus, Tachycardia, Hot flush, Pulmonary embolism, Dyspnoea, Cough, Oropharyngeal pain, Epistaxis, Rhinorrhoea, Nausea, Constipation, Diarrhoea, Vomiting, Abdominal pain, Stomatitis, Dry mouth, Dyspepsia, Gastrooesophageal reflux disease, Abdominal distension, Alopecia, Rash, Pruritus, Nail disorder, Night sweats, Dry skin, Erythema, Hyperhidrosis, Palmar plantar erythrodysaesthesia, Arthralgia and myalgia, Back pain, Pain in extremity, Bone pain, Muscle spasms, Musculoskeletal pain, Musculoskeletal chest pain, Muscular weakness, Fatigue/Asthenia, Pyrexia, Mucosal Inflammation , Peripheral oedema, Pain, Chills, Chest pain, Influenza like illness, Weight decreased.
Paclitaxel	Infections, Neutropenia, Anaemia, Thrombocytopenia, Leukopenia, Bleeding, Flushing , Rash, Peripheral neuropathy, Bradycardia, Hypotension, Diarrhoea, Vomiting, Nausea, Mucosal inflammation, Alopecia, Transient and mild nail and skin changes, Arthralgia, Myalgia, Injection site reactions - including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis.
Vinorelbine	Infections, Neutropenia, Thrombocytopenia, Allergic reactions, Neurological disorders, Constipation, Nausea, Vomiting, Stomatitis, Oesophagitis, Diarrhoea , Alopecia, Myalgia, arthralgia, jaw pain, Asthenia, Fatigue, Fever Pain, Pain at the tumour site, Reactions at the injection site - erythema, burning pain, vein discolouration and local phlebitis.
Immunotherapy	
Atezolizumab	Urinary tract infection, Decreased appetite, Cough, Dyspnoea, Nausea, Vomiting, Diarrhoea Rash, Pruritus, Arthralgia, Back pain, Pyrexia, Fatigue, Asthenia

9.1.5 Phase I: Patient information sheet

Development of a Quality of Life Questionnaire for patients with Metastatic Breast Cancer

Participant Information Sheet

Introduction

We would like to invite you to take part in a research study which aims to help us better understand the impact metastatic breast cancer, and its treatment, has on people's lives. This study involves taking part in a one-off interview to discuss your experiences of living with metastatic breast cancer, however before you decide whether you would like to take part, it is important you understand why this research is being done and what it will involve. Please take time to read the following information carefully. If you wish, you may take this information sheet away with you and discuss it with friends, relatives and your GP. If you would like more information or have questions contact details can be found at the bottom of the page.

What is the purpose of this study?

The purpose of this study is to conduct interviews to explore, and better understand, the quality of life related issues women living with metastatic breast cancer experience.

When evaluating the impact of an illness such as cancer, one of the most important areas to consider is the effect it has on quality of life. There is currently an unmet need for a new cancer-specific questionnaire that better measures quality of life in this patient group. Questionnaires currently in use were designed to measure the general quality of life of patients across all stages of breast cancer and therefore may not include the specific issues that are relevant to those with metastatic breast cancer.

This study forms part of a wider research project that aims to develop a new quality of life questionnaire specific to metastatic breast cancer.

What will be involved?

If you choose to take part, you will be invited to take part in a one-off interview, lasting approximately 30-40 minutes. The interviews will take place in quiet private room based in the Leeds Cancer Centre (Bexley Wing, St James's University Hospital, Leeds) or an alternative location convenient to you. During

the interview you will be given the opportunity to discuss how living with metastatic breast cancer impacts your quality of life and provide feedback on issues you feel are relevant and important to you. Throughout the interview summary notes of the topics discussed will be taken by the interviewer and the interview may also be audio-recorded. Before beginning the interview you will be asked to sign a consent form stating you understand what the study involves and that you agree to take part.

We may ask your permission to look at your medical records to clarify details about your illness and the treatments you have received. This information will only be viewed following your permission and will be kept strictly confidential.

Are there any benefits of taking part?

Whilst you may not receive any direct benefit from taking part in this study, it is hoped that the information you provide will contribute to help us better understand and measure the quality of life issues experienced by future patients. Reasonable travel costs will be reimbursed for those making additional journeys to partake in this study. If you are interested, updates from the study can be found here https://qol.eortc.org/questionnaire/metastatic-breast-cancer/.

Are there any disadvantages of taking part?

We do not think that taking part will involve any disadvantages or pose any specific risks to you. While some people find it helpful to think and talk about the issues they experience, others may find this process upsetting. You will be able to pause or stop the interview at any time, and contact details for further support would be made available to you.

Do I have to take part?

No, the choice is entirely yours. You can take as much time as you need to make the decision and any decision that you make will be respected. If you agree and then later decide against taking part, you are free to withdraw from the study without giving a reason. If you complete the interview and then wish to withdraw, you will have two weeks to request your data be removed from the study. Please note: deciding not to take part will have no effect on the usual standard of care you are receiving.

Who is funding this research?

This project is funded by the European Organisation for Research and Treatment of Cancer Quality of Life Group (EORTC-QLG). The EORTC is a leading non-profit organisation that conducts international research into cancer, its treatments and quality of life. Funding for this project has been secured and will not be

affected if and when the UK leaves the European Union. Approximately 180 participants from across 9 countries will be involved in this study.

Will my confidentiality be maintained?

Yes. All information collected about you during the study will be kept strictly confidential and securely stored. Documents and files containing personal information will be stored in locked filing cabinets and/or electronically stored in password protected folders on secure University servers. Access to files will only be available to members of the research team at the University of Leeds. To help us maintain your confidentiality you will be assigned a unique study ID that will replace your name on the study documents. Study results are likely to be published in a scientific journal and presented to the EORTC, however it will not be possible to identify you in any publication of the research findings.

If serious concerns over your health and well-being are raised, the researcher would have a responsibility to inform the appropriate professional, such as your GP or hospital consultant. If this situation was to arise, every effort would be made to discuss our reasoning and to keep you involved before information was shared.

Audio-recorded files (where applicable) will be encrypted and electronically stored in password protected folders on secure University servers, and all personally identifiable information removed during transcription. The transcript will only be linked to you by your study ID. As far as possible, the researcher undertaking this research will transcribe your interview. Should time become limited, a University approved transcription company may carry out this process.

Further information on how we will use and manage your information can be found in appendix 1. This study has been reviewed by an NHS Research Ethics Committee.

Thank you for taking the time to read this information sheet.

You are welcome to take as much time as you need to consider all of the information you have just read. Please let the research team know whether or not you would like to help with the study, or if you have any further questions using the contact details below. If you would like more time to make your decision we can arrange to speak to you at your next appointment or contact you at a later date.

Please keep this information sheet for future reference

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9.1.6 Phase I: Interview guide - Patient

Interview Guide - Patient

Part 1. Introduction

The researcher should begin the interview with some introductory remarks to explain its nature and purpose. For example:

- *"Thank you for taking the time to talk to us about your experience of cancer today. We are asking for your help in developing a questionnaire which will be used to monitor the quality of life of patients who have metastatic breast cancer. There are no right or wrong answers, we are simply interested in understanding more about your experiences."*

Assurance of anonymity

- *"All of the information you provide will remain confidential, your data will be assigned a unique research number so that identifiable information will not appear if the data are used in the future. There is no obligation for you to answer the questions and you can pause or stop the interview at any stage."*

Complete the **'Consent'** and the '**Patient demographics**' form.

Part 2. Open Question

Once informed consent has been obtained the interview can commence.

The interview begins with open questions about the patient's experience of metastatic breast cancer. For example;

- *"What are some of the (most important) issues you have experienced since being diagnosed with metastatic breast cancer?"*
- *"Can you tell me about the experiences you have had as a result of your treatment?"*
- *"Could you tell me about the symptoms you experience because of your cancer."*

Let the patient mention as many issues as they can. Encourage the patient to provide more issues by probing comments.

Neutral probes should be used to elicit more information.

- *"Can you tell me more about that?", "Can you think of any additional*

experiences?", "How did that affect you?" or "was that something you were expecting?"

Continue questioning until no new issues are raised.

Part 3. Issue list

The list of issues may be shown to the patient after they have provided issues which arise spontaneously. The list may serve as a prompt to stimulate further suggestions.

- "I'm now going to show you a list of issues that people with metastatic breast cancer sometimes experience. We are interested in how relevant and important these issues are to you."

Place the list of issues before the patient and continue as follows:

- *"Here you see the list of symptoms/issues. Using the scale provided, please could you indicate the relevance each issue has to you? For each issue you can respond 'not at all', to 'a little', to 'quite a bit', to ' very much' to indicate its relevance. When we say "relevance" we mean how closely connected is the issue to your cancer, for example is the issue something you have experienced."*

Following this, provide the opportunity for patients to indicate the importance of the issues:

- *"Now you have completed this, I am going to ask you to select some issues that you feel should be included in the questionnaire*. Please select the issues you feel are most important to you by ticking the box next to the issue. By "importance" we mean how much do you care about that issue."*

Note: Inform the patient of how many issues they should select.

* If the total number of issues is small (15-20); it may be sufficient to ask patients to identify five key issues; however for larger number of issues it may be necessary to ask patients to identify 10-15 issues.

Part 4. Conclusion

Provide an opportunity for the patient to discuss any issues they feel are missing from the item list and/or issues they feel should be removed from the list.

- "We are now at the end of the interview. Is there anything you want to talk about that we havent covered?"

a. *Would you like to add or remove any issues from the list?*

Thank the patient for sharing their experiences with us and for providing feedback on the item list.

🗣 “Thank you for taking part in the study today.”

9.1.7 Phase I: Interview guide – Healthcare professional

Part 1. Introduction

The researcher should begin the interview with some introductory remarks to explain its nature and purpose. For example:

- *"Thank you for taking the time to talk to us today. We are asking for your help in developing a new questionnaire which will be used to assess the quality of life of patients with metastatic breast cancer. We are interested in understanding the different issues these patients report as a result of living with, and treated for metastatic breast cancer."*

- *"We have a questionnaire assessing quality of life aspects of cancer patients in general, however there is no questionnaire specific to this patient group. Following the EORTC guidelines we aim to develop a new disease specific quality of life questionnaire for patients with metastatic breast cancer."*

Assurance of anonymity

- *"All of the information you provide will remain confidential, your data will be assigned a unique research number so that identifiable information will not appear if the data are used in the future. There is no obligation for you to answer the questions and you can pause or stop the interview at any stage."*

Part 2. Open Question

The interview begins with open questions relating to the patient's experience of metastatic breast cancer. For example;

- *"What are some of the (most important) issues patients report as a result of being diagnosed with metastatic breast cancer?"*
- *"Can you tell me about the experiences patients report as a result of their treatment?"*
- *"Could you tell me about the symptoms patients experience because of their cancer."*

Let the participant mention as many issues as they can. Encourage them to provide more issues by probing comments and continue questioning until no new issues are raised.

Neutral probes should be used to elicit more information.

- *"Can you tell me more about that?", "Can you think of any additional experiences?, "how severe is that?" or "How long does that last for"*

Continue questioning until no new issues are raised.

Part 3. Issue list

The list of issues may be shown to the participant after they have provided issues which arise spontaneously. The list may serve as a prompt to stimulate further suggestions.

- *"I'm now going to show you a list of issues that people with metastatic breast cancer sometimes experience.* We are interested in how relevant and important these issues are to this patient group.

Place the list of issues before the participant and continue as follows:

Relevance

- *"Here you see the list of issues. Using the scale provided, please could you indicate the relevance each issue has to women with metastatic breast cancer? For each issue you can respond 'not at all', to 'a little', to 'quite a bit', to ' very much' to indicate its relevance. When we say "relevance" we mean how closely connected is the issue to the cancer and/or treatment."*

Following this, the interviewer asks:

- *"Please could you tell me for each issue you circled 1 (not relevant) or 2 (a little relevant) why you consider it not or only a little relevant?"*

Interviewer notes down the reasons.

Now provide the opportunity for participants to indicate the importance of the issues:

Importance

- *"Now you have completed this, I am going to ask you to select some issues that you feel should be included in the questionnaire*. Please select the issues you feel are most important to this patient group by ticking the box next to the issues. By "importance" we mean the issues that affect patients the most. If there are items that you think should definitely be excluded please mark these also and say why you think they are not a priority"*

Note: Inform the participant of how many issues they should select.
* If the total number of issues is small (15-20); it may be sufficient to ask participant to identify five key issues; however for larger number of issues it may be necessary to ask them to identify 10-15 issues.

Part 4. Conclusion

Provide an opportunity for the patient to discuss any issues they feel are missing from the item list and/or issues they feel should be removed from the list.

- "We are now at the end of the interview. Is there anything you want to talk about that we havent covered?"
    a. *Would you like to add or remove any issues from the list?*

Thank the participant for sharing their experiences with us and for providing feedback on the item list.

- "Thank you for taking part in the study today."

9.1.8 Phase I: Issue list Questionnaire

Relevance and Importance Ratings - Patient

Here you can see a list of issues that may or may not impact your quality of life.

1. Please indicate the extent to which you find each issue relevant for you.
2. Furthermore, we would like to ask you to select (15) issues which, in your opinion should definitely be included in the questionnaire.

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
Symptom Burden						
General						
1	Difficulty doing strenuous activities	☐	☐	☐	☐	☐
2	Difficulty walking long distances	☐	☐	☐	☐	☐
3	Difficulty walking short distances	☐	☐	☐	☐	☐
4	Need to stay in bed/chair	☐	☐	☐	☐	☐
5	Need help eating, dressing or washing	☐	☐	☐	☐	☐
6	Reduced daily activities	☐	☐	☐	☐	☐
7	Pain	☐	☐	☐	☐	☐
8	Need to rest	☐	☐	☐	☐	☐
9	Pain affecting daily activities	☐	☐	☐	☐	☐
10	Injection site pain	☐	☐	☐	☐	☐
11	Injection site reaction	☐	☐	☐	☐	☐
12	Bladder problems	☐	☐	☐	☐	☐
13	Loss or lack of energy	☐	☐	☐	☐	☐
14	Fatigue	☐	☐	☐	☐	☐
15	Extreme fatigue	☐	☐	☐	☐	☐
16	Feeling unwell	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
17	Impact of cancer symptoms	☐	☐	☐	☐	☐
18	Treatment side effects	☐	☐	☐	☐	☐
19	Health instability caused by treatment and symptoms	☐	☐	☐	☐	☐
Eyes and nose						
20	Eye disorders: watery, irritated or painful	☐	☐	☐	☐	☐
21	Runny nose	☐	☐	☐	☐	☐
22	Nose bleeds	☐	☐	☐	☐	☐
Stomach and mouth						
23	Nausea	☐	☐	☐	☐	☐
24	Vomiting	☐	☐	☐	☐	☐
25	Constipation	☐	☐	☐	☐	☐
26	Diarrhoea	☐	☐	☐	☐	☐
27	Bloated	☐	☐	☐	☐	☐
28	Indigestion	☐	☐	☐	☐	☐
29	Dry mouth	☐	☐	☐	☐	☐
30	Difficulty swallowing	☐	☐	☐	☐	☐
31	Sore throat	☐	☐	☐	☐	☐
32	Mouth sores	☐	☐	☐	☐	☐
Infections						
33	Flu symptoms	☐	☐	☐	☐	☐
34	Infections	☐	☐	☐	☐	☐
35	Chills	☐	☐	☐	☐	☐
36	Fever	☐	☐	☐	☐	☐
37	Bladder infection	☐	☐	☐	☐	☐
38	Chest infection	☐	☐	☐	☐	☐
Weight and appetite						

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
39	Decreased appetite	☐	☐	☐	☐	☐
40	Loss of appetite	☐	☐	☐	☐	☐
41	Weight decrease	☐	☐	☐	☐	☐
42	Increased appetite	☐	☐	☐	☐	☐
43	Weight increased	☐	☐	☐	☐	☐
44	Severe weight loss (Anorexia)	☐	☐	☐	☐	☐
<u>The body - muscles and joints</u>						
45	Feeling weak	☐	☐	☐	☐	☐
46	Muscle aches/pains	☐	☐	☐	☐	☐
47	Muscle spasms	☐	☐	☐	☐	☐
48	Muscle weakness	☐	☐	☐	☐	☐
49	Joint aches, pains and stiffness	☐	☐	☐	☐	☐
50	Bone pain	☐	☐	☐	☐	☐
51	Back pain	☐	☐	☐	☐	☐
52	Abdominal pain	☐	☐	☐	☐	☐
53	Chest pain	☐	☐	☐	☐	☐
54	Pain in hands or feet	☐	☐	☐	☐	☐
55	Arm/shoulder pain	☐	☐	☐	☐	☐
56	Difficulty raising arm	☐	☐	☐	☐	☐
57	Decreased grip strength	☐	☐	☐	☐	☐
<u>Nervous system</u>						
58	Problems with coordination	☐	☐	☐	☐	☐
59	Problems with speech	☐	☐	☐	☐	☐
60	Problems with balance	☐	☐	☐	☐	☐
61	Changes in taste	☐	☐	☐	☐	☐
62	Headaches	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
63	Numbness, tingling or burning sensation in hands and feet	☐	☐	☐	☐	☐
64	Numbness in other areas of the body	☐	☐	☐	☐	☐
65	Tremor	☐	☐	☐	☐	☐
66	Dizziness	☐	☐	☐	☐	☐
<u>Reproductive</u>						
67	Breast pain	☐	☐	☐	☐	☐
68	Swollen breast	☐	☐	☐	☐	☐
69	Sensitive breast area	☐	☐	☐	☐	☐
70	Vaginal dryness	☐	☐	☐	☐	☐
71	Vaginal bleeding	☐	☐	☐	☐	☐
72	Vaginal discharge	☐	☐	☐	☐	☐
73	Decreased sexual activity	☐	☐	☐	☐	☐
74	Decreased sexual enjoyment	☐	☐	☐	☐	☐
75	Decreased sexual interest	☐	☐	☐	☐	☐
<u>Lungs</u>						
76	Shortness of breath	☐	☐	☐	☐	☐
77	Wheezing	☐	☐	☐	☐	☐
78	Cough	☐	☐	☐	☐	☐
<u>Skin</u>						
79	Acne	☐	☐	☐	☐	☐
80	Dry skin	☐	☐	☐	☐	☐
81	Redness and/or peeling of skin	☐	☐	☐	☐	☐
82	Severe itching	☐	☐	☐	☐	☐
83	Rash	☐	☐	☐	☐	☐
84	Skin discoloration	☐	☐	☐	☐	☐
85	Hair loss	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
86	Hand-foot syndrome	☐	☐	☐	☐	☐
87	Sweating	☐	☐	☐	☐	☐
88	Nail problems	☐	☐	☐	☐	☐
89	Skin problems around breast	☐	☐	☐	☐	☐
90	Wound healing complications	☐	☐	☐	☐	☐
Vascular						
91	Hot flush	☐	☐	☐	☐	☐
92	Swelling of arms	☐	☐	☐	☐	☐
93	Swelling of legs	☐	☐	☐	☐	☐
Psychological experiences						
94	Difficulty concentrating	☐	☐	☐	☐	☐
95	Feeling tense	☐	☐	☐	☐	☐
96	Worrying	☐	☐	☐	☐	☐
97	Feeling irritable	☐	☐	☐	☐	☐
98	Depression	☐	☐	☐	☐	☐
99	Memory issues	☐	☐	☐	☐	☐
100	Feeling less attractive	☐	☐	☐	☐	☐
101	Feeling less feminine	☐	☐	☐	☐	☐
102	Change in appearance	☐	☐	☐	☐	☐
103	Difficult to look at self-naked	☐	☐	☐	☐	☐
104	Dissatisfied with body image	☐	☐	☐	☐	☐
105	Loss of identity	☐	☐	☐	☐	☐
106	Depressed mood/ feeling sad/ down	☐	☐	☐	☐	☐
107	Distress	☐	☐	☐	☐	☐
108	Anxiety	☐	☐	☐	☐	☐
109	Anxiety about advanced aspect	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
110	Mood disturbance	☐	☐	☐	☐	☐
111	Feeling angry	☐	☐	☐	☐	☐
112	Bad tempered	☐	☐	☐	☐	☐
113	Less tolerant	☐	☐	☐	☐	☐
114	Intrusive thoughts	☐	☐	☐	☐	☐
115	Nervousness	☐	☐	☐	☐	☐
116	Feeling guilty	☐	☐	☐	☐	☐
117	Helplessness	☐	☐	☐	☐	☐
118	Hopelessness/ Loss of hope	☐	☐	☐	☐	☐
119	Feeling afraid	☐	☐	☐	☐	☐
120	Fear of dying	☐	☐	☐	☐	☐
121	Fear of disease progression	☐	☐	☐	☐	☐
122	Hyper-alertness to symptoms	☐	☐	☐	☐	☐
123	Fear of making symptoms worse	☐	☐	☐	☐	☐
124	Fear of stress	☐	☐	☐	☐	☐
125	Stress	☐	☐	☐	☐	☐
126	Stress avoidance	☐	☐	☐	☐	☐
127	Long-term health concerns	☐	☐	☐	☐	☐
128	Feeling confused	☐	☐	☐	☐	☐
129	Hallucinations	☐	☐	☐	☐	☐
130	Reduced ability to cope	☐	☐	☐	☐	☐
131	Difficulty finding a purpose	☐	☐	☐	☐	☐
132	Trouble thinking positively	☐	☐	☐	☐	☐
133	Change of perspective	☐	☐	☐	☐	☐
134	Difficulty accepting fate	☐	☐	☐	☐	☐
<u>Sleep</u>						
135	Difficulty sleeping	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
136	Tiredness	☐	☐	☐	☐	☐
137	Difficulty falling asleep	☐	☐	☐	☐	☐
138	Difficulty waking/getting up	☐	☐	☐	☐	☐
139	Lack of sleep	☐	☐	☐	☐	☐
140	Low quality sleep	☐	☐	☐	☐	☐
141	Waking during the night	☐	☐	☐	☐	☐
142	Feeling drowsy	☐	☐	☐	☐	☐
<u>Emotional</u>						
143	Emotions not recognised by others	☐	☐	☐	☐	☐
144	Decreased emotional restraint or control	☐	☐	☐	☐	☐
145	Greater emotional hardship	☐	☐	☐	☐	☐
146	Difficulty expressing emotions to others	☐	☐	☐	☐	☐
147	Negative reactions from others	☐	☐	☐	☐	☐
148	Lack of understanding from others	☐	☐	☐	☐	☐
149	Being viewed as a ‘cancer victim’	☐	☐	☐	☐	☐
150	Managing illness perceptions	☐	☐	☐	☐	☐
151	Feeling bitter	☐	☐	☐	☐	☐
152	Worried about family	☐	☐	☐	☐	☐
153	Parenting worries	☐	☐	☐	☐	☐
154	Fear leaving family behind	☐	☐	☐	☐	☐
<u>Future perspective</u>						
155	Worries about the future	☐	☐	☐	☐	☐
156	Unknown future	☐	☐	☐	☐	☐
157	Unknown prognosis	☐	☐	☐	☐	☐
158	Loss of future	☐	☐	☐	☐	☐
159	Future perspective	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
160	Uncertainty	☐	☐	☐	☐	☐
161	Sense of missing out	☐	☐	☐	☐	☐
Clinical services						
162	No opportunity to enhance your QOL	☐	☐	☐	☐	☐
163	Lack of symptom management	☐	☐	☐	☐	☐
Need for independent living						
164	Limited in pursuing hobby/leisure activities	☐	☐	☐	☐	☐
165	Loss of independence	☐	☐	☐	☐	☐
166	Dependency on others	☐	☐	☐	☐	☐
167	Reduced ability to take control	☐	☐	☐	☐	☐
168	Loss of normality	☐	☐	☐	☐	☐
169	Isolation	☐	☐	☐	☐	☐
Work, finance and benefits						
170	Reduced ability to work	☐	☐	☐	☐	☐
171	Financial difficulties	☐	☐	☐	☐	☐
172	Unable to maintain employment	☐	☐	☐	☐	☐
173	Financial impact on children	☐	☐	☐	☐	☐
174	Financial impact on family	☐	☐	☐	☐	☐
175	Medicalised lifestyle	☐	☐	☐	☐	☐
Support pathways						
176	Impact on family life	☐	☐	☐	☐	☐
177	Impact on social activities	☐	☐	☐	☐	☐
178	Reduced social support	☐	☐	☐	☐	☐
179	Altered social roles or responsibilities	☐	☐	☐	☐	☐
180	Altered family roles	☐	☐	☐	☐	☐
181	Needing help from family/children	☐	☐	☐	☐	☐

		Relevance				Priority for inclusion
No	**Issue**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Yes**
182	Altered partner relationships	☐	☐	☐	☐	☐
183	Burden on partner relations	☐	☐	☐	☐	☐
184	Negative impact on relationships	☐	☐	☐	☐	☐
185	Negative impact on family/children	☐	☐	☐	☐	☐

Are there any further issues that should be included in a questionnaire assessing the quality of life in metastatic breast cancer patients?

_____

_____

_____

_____

_____

_____

Thank you for your help!

9.1.9 Phase I: Excluded issues ranked by patient priority.

	Patient Response			HCP Response		
Issue	**N**	**Mean**	**Priority**	**N**	**Mean**	**Priority**
Q185 Negative impact on family children	185	1.86	13.0%	41	3.20	12.2%
Q140 Low quality sleep	185	2.06	11.9%	41	2.93	7.3%
Q055 Arm shoulder pain	186	1.94	11.8%	41	2.46	2.4%
Q061 Changes in taste	187	1.76	11.2%	41	2.80	4.9%
Q029 Dry mouth	187	2.13	11.2%	41	2.73	0.0%
Q149 Being viewed as a 'cancer victim'	184	1.98	10.9%	41	2.73	4.9%
Q122 Hyper alertness to symptoms	187	2.29	10.7%	41	3.02	7.3%
Q062 Headaches	185	1.73	10.3%	41	2.98	9.8%
Q180 Altered family roles	185	1.99	10.3%	40	2.95	4.9%
Q054 Pain in hands feet	185	1.95	10.2%	41	2.78	0.0%
Q020 Eye disorders watery irritated or painful	186	1.82	10.2%	41	2.54	4.9%
Q088 Nail problems	185	1.98	9.7%	41	2.73	2.4%
Q080 Dry skin	185	2.16	9.7%	40	2.65	10.0%
Q168 Loss of normality	186	2.17	9.1%	40	3.13	12.5%
Q101 Feeling less feminine	187	2.00	9.1%	41	2.88	4.9%
Q056 Difficulty raising arm	186	1.84	9.1%	40	2.60	7.3%
Q145 Greater emotional hardship	184	1.98	8.7%	41	2.85	2.4%
Q032 Mouth sores	186	1.66	8.6%	41	2.90	9.8%
Q043 Weight increased	186	1.61	8.6%	40	2.25	0.0%
Q107 Distress	185	1.99	8.1%	41	3.24	4.9%
Q158 Loss of future	187	2.31	8.0%	41	3.41	12.2%
Q110 Mood disturbance	187	2.14	8.0%	41	3.20	4.9%
Q133 Change of perspective	187	2.25	8.0%	41	2.95	2.4%
Q041 Weight decrease	187	1.73	8.0%	40	2.95	17.5%
Q111 Feeling angry	186	1.98	7.5%	41	2.83	4.9%
Q027 Bloated	186	1.78	7.5%	41	2.56	4.9%

Q183 Burden on partner relations	179	1.81	7.3%	40	3.15	7.5%
Q172 Unable to maintain employment	180	1.86	7.2%	41	3.10	2.4%
Q086 Hand foot syndrome	182	1.55	7.1%	41	3.10	9.8%
Q137 Difficulty falling asleep	185	2.15	7.0%	41	3.05	7.3%
Q100 Feeling less attractive	186	2.01	7.0%	41	2.95	9.8%
Q146 Difficulty expressing emotions	186	1.87	7.0%	41	2.83	9.8%
Q174 Financial impact on family	181	1.63	6.6%	40	3.18	9.8%
Q179 Altered social roles or responsibilities	183	1.93	6.6%	41	2.78	2.4%
Q139 Lack of sleep	185	1.95	6.5%	40	2.90	5.0%
Q048 Muscle weakness	185	2.24	6.5%	41	2.73	2.4%
Q141 Waking during the night	185	2.24	6.5%	40	2.93	2.5%
Q128 Feeling confused	186	1.72	6.5%	40	2.65	2.5%
Q082 Severe itching	186	1.62	6.4%	41	2.83	9.8%
Q113 Less tolerant	185	2.01	5.9%	41	2.73	0.0%
Q125 Stress	186	2.06	5.9%	40	3.20	12.5%
Q161 Sense of missing out	186	2.22	5.9%	40	2.95	4.9%
Q103 Difficult to look at self-naked	186	1.79	5.9%	41	2.93	9.8%
Q114 Intrusive thoughts	186	1.94	5.9%	41	2.76	4.9%
Q087 Sweating	187	1.85	5.9%	40	2.53	2.5%
Q010 Injection Site Pain	182	1.55	5.5%	41	2.22	2.4%
Q040 Loss of appetite	184	1.51	5.4%	40	3.33	29.3%
Q105 Loss of identity	184	1.58	5.4%	41	3.12	14.6%
Q047 Muscle spasms	186	1.68	5.4%	40	2.60	2.4%
Q117 Helplessness	187	1.97	5.3%	41	3.05	7.3%
Q167 Reduced ability to take control	185	1.92	4.9%	41	3.05	0.0%
Q144 Decreased emotional restraint or control	185	1.86	4.9%	41	2.80	12.2%
Q028 Indigestion	187	1.75	4.8%	41	2.54	4.9%
Q173 Financial impact on children	179	1.56	4.5%	41	3.07	2.4%
Q150 Managing illness perceptions	183	1.99	4.4%	41	2.66	4.9%
Q184 Negative impact on relationships	184	1.85	4.3%	40	2.93	2.4%

Q015 Extreme fatigue	185	1.93	4.3%	39	3.28	22.5%
Q148 Lack of understanding from others	186	1.77	4.3%	40	2.83	12.2%
Q042 Increased appetite	186	1.38	4.3%	40	1.93	2.4%
Q012 Bladder Problems	187	1.48	4.3%	41	2.34	7.3%
Q069 Sensitive breast	187	1.72	4.3%	41	2.24	0.0%
Q162 No opportunity to enhance your QOL	181	1.83	3.9%	40	2.80	9.8%
Q163 Lack of symptom management	181	1.61	3.9%	41	2.78	4.9%
Q143 Emotions not recognised by others	185	1.91	3.8%	39	2.77	7.5%
Q118 Hopelessness Loss of hope	186	1.78	3.8%	41	3.27	22.0%
Q044 Severe weight loss Anorexia	186	1.25	3.8%	40	2.98	24.4%
Q115 Nervousness	186	2.16	3.8%	41	2.93	0.0%
Q066 Dizziness	187	1.49	3.8%	41	2.68	0.0%
Q142 Feeling drowsy	186	2.03	3.8%	40	2.63	0.0%
Q067 Breast pain	186	1.71	3.8%	41	2.61	12.2%
Q116 Feeling guilty	186	1.66	3.8%	40	2.45	4.9%
Q134 Difficulty accepting fate	187	1.91	3.7%	41	3.17	7.3%
Q060 Problems with balance	187	1.53	3.7%	40	2.90	15.0%
Q092 Swelling of arms	187	1.76	3.7%	41	2.80	4.9%
Q030 Difficulty swallowing	187	1.40	3.7%	41	2.68	0.0%
Q068 Swollen breast	187	1.52	3.7%	40	2.43	5.0%
Q178 Reduced social support	184	1.80	3.3%	41	2.76	0.0%
Q089 Skin problems around breast	185	1.62	3.2%	41	2.37	0.0%
Q021 Runny nose	185	1.59	3.2%	41	2.00	2.4%
Q081 Redness peeling of skin	185	1.66	3.2%	41	2.71	0.0%
Q038 Chest infection	184	1.28	2.7%	41	2.51	2.4%
Q138 Difficulty waking getting up	185	1.81	2.7%	40	2.73	2.5%
Q131 Difficulty finding a purpose	186	1.73	2.7%	41	2.88	4.9%
Q112 Bad tempered	186	1.75	2.7%	41	2.63	0.0%
Q147 Negative reactions from others	186	1.63	2.7%	41	2.49	4.9%
Q022 Nose bleeds	186	1.39	2.7%	41	2.27	2.4%

Q124 Fear of stress	187	1.89	2.7%	41	2.83	2.4%
Q058 Problems with coordination	186	1.33	2.7%	40	2.80	17.1%
Q078 Cough	187	1.48	2.7%	41	2.76	9.8%
Q090 Wound healing complications	187	1.52	2.7%	41	2.66	4.9%
Q077 Wheezing	187	1.49	2.7%	41	2.54	4.9%
Q053 Chest pain	185	1.48	2.2%	40	2.53	4.9%
Q130 Reduced ability to cope	186	1.69	2.2%	41	2.90	17.1%
Q031 Sore throat	186	1.40	2.2%	41	2.37	2.4%
Q052 Abdominal pain	187	1.39	2.1%	41	2.76	9.8%
Q083 Rash	186	1.46	2.1%	41	2.71	2.4%
Q093 Swelling of legs	187	1.71	2.1%	41	2.56	2.4%
Q033 Flu symptoms	187	1.25	2.1%	41	2.32	2.4%
Q065 Tremor	187	1.33	2.1%	41	2.29	2.4%
Q126 Stress avoidance	184	1.88	1.6%	41	2.54	2.4%
Q059 Problems with speech	187	1.16	1.6%	41	2.73	14.6%
Q151 Feeling bitter	186	1.84	1.6%	40	2.68	5.0%
Q084 Skin discoloration	185	1.45	1.6%	40	2.40	7.5%
Q072 Vaginal discharge	186	1.22	1.6%	41	2.32	0.0%
Q132 Trouble thinking positively	187	1.87	1.6%	41	2.93	4.9%
Q037 Bladder infection	187	1.35	1.6%	41	2.51	2.4%
Q011 Injection Site Reaction	180	1.42	1.1%	41	2.02	2.4%
Q035 Chills	183	1.46	1.1%	40	2.50	2.5%
Q064 Numbness in other areas of the body	185	1.41	1.1%	39	2.36	0.0%
Q071 Vaginal bleeding	187	1.12	0.5%	41	2.44	2.4%
Q129 Hallucinations	186	1.10	0.0%	41	2.49	4.9%
Q079 Acne	185	1.23	0.0%	41	2.22	2.4%

9.1.10 Provisional Questionnaire – QLQ-MBR44

ENGLISH

EORTC QLQ-MBR44

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	Have you lacked the energy to do things?	1	2	3	4
2.	Have you felt exhausted?	1	2	3	4
3.	Have you had aches or pains in your muscles or joints?	1	2	3	4
4.	Have you had stiffness in your joints?	1	2	3	4
5.	Have you had aches or pains in your bones?	1	2	3	4
6.	Have you had pain in your back?	1	2	3	4
7.	Have you worried about getting an infection?	1	2	3	4
8.	Have you had a fever?	1	2	3	4
9.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
10.	Have you had problems opening a jar or bottle because of weakness in your hands?	1	2	3	4
11.	Have you lost any hair?	1	2	3	4
12.	Have you been upset by how the treatment has affected your hair?	1	2	3	4
13.	Have you had hot flushes?	1	2	3	4
14.	Have you had soreness in your mouth?	1	2	3	4
15.	Have you felt ill or unwell?	1	2	3	4
16.	To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
17.	Have you felt that nothing could cheer you up?	1	2	3	4
18.	Have you felt anxious?	1	2	3	4

Please go on to the next page

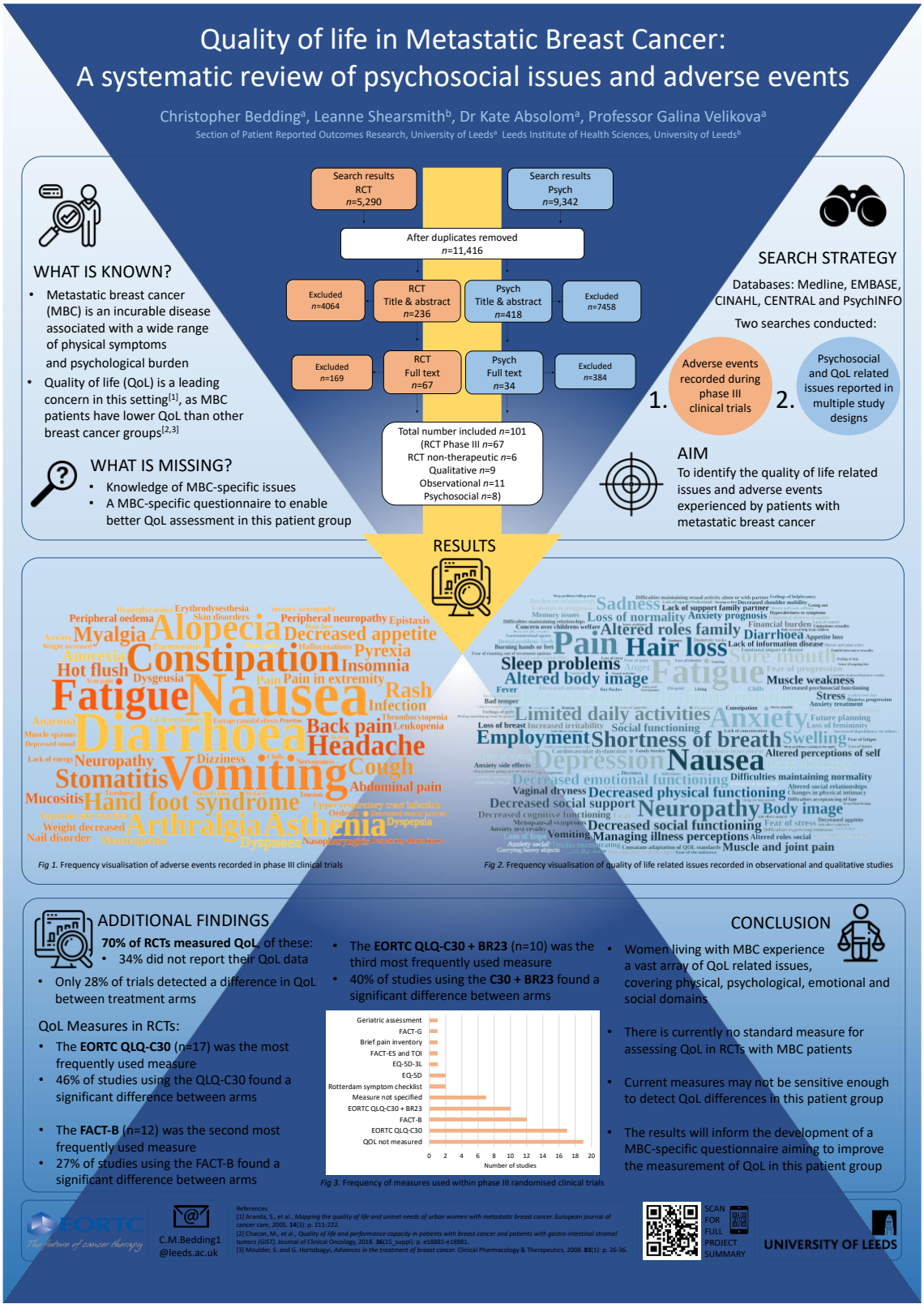
During the past four weeks:			**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
19.	How much have your disease and treatment been a burden to you?		1	2	3	4
20.	Has attending hospital visits and treatment interfered with your daily life?		1	2	3	4
21.	Has your health been unstable as a result of your disease or treatment?		1	2	3	4
22.	Has your appearance changed as a result of your disease or treatment?		1	2	3	4
23.	Have you been dissatisfied with your physical appearance?		1	2	3	4
24.	Have you worried about the future of people who are important to you?		1	2	3	4
25.	Have you worried about the impact of your cancer on your children? (If you do not have children, please select N/A)	N/A	1	2	3	4
26.	Has your physical condition or medical treatment altered the relationship with your partner? (If you do not have a partner, please select N/A)	N/A	1	2	3	4
27.	Have you felt isolated from those close to you (e.g., family, friends)?		1	2	3	4
28.	Have you felt able to talk to your family about your illness?		1	2	3	4
29.	Have you needed help from your family or friends with managing daily life?		1	2	3	4
30.	Have you worried that you are a burden to other people?		1	2	3	4
31.	Have you worried about becoming more dependent on others?		1	2	3	4
32.	Have you been afraid of disease progression?		1	2	3	4
33.	Have you worried about the results of examinations and tests?		1	2	3	4
34.	Have you worried that your daily activities might worsen your symptoms?		1	2	3	4
35.	Have you worried about what might happen towards the end of your life?		1	2	3	4
36.	Have you been worried about dying?		1	2	3	4

Please go on to the next page

During the past four weeks:			Not at All	A Little	Quite a Bit	Very Much
37.	Has it been difficult to cope with the uncertain prognosis of your disease?		1	2	3	4
38.	Have you felt uncertain about the future?		1	2	3	4
39.	Have you had to limit your life plans or goals?		1	2	3	4
40.	Has the experience of cancer helped you to distinguish between important and unimportant things in life?		1	2	3	4
41.	Have you had a dry vagina?		1	2	3	4
42.	Have you been interested in sex?		1	2	3	4
43.	Have you been sexually active (with or without sexual intercourse)?		1	2	3	4
44.	Has sexual activity been enjoyable for you? (If you have not been sexually active, please select N/A)	N/A	1	2	3	4

9.1.11 Dissemination

Bedding, C., Absolom, K., Cardoso, F., & Velikova, G. (2020). Quality of life in metastatic breast cancer: A systematic review of psychosocial issues and adverse events. PSYCHO-ONCOLOGY, 29, 25-25.



The European Organisation for Research and Treatment of Cancer (EORTC): Module Development for Metastatic Breast Cancer (Phase I-III)

Christopher Bedding[a], Dr Kate Absolom[a], Dr Fatima Cardoso[b], Dr Katarzyna Pogoda[c], Professor Galina Velikova[a]

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Background

- Metastatic breast cancer (MBC) is an incurable disease which affects multiple organs and requires continuous therapy [1].
- Quality of life (QoL) has been identified by patients as an area requiring more attention from care providers [2].
- Current questionnaires used to assess QoL in MBC patients may overlook the wide range of physical symptoms and psychological burden of living with a chronic disease [3].
- There is an unmet need for tools that can better evaluate QoL in this population [4].

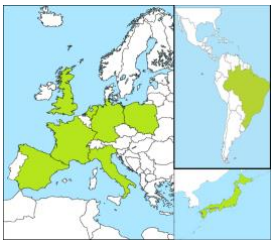
Objective

Following the EORTC module development guidance, the aim is to create a new, MBC-specific module to supplement the EORTC QLQ-C30 core questionnaire.

International Collaboration

Semi-structured interviews with MBC patients (Phase I) will be conducted in 21 sites across 9 countries.

Country	Number of participating sites
UK	3
Italy	5
France	3
The Netherlands	3
Germany	2
Poland	2
Spain	1
Brazil	1
Japan	1



Semi-structured Interviews will be conducted with 180 MBC patients and 25 healthcare professionals from centres across the world.
They will consist of two main stages;
(1) Concept elicitation
(2) Issue evaluation

(2) Patients view a list of issues identified in the literature and rate their importance and relevance.

(1) Concepts (e.g. symptoms) are identified via open-ended questions.

Online Forum Review Exploration of quality of life issues discussed by users of *Breast Cancer Now*'s online forums.

Summary of Product Characteristics review 29 drug information brochures for patients were reviewed for "very common" side effects. Treatments included: chemotherapy, targeted and endocrine therapies.

Systematic Review A review of current evidence on the QoL related issues associated with MBC and its treatments (including physical and psychosocial issues) is ongoing.

Phase I
Generation of Issues
Aim:
Compile an extensive list of quality of life issues relevant to patients with metastatic breast cancer

Phase II
Item Development
Aim:
To develop a provisional list of items (questions) comparable to the EORTC QLQ-C30

Development of provisional item list The relevance and importance scores from phase I interviews will determine whether an item is retained or removed from the list.

Avoid duplication Issues will be cross-checked against the EORTC's Item Library for related items. The Item Library contains questions and their translations from questionnaires developed by the EORTC.

Operationalisation New issues will be developed into items and translated into relevant languages

Phase III
Pilot testing
Aim:
To assess the overall acceptability of the provisional module

Structured interviews will be conducted with ~360 MBC patients from centres in at least 6 countries. This will allow qualitative exploration of the included items.

Preliminary analysis of the questionnaire's psychometric properties (whether the questionnaire measures what it intends to measure) will be conducted using data from the completed questionnaire.

Conclusion

Completion of this PhD project will result in a phase III validated EORTC QoL questionnaire for assessing quality of life of patients with metastatic breast cancer. Full international validation of the module will take place before becoming available for use with MBC patients in clinical settings worldwide.

[1] Zubair, H. and A. Ahmad, *Cancer Metastasis: An Introduction*, in *Introduction to Cancer Metastasis*. 2017, Elsevier. p. 3-12.
[2] Cardoso, F., et al., *Evolving psychosocial, emotional, functional, and support needs of women with advanced breast cancer: results from the Count Us, Know Us, Join Us and Here & Now surveys.* The Breast, 2016. **28**: p. 5-12.
[3] Cardoso, F., et al., *Global status of advanced/metastatic breast cancer. 2005-2015 decade report.* Pfizer Inc., New York, 2018.
[4] Ganz, P.A. and Stanton, A.L., 2015. Living with metastatic breast cancer. In *Improving Outcomes for Breast Cancer Survivors* (pp. 243-254). Springer, Cham.

Improving Health-Related Quality of Life in Metastatic Breast Cancer

Taking stock of achievements and delivering better measurement?

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Significant progress has been made in the management of Metastatic/Advanced Breast Cancer (MBC/ABC), and an increasing number of patients live with their disease for years rather than months [1]. MBC is very different to early breast cancer, not only biologically and clinically, but also in the wider psychosocial impact it can have on patients and their families. MBC is an incurable albeit treatable disease which can affect multiple organs and requires continuous therapy, resulting in a wide range of physical symptoms and psychological burden. To address these unique experiences, and the urgent need for specific quality of life evaluation tools, we aim to develop a disease-specific questionnaire for assessing Health Related Quality of Life (HRQOL) in this patient group.

The project is led by Professor Galina Velikova from EORTC Quality of Life group at the Patient Centred Outcomes Research group, University of Leeds, UK and Dr Fatima Cardoso from the EORTC – Breast Group, at the Champalimaud Clinical Centre, Lisbon, Portugal and builds upon the EORTC-BR23 module update. The development of the MBC questionnaire provides an ideal opportunity for collaboration across the EORTC. Members of both the Quality of Life (QLG) and Breast Cancer Groups (BCG) have been invited to work together on the project, with the aim of combining the methodological and clinical expertise of members. The project remains in its early stages, but has already received a high level of interest from both groups with over 50 sites from 14 countries expressing an interest in participating. We are currently in the process of selecting centres for Phase I.

Working within the framework of EORTC QLG module development guidelines, relevant HRQOL issues will be generated by systematically reviewing the literature and conducting semi-structured interviews with patients and healthcare professionals from centres across Europe and the rest of the world. A comprehensive search of bibliographic databases, such as PubMed and PsycINFO, is currently being conducted to identify relevant physical and psychosocial HRQOL issues for MBC patients. A purposive sample of patients and healthcare professionals will take part in semi-structured interviews, in which the list of issues generated from the review will be assessed for its relevance and breadth of coverage. We aim to have the issues prepared for review at EGAM in March and will continue to follow the development guidelines as the project progresses into Phase II and III.

For additional information about the MBC module development project or if you are interested in collaborating, please contact either Galina Velikova (g.velikova@leeds.ac.uk) or Christopher Bedding (umcmb@leeds.ac.uk).

References

1. Cardoso, F., Senkus, E., Costa, A., Papadopoulos, E., Aapro, M., André, F., Harbeck, N., Aguilar Lopez, B., Barrios, C.H., Bergh, J. and Biganzoli, L., 2018. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4). Annals of Oncology, 29(8), pp.1634-1657.