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Which quality of life issues are important to patients with metastatic breast cancer: Phase 1 and 2 development of European Organisation for Research and Treatment of Cancer metastatic breast cancer module (EORTC QLQ-MBR)

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ABSTRACT

Background: Metastatic breast cancer (MBC) remains a treatable, but incurable disease. Anti-cancer treatments and supportive therapies aim to control disease, prolong survival, ameliorate physical symptoms and improve quality of life (QoL). Currently, no validated MBC-specific patient-reported outcome measures exist, and existing tools may lack specific content and sensitivity to measure the impact of MBC. This study aims to develop a European Organisation for Research and Treatment of Cancer (EORTC) module for MBC.

Methods: Development followed EORTC module guidelines. In phase 1, QoL issues were identified via systematic literature reviews and assessed by semi-structured interviews with healthcare professionals (HCPs) and patients. In phase 2, the most relevant and important issues were converted into questionnaire items using the EORTC Item Library to form the provisional module.

Results: The review included 103 papers (phase III clinical trials n = 70 and observational or qualitative studies n = 33), from which 185 issues were extracted, spanning physical, psychological, emotional and social domains. Interviews with 41 HCPs and 187 patients from eight countries refined this list to 44. After expert panel review, the provisional module consisted of 40 issues, assessed by 44 items (EORTC QLQ-MBR44). A sub-analysis of the EORTC QLQ-C30 revealed its content to be considered relevant to MBC by HCP and patients.

Conclusion: The provisional EORTC MBC-specific module aims to enhance understanding and measurement of QoL in clinical research and care and be the first QoL tool dedicated to MBC. The standardised tool contains relevant QoL issues and is currently undergoing qualitative and psychometric testing.

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1. Introduction

Female breast cancer accounts for almost 12% of all cancers globally [1]. An estimated 13-23% of patients diagnosed with early breast cancer will develop metastatic recurrence and 3-12% are diagnosed with metastases at initial presentation in developed countries, while in developing countries *de novo* metastatic breast cancer (MBC) can be as high as 60% [2–5]. The population of patients living with MBC is increasing, largely due to improved survival associated with the introduction of targeted systemic anticancer therapies and the optimisation of multidisciplinary evidence-based care. Despite the significant treatment advancements over recent years, MBC remains treatable but still incurable [6,7].

The Advanced Breast Cancer (ABC) Global Alliance's charter aims to address the urgent and actionable gaps within this patient group, one of which is to improve quality of life (QoL) and support for psychological, social and existential challenges [8,9]. The current tools for assessing QoL in MBC include generic cancer measures which capture the wider 'cancer experience' and breast cancer specific measures which often, but not always, supplement the generic measures [10,11]. The most frequently used include the EORTC QLQ-C30 (a generic cancer measure), the EORTC QLQ-C30 plus QLQ-BR23/QLQ-BR42 (breast cancer specific module) and the FACT-B [12].

Existing breast cancer-specific measures were primarily developed in early-stage breast cancer and may lack the sensitivity needed to detect changes in MBC [11]. Early and MBC differ significantly biologically, clinically and in the wider impact they have on the individual [13]. Patients with MBC are often not well represented in the early phases of questionnaire development which may result in their issues being overlooked [14]. As many of the innovative anticancer drugs are initially tested in MBC, using generic measures may fail to capture important patient-centred adverse effects or benefits.

Disparities in QoL also exist across the various MBC subtypes as highlighted in the 2015-2025 Global Decade Report [9], furthering the need for a MBC-specific QoL questionnaire to facilitate the design of adequate interventions to improve QoL and impact in this patient group [9,11]. The Health Outcomes Observatory (H2O) consortium Delphi study recently developed a core outcome set (COS) for MBC. The COS included 101 variables including QoL and adverse events, patient characteristics and clinical variables and was designed to facilitate decision making at an individual and population level within clinical practice and research [15].

The need for a MBC-specific tool and a standardised approach in the assessment of QoL in MBC has long been discussed, as evidenced in the ABC Global Alliance Global Decade Report 2015-2025 [9] and its new Global Charter 2025-2035 [16] as well as the ABC International Consensus Guidelines [17].

In this current study we aim to develop a new EORTC module that is to be used alongside EORTC QLQ-C30 to specifically assess QoL in patients with metastatic breast cancer.

2. Materials and methods

The EORTC module development guidelines (version 4) were followed (Table 1) [18]. This paper presents the first two developmental phases which include: 1. Content generation and 2. Item development and construction of the provisional module.

2.1. Phase 1: Content generation

2.1.1. Conceptual framework

The Department of Health (UK) Generic Choice Model for long term conditions (DoH-GCM) was chosen as the conceptual framework [19]. This model, based on the needs of patients living with a chronic illness, covers 6 themes: 1) Clinical services – continuity of care, treatment decisions; 2) Symptom burden (including side-effects) and self-management; 3) Needs for independent living; 4) Work, finance and benefits; 5) Psychological experiences - living with uncertainty; burdening others, emotional support; 6) Support pathways. The model captures the wider range of problems associated with MBC. People with MBC often live for years with an incurable disease, requiring sequential treatments.

2.1.2. Systematic review

A systematic review was conducted in 2019 using Centre for Reviews and Dissemination's guidance for reviews in healthcare [20]. The review aimed to identify the wider QoL issues experienced in MBC. Two search strategies were developed. Search 1 targeted Phase III Randomised Clinical Trials of Investigational Medicinal Products (CTIMPs). Search 2 focused on observational and qualitative research studies (non-CTIMPs). Publications between 2000 and 2019 across the Medline, EMBASE, PsychINFO, Central and CINAHL databases were searched (for details see; supplement (1-2). Papers were independently reviewed for inclusion by two reviewers. A narrative synthesis informed the initial list of QoL-related issues.

2.1.3. Investigator brochure review

A review of the treatment investigator brochures (IBs) of drugs recently approved for clinical practice was conducted to supplement the systematic review (2019). Following methods outlined by Arksey and O'Malley [21], IBs were reviewed to identify the most common adverse events (AEs) associated with MBC treatments. Existing treatments were those entering clinical practice, as identified from clinical trials and clinical practice guidelines, such as National Institute for Health and Care Excellence (NICE), Advanced Breast Cancer international

Table 1
EORTC module development phases and key tasks completed.

Phase	Task
Phase 1: Content Generation	Developed conceptual framework Systematic review & investigator brochure review - Developed issue list (185 issues) Healthcare professional interviews (n = 41) Patient interviews (n = 187) Analysis – 44/185 issues rated as relevant and important to enter Phase 2
Phase 2: Item development (Construction of the provisional questionnaire)	Operationalisation of issues - EORTC Item Library review - Development of novel or modified items - Mapped to conceptual framework Review of draft v1.0 – 44 issues (50-items) – 5 issues removed due to duplication/ overlap – 1 issue added ('sore mouth') Review from collaborators and patient advocates Review of draft v2.0 – 40 issues (44-items) Submission of provisional module
Phase 3a/b: Preliminary testing of the provisional module	Proposed 44 item module - Physical symptoms (side-effects) (10 items), Fear-uncertainty (9), Family impact (5), Musculoskeletal pain (4), Sexual issues (4), Treatment (disease) impact (3), Independence-needing help (3), Fatigue (2), Body image (2), Anxiety-depression (2) Structured patient interviews Analysis - Quantitative and qualitative analysis - Preliminary psychometric evaluations
Phase 4: Field testing	International validation of acceptability, reliability, validity, responsiveness and cross-cultural applicability

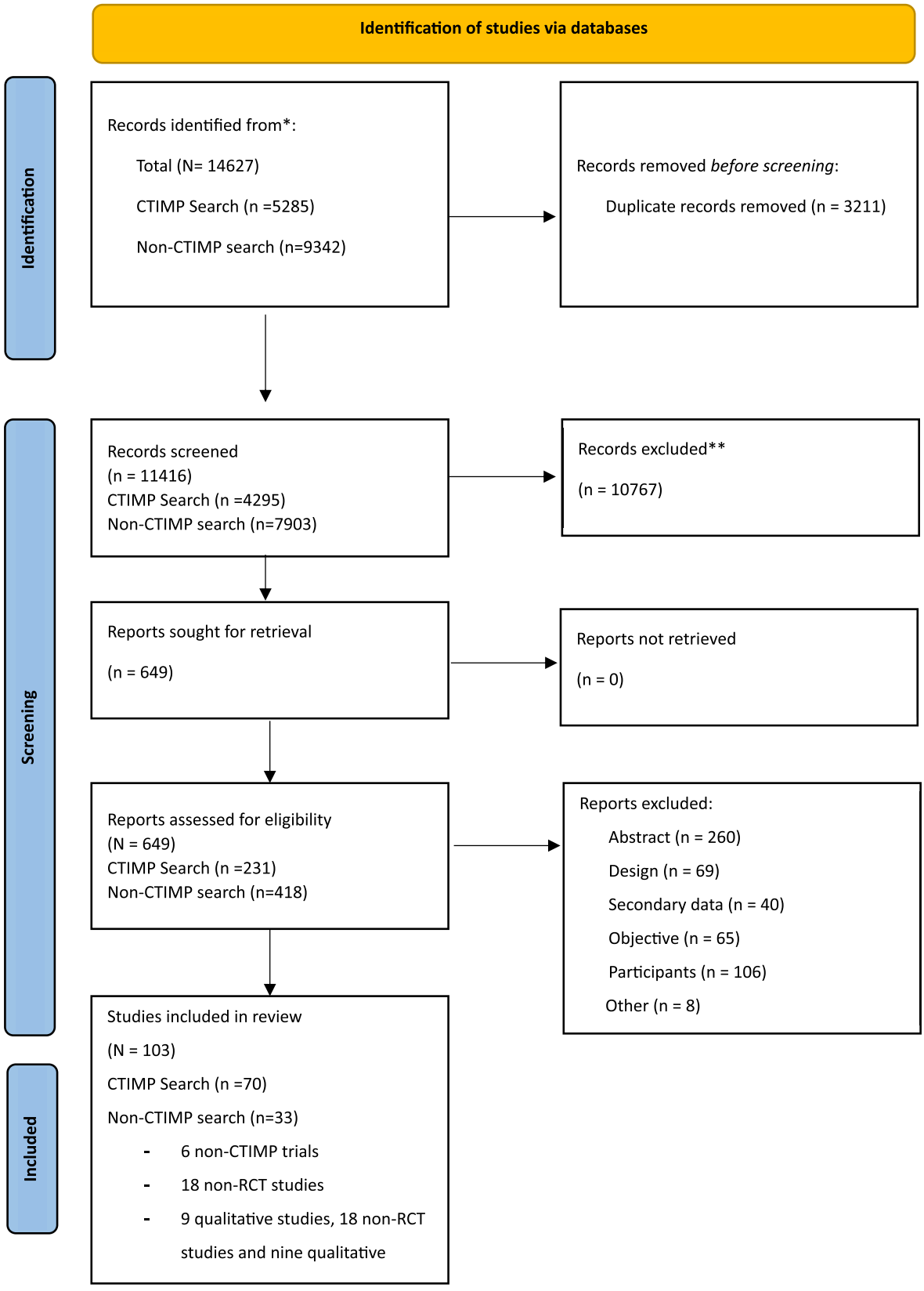


Fig. 1. Systematic review PRISMA diagram.

consensus group (ABC) and European Society for Medical Oncology (ESMO). The very common AEs (≥10%) were extracted into an excel database. The study team reviewed the AEs and extracted issues amenable to 'self-reporting'. The findings from the literature and IB review were organised according to the DoH-GCM domains and used to generate the QoL issue list, to be used in subsequent interviews. The IB review was subsequently updated to include new treatments that entered clinical practice between 2019 and 2022. Newly identified AE's

Table 2
The 15 most common issues identified in systematic review (CTIMP vs non-CTIMP) and investigator brochure review.

CTIMP Search (n = 70)		Non-CTIMP Search (n = 33)		IB review (n = 29)	
Issue	Number of studies (%)	Issue	Number of studies (%)	Issue	Number of treatments (%)
Diarrhoea	37 (53%)	**Pain**	17 (51%)	**Nausea**	21 (72%)
Nausea	35 (50%)	**Fatigue**	17 (51%)	Vomiting	17 (59%)
Vomiting	33 (47%)	**Nausea**	10 (30%)	**Fatigue**	16 (55%)
Fatigue	32 (46%)	Depression	10 (30%)	**Diarrhoea**	15 (52%)
Alopecia	22 (31%)	Anxiety	8 (24%)	Stomatitis	13 (45%)
Stomatitis	21 (30%)	Difficulty sleeping	7 (21%)	**Asthenia**	13 (45%)
Asthenia	20 (29%)	Body image	5 (15%)	**Alopecia**	12 (41%)
Constipation	20 (29%)	Fear of progression	5 (15%)	Dyspnoea	12 (41%)
Arthralgia	17 (24%)	**Hair loss**	5 (15%)	Rash	11 (38%)
Rash	15 (21%)	Shortness of breath	4 (12%)	Headache	10 (34%)
Headache	15 (21%)	**Lack of energy**	4 (12%)	Hot flushes	10 (34%)
Cough	13 (19%)	**Diarrhoea**	4 (12%)	**Arthralgia**	10 (34%)
Myalgia	12 (17%)	Difficulty concentrating	4 (12%)	Abdominal pain	10 (34%)
Hand–foot syndrome	12 (17%)	Unemployment	4 (12%)	Cough	9 (31%)
Mucositis	11 (16%)	Reduced daily activities	3 (9%)	Constipation	9 (31%)

Issues in **bold** highlight those identified across each review. CTIMP = Clinical Trial of an Investigational Medicinal Product. IB = investigator brochure.

were cross-referenced against the QoL issue list to ensure comprehensive coverage. Existing evidence and clinical expertise were then used to determine whether missing issues were incorporated into the module.

2.1.4. Patient and healthcare professional interviews

Ethical approval was obtained in eight countries (France, Germany, Italy, Japan, Jordan, Poland, Spain, UK). Eligible patients were adult females with a confirmed diagnosis and treatment history for MBC (stage IV), conversant in the language of questionnaire administration with capacity to provide informed consent. Those with a psychiatric condition or cognitive impairment were excluded. A purposive sampling matrix was developed to ensure a balanced distribution in terms of age ($\leq$50, 51-69 and $\geq$70 years old), time since metastases diagnosis (<6months, 7-24months and >25months), treatment types (endocrine therapy, targeted therapy, chemotherapy or combinations), sites and number of metastases, number of previous treatment lines, and breast cancer subtype (e.g. HER2), resulting in an estimated sample size of 180 patients (supplement 3). The target sample size for healthcare professionals (HCPs) was 25 targeting oncologists, nurses and other allied health professionals with experience in the treatment and care of patients with MBC.

Semi-structured interviews were conducted either face-to-face, or remotely (due to COVID-19 related restrictions). Interviews began with an open-ended concept elicitation to explore the impact MBC and its treatment on QoL. Participants were then asked to complete the issue list for relevance and importance (supplement 4). The list consisted of issues identified in the systematic review, investigator brochure review and core issues from existing questionnaires such as the EORTC QLQ-C30 (excluding global health status and QoL) and EORTC breast module. The issue list was translated in seven languages (Arabic, French, German, Italian, Japanese, Polish and Spanish). Participants ranked each issue for its relevance (whether it was experienced or not) on Likert scale (1-not at all to 4-very much) and then selected the 15 most important issues to be included in the new questionnaire. A free-text option was available to document any missing issues. A think-aloud approach was adopted, and researcher notes were taken throughout to capture observations and feedback from the participants.

2.1.5. Analysis

A descriptive data analysis was performed by the coordinating site (SPSS version 28). Mean relevance scores, and frequency data from the importance scores were calculated for both patients and HCPs. Four a-priori thresholds including, mean relevance ratings $\geq$2 (patient and HCP) and importance ratings $\geq$15% (patient and HCP) guided decision-making. Priority was given to patient data. Issues meeting three or more of the criteria were included, as were those with scores close to thresholds, and/or of clinical importance. Content analysis of the qualitative data from the interviews was used to support the issue selection for borderline scores. We performed separate analysis comparing those <50 years to the two older age groups, as younger breast cancer patients may have more aggressive disease, as well as specific QoL impact due to responsibilities for young families or work-related problems. Issues identified for exclusion were reviewed by the study team and international collaborators. The issues already covered in the EORTC QLQ-C30 were analysed separately for their relevance and importance.

2.2. Phase 2: Item development (Construction of the provisional questionnaire)

In Phase 2, the selected issues were operationalised into questionnaire items to create the provisional module. Each issue was searched for in the EORTC Item Library, which consists of over 1070 pre-existing items. Relevant items were extracted and reviewed for inclusion by the study team and collaborators using iterative consensus-group feedback. In collaboration with the EORTC translation unit, novel items and modified wordings were developed for issues not covered by the Item library. The provisional module was presented at EORTC Quality of life group meetings, peer reviewed and approved by the Project and Module Development Committee.

3. Results

3.1. Phase I: Content generation

3.1.1. Literature review

The two searches resulted in a total of 11,416 papers. 10,767 papers were excluded at title and abstract screening as they did not fulfil the inclusion criteria, leaving 649 relevant studies. After full-text screening, 103 papers were included in the review. Of these, 70 were Phase III RCTs of medicinal products and 33 were of various study design of non-medicinal studies (Fig. 1). The most common issues (Table 2) reported in CTIMP studies were physical symptoms and side-effects (diarrhoea, nausea and vomiting), whereas in non-CTIMP studies both physical and psychosocial issues were identified (pain, fatigue, depression and anxiety). The most frequently used QoL measure was the EORTC QLQ-C30, 28/103 (27.2%), followed by the EORTC QLQ-C30 + QLQ-BR23 16/103 (15.5%) and FACT-B 16/103 (15.5%). No MBC-specific measure was identified.

3.1.2. Investigator brochure review

Overall, 29 treatments were identified including chemotherapy (12), targeted therapy (9), endocrine therapy (7) and immunotherapy (1)

Table 3
All issues (185) presented to patients and healthcare professionals within the interviews, organised by the Generic choice model.

Generic choice domains	Number of issues (N = 185)	Issues
1. Symptom Burden	**93 (50%)**	
General	19	Difficulty doing strenuous activities, Difficulty walking long distances, Difficulty walking short distances, Need to stay in bed/chair, Need help eating, dressing or washing, Reduced daily activities, Pain, Need to rest, Pain affecting daily activities, Injection site pain, Injection site reaction, Bladder problems, Loss or lack of energy, Fatigue, Extreme fatigue, Feeling unwell, Impact of cancer symptoms, Treatment side effects, Health instability caused by treatment and symptoms
Eyes and nose	3	Eye disorders: watery, irritated or painful, Runny nose, Nose bleeds
Stomach and mouth	10	Nausea, Vomiting, Constipation, Diarrhoea, Bloated, Indigestion, Dry mouth, Difficulty swallowing, Sore throat, Mouth sores
Infections	6	Flu symptoms, Infections, Chills, Fever, Bladder infection, Chest infection
Weight and appetite	6	Decreased appetite, Loss of appetite, Weight decrease, Increased appetite, Weight increased, Severe weight loss (Anorexia)
The body - muscles and joints	13	Feeling weak, Muscle aches/pains, Muscle spasms, Muscle weakness, Joint aches, pains and stiffness, Bone pain, Back pain, Abdominal pain, Chest pain, Pain in hands or feet, Arm/shoulder pain, Difficulty raising arm, Decreased grip strength
Nervous system	9	Problems with coordination, Problems with speech, Problems with balance, Changes in taste, Headaches, Numbness, tingling or burning sensation in hands and feet, Numbness in other areas of the body, Tremor, Dizziness
Reproductive	9	Breast pain, Swollen breast, Sensitive breast area, Vaginal dryness, Vaginal bleeding, Vaginal discharge, Decreased sexual activity, Decreased sexual enjoyment, Decreased sexual interest
Lungs	3	Shortness of breath, Wheezing, Cough
Skin	12	Acne, Dry skin, Redness and/or peeling of skin, Severe itching, Rash, Skin discoloration, Hair loss, Hand-foot syndrome, Sweating, Nail problems, Skin problems around breast, Wound healing complications
Vascular	3	Hot flush, Swelling of arms, Swelling of legs
2. Psychological experiences	**68 (37%)**	
Psychological experiences	41	Difficulty concentrating, Feeling tense, Worrying, Feeling irritable, Depression, Memory issues, Feeling less attractive, Feeling less feminine, Change in appearance, Difficult to look at self-naked, Dissatisfied with body image, Loss of identity, Depressed mood/ feeling sad/down, Distress, Anxiety, Anxiety about advanced aspect, Mood disturbance, Feeling angry, Bad tempered, Less tolerant, Intrusive thoughts, Nervousness, Feeling guilty, Helplessness, Hopelessness/Loss of hope, Feeling afraid, Fear of dying, Fear of disease progression, Hyper-alertness to symptoms, Fear of making symptoms worse, Fear of stress, Stress, Stress avoidance, Long-term health concerns, Feeling confused, Hallucinations, Reduced ability to cope, Difficulty finding a purpose, Trouble thinking positively, Change of perspective, Difficulty accepting fate
Sleep	8	Difficulty sleeping, Tiredness, Difficulty falling asleep, Difficulty waking/getting up, Lack of sleep, Low quality sleep, Waking during the night, Feeling drowsy
Emotional	12	Emotions not recognised by others, Decreased emotional restraint or control, Greater emotional hardship, Difficulty expressing emotions to others, Negative reactions from others, Lack of understanding from others, Being viewed as a 'cancer victim', Managing illness perceptions, Feeling bitter, Worried about family, Parenting worries, Fear leaving family behind
Future perspective	7	Worries about the future, Unknown future, Unknown prognosis, Loss of future, Future perspective, Uncertainty, Sense of missing out
3. Clinical services	**2 (1%)**	No opportunity to enhance your QOL, Lack of symptom management
4. Need for independent living	**6 (3%)**	Limited in pursuing hobby/leisure activities, Loss of independence, Dependency on others, Reduced ability to take control, Loss of normality, Isolation
5. Work, finance and benefits	**6 (3%)**	Reduced ability to work, Financial difficulties, Unable to maintain employment, Financial impact on children, Financial impact on family, Medicalised lifestyle
6. Support pathways	**10 (6%)**	Impact on family life, Impact on social activities, Reduced social support, Altered social roles or responsibilities, Altered family roles, Needing help from family/children, Altered partner relationships, Burden on partner relations, Negative impact on relationships, Negative impact on family/children

(supplement 5). Table 2 shows the 15 most common issues. The most affected body systems were the gastrointestinal system (nausea, vomiting, diarrhoea, constipation), followed by general issues (fatigue, asthenia) and skin-related issues (alopecia, rash). Sore mouth was identified as a prevalent issue, particularly in the newer (post 2019) treatments. The triangulation of the two reviews resulted in a list containing 185 issues suitable for inclusion in a patient-reported outcome measure. Table 3 shows all included issues organised by DoH-GCM themes. Issues covered by EORTC QLQ-C30 were included in the relevant sections to allow participants to judge their relevance to MBC.

3.1.3. Healthcare professional and patient interviews

Between July 2020 – March 2021, 41 experienced healthcare professionals (oncologists, nurses, psychologists and surgeons) were recruited from nine countries, as well as 187 women with MBC from eight countries (Table 4) Patient's ages ranged from 29 to 85 years old, with a median age of 59 (*Mean age* = 58.6 years, *SD* = 13.03). The main treatment modalities were chemotherapy 41.7% (78/187), endocrine therapy alone 21.4% (40/187), endocrine therapy + targeted therapy 20.9% (39/187) and targeted therapy alone 13.4% (25/187).

Table 4
Sample characteristics for patients and healthcare professionals.

Characteristics	Patients		Healthcare professionals	
	N	Mean	N	Mean
Age	187	58.55 (SD 13.03)	40	42.55 (SD 10.82)
Missing	0	-	1	-
Age split	N	%	N	%
<50	57	30.5	-	-
51-69	79	42.2	-	-
>70	51	27.3	-	-
Gender				
Female	187	100	31	75.6
Male	0	0	10	24.4
Country				
English speaking				
UK	28	15	8	19.5
Northern Europe				
Germany	2	1.1	-	-
Belgium	-	-	3	7.3
Sweden	-	-	1	2.4
Southern Europe				
Italy	51	27.3	6	14.6
Spain	27	14.4	5	12.2
France	9	4.8	5	12.2
Switzerland	-	-	2	4.9
Greece	-	-	1	2.4
Eastern Europe				
Poland	9	4.8	-	-
Non-European				
Japan	37	19.8	-	-
Jordan	24	12.8	10	24.4
Total	187	100	41	100
Living situation				
Living with partner/spouse	111	59.4	-	-
Living alone	35	18.7	-	-
Living with children	28	15	-	-
Living with others	7	3.7	-	-
Other	6	3.2	-	-
Employment				
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	-	-
Compulsory school or less	54	29.2	-	-
University level	39	21.1	-	-
Other	5	2.7	-	-
Missing	2	-	-	-
Profession				
Oncologist	-	-	19	46.3
Nurse	-	-	14	34.1
Other	-	-	4	9.8
Psychologist	-	-	3	7.3
Surgeon	-	-	1	2.4
Experience in Years				
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	-
Clinical Characteristics				
Treatments				
Chemotherapy	78	41.7	-	-
Endocrine therapy only	40	21.4	-	-
Endocrine 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	-	-

(*continued on next page*)

Table 4 (*continued*)

Characteristics	Patients		Healthcare professionals	
	N	Mean	N	Mean
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	-	-
Lymph nodes	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	-	-

HCPs rated almost all issues as relevant, with 44% (81/185) having high mean relevance scores >3.0 (Table 5). With the exclusion of EORTC QLQ-C30 issues, only one physical issue (fatigue) was amongst the 10 most relevant issues according to HCPs.

Patients rated less than half of the issues as relevant, with 39% (73/185) having mean relevance scores >2.0 (Table 5). In the top 10 patient issues, 8 were psychological and 2 were related to the physical domain (fatigue and lack of energy). Overlap between patient and HCP perspectives were noted in 5 of the top 10 scored issues where both groups scored highly issues relating to 'worries and fears'. Fatigue was the most relevant physical issue in both groups. No new issues were added by HCPs or patients.

3.1.4. Patient ratings of EORTC QLQ-C30 core questionnaire items

A sub-analysis of the included 28 EORTC QLQ-C30 issues explored the relevance of this questionnaire for MBC patients (supplement 6). HCPs rated all 28 questionnaire issues as highly relevant (mean scores > 2.93). Patients rated 16 out of 28 issues as relevant (mean score >2.0). Issues related to role function, impact on family and social life, higher levels of physical functioning (items 1-3), emotional function, pain, fatigue, difficulty concentrating and trouble sleeping were highly rated. Patients rated physical function (QLQ-C30 items 3-5), symptoms (nausea/vomiting, lack of appetite, constipation, diarrhoea, breathlessness) and financial difficulties issues as less relevant.

3.1.5. Issue selection for the provisional module

The relevance and importance scores, analysed alongside qualitative data, resulted in the selection of 44 issues for inclusion in the provisional module (supplement 7). Four issues were borderline for the full sample ('needing help from family or children', 'parenting worries', 'vaginal dryness' and 'dissatisfied with body image'), however were relevant to the younger patients and thus included. Fourteen issues overlapped with the existing EORTC breast module, mostly related to side-effects of common treatments (endocrine or chemotherapy) (supplement 8).

3.2. Phase 2: Item development

The EORTC Item Library [22] search yielded 119 items. Novel items were developed to assess 3 missing issues (anxiety, fear of making symptoms worse and health instability caused by treatment), and 7 issues where the item library items did not accurately correspond to the original meaning of the core issue. In total, 50 items were selected to assess the 44 issues forming the initial draft version 1.0. Following an expert review, 5 issues were removed due to duplication and/or repetition ('long term health concerns', 'worries about the future', 'fear leaving family behind', 'uncertainty' and 'feeling afraid'), and one issue re-added (sore mouth) due to its clinical significance and increased prevalence in emerging treatments as identified in the updated investigator review (patient mean relevance 1.66, importance 8.60%; HCP relevance 2.90, importance 9.80%). This resulted in the provisional module (version 2.0), consisting of 40 core issues assessed via 44 items (34 items from the EORTC Item Library, 7 modified Item Library items and 3 novel items).

Issues were grouped into hypothesized scales during the expert review panel, based on the content and the generic heath model (Table 6). Anxiety and depression (2-items), body image (2-items), family impact (5-items), fatigue (2-items), fear-uncertainty (9-items), independence (3-items), musculoskeletal pain (4-items), physical symptom/side-effects (10-items), sexual issues (4-items) and treatment/disease impact (3-items).

During collaborators discussions, concerns were raised that sexual issues may be considered inappropriate in some cultures. As a result, the sexual issues were grouped at the end of the questionnaire to allow patients to omit questions they feel uncomfortable answering.

4. Discussion

The completion of phases 1-2 of the EORTC module development guidelines resulted in the development of a new, provisional, MBC-specific module (QLQ-MBR44) to be used with QLQ-C30. The comprehensive methodology utilised a systematic literature review, treatment investigator brochure review, and interviews with a large, international groups of patients, and their healthcare professionals. Interviews resulted in the identification of 40 issues deemed relevant and important in the assessment of QoL in MBC. These core issues formed the provisional module of 44 questionnaire items.

The content of the module was tailored to MBC and covered a broad range of domains including, physical, psychological, social, and family issues. A number of issues were common in both early and MBC, for example hair loss and neuropathy. The included issues were comparable to those included within the MBC core outcome set developed by Health Outcomes Observatory (H2O) project, with the exception of 6 issues (cough, headaches, rash, hand-foot syndrome, weight decrease or increase, sore mouth) [15]. This comparison led to the re-inclusion of 'sore mouth', which was omitted in phase 1. There was strong consensus among experts that sore mouth is a common adverse event of many anticancer treatments, and this was supported by evidence from the updated IB review. The remaining 5 issues were identified in phase 1, but were not rated as relevant or important to patients. These similarities support the content coverage of the combined approach of the EORTC QLQ-C30 plus our provisional module.

The provisional module has a relative predominance of psychosocial

Table 5
Top 10 issues (excluding QLQ-C30 issues) for patients and healthcare professionals ranked by mean relevance scores.

Rank	Top patient issues	Mean	Priority	Rank	Top HCP issues	Mean	Priority
1	**Fear of disease progression**	2.68	27.8%	1	**Worries about the future**	3.73	39.0%
2	**Worried about family**	2.68	25.8%	2	**Fear of disease progression**	3.68	34.1%
3	Long term health concerns	2.66	20.5%	3	Anxiety	3.66	24.4%
4	**Worries about the future**	2.61	24.2%	4	Fear of dying	3.63	26.8%
5	Unknown future	2.59	16.8%	5	**Fatigue**	3.58	43.9%
6	**Fear leaving family behind**	2.58	22.0%	6	Anxiety about advanced aspect	3.56	17.1%
7	Fear of making symptoms worse	2.53	16.0%	7	**Fear leaving family behind**	3.54	19.5%
8	**Fatigue**	2.48	21.9%	8	Depressed mood feeling sad down	3.54	22.0%
9	Unknown prognosis	2.48	12.4%	9	**Worried about family**	3.50	24.4%
10	Loss or lack of energy	2.47	15.6%	10	Parenting worries	3.44	12.2%

Mean = mean relevance score. Priority = proportion of participants selecting the issue as important for inclusion. Green = mean relevance ratings $\geq$ 2 (patient and HCP) and importance ratings $\geq$ 15% (patient and HCP). Bold = overlapping issues between patients and HCPs.

aspects related to living with advanced cancer over the physical symptoms and side-effects of treatments. These findings are in line with the conceptual model used and supported by the ABC Decade report 2.0 2015-2025 whereby the negative impact of MBC on the psychosocial wellbeing of patients has been widely reported [9]. In addition, many psychological issues could relate to how well the disease is controlled and therefore a drug that is efficacious may also improve these issues. These results were discussed with experts at the EORTC Quality of Life Group over concerns raised as to appropriateness of such issues for use in clinical trials of new treatments. To address this concern, in the future validation we will explore the development of a summary score of predominantly physical symptoms, in line with Giesinger et al. [23] methodology, to create a clinical trials index, similar to the trial outcome index recommended by FACIT [24].

Many issues from the core cancer questionnaire, EORTC QLQ-C30, were reported as relevant by patients and HCPs. This new evidence confirms that, although not disease specific, the core questionnaire is a useful measure of QoL in MBC, and historical clinical trials using EORTC QLQ-C30 (including recent trials of new treatments) still capture important aspects of MBC QoL. It is likely that some major concerns of cancer patients are independent of cancer site, especially common physical problems (pain, nausea, fatigue) or psychological and social issues. These findings support the EORTC policy of using a disease-specific module in combination with EORTC QLQ-C30, and points against using the MBC module as a stand-alone measure, as such an approach may miss important QoL issues [25].

The methodological approach, using the EORTC module development guidelines v4, is a strength of this study [18]. This standardised methodology for developing patient-reported outcome measures has produced multiple high-quality measures, used across cancer clinical trials and routine care. In addition, this multi-centre study included a network of leading experts and global collaborators resulting in a large and culturally diverse sample. The sample exceeded that of other breast cancer related modules at Phase 1 [14], which expands the generalisability and cross-cultural validity of the results. In addition, the sampling strategy was broad and balanced and included both younger and older patients. A subgroup analysis of these groups was conducted to ensure the perspectives and needs of each were adequately represented within the module. In Phase 3a and the psychometric evaluation, age-specific known-groups comparisons will also be undertaken across additional countries and languages.

Limitations of the study were in part due to the rapid development and adoption of novel treatments for MBC. As treatments evolve and new drugs with different side effect profiles enter clinical practice, the content of QoL measures may not capture new and emerging issues. In this study, we faced the challenge of many new drugs entering clinical practice since 2019 when the systematic review was conducted (including Tucatinib, Margetuximab, Alpelisib, Trastuzumab deruxtecan, Pembrolizumab, Abemaciclib). Whilst it was not feasible to update the systematic review within the project timeframe, these treatments were identified and evaluated via a review of the investigator brochures. The content of the questionnaire was cross-referenced against the side effects of these treatments. To address this limitation, future studies could consider developing an EORTC item list to supplement the module and the overall measurement strategy, thereby ensuring comprehensive assessment [25]. An additional limitation was the inclusion of only female patients; however metastatic breast cancer in males is rare and a separate module dedicated to male breast cancer is currently being developed by the EORTC QLG [26,27].

5. Conclusion

The completion of phases 1-2 of the new EORTC QLQ-MBR44 has resulted in a provisional new QoL module, the first one specific for MBC. Phase 3 is currently underway, including qualitative pre-testing with patients and initial psychometric evaluation of the module [28]. Once complete, the module will provide a standardised tool for assessing the QoL of people with MBC, enabling better understanding and measurement in clinical research as well as aiding HCPs to best support and care to their patients.

CRediT authorship contribution statement

Christopher Bedding: Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kate Absolom:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Katarzyna Pogoda:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis. **Akihiko Shimomura:** Writing – review & editing, Investigation. **Hiroto Ishiki:** Writing – review & editing, Investigation. **Juan Ignacio Arraras:** Writing – review & editing, Investigation. **Julien Peron:** Writing –

Table 6
Phase 2 results: The 40 core issues included in the provisional module grouped by proposed scale domain.

	Patients			Healthcare professionals		
Issue	N	Mean	Priority %	N	Mean	Priority %
Anxiety-depression						
Anxiety	184	2.25	12.0	41	3.66	24.4
Depressed mood feeling sad down	187	2.17	12.3	41	3.54	22.0
Body image						
Change in appearance	187	2.28	15.0	41	3.12	9.8
Dissatisfied with body image	187	1.96	5.3	41	2.95	14.6
Family impact						
Worried about family	186	2.68	25.8	40	3.5	24.4
Parenting worries	180	2.27	12.2	41	3.44	12.2
Isolation	186	1.83	8.1	39	3.13	17.5
Altered partner relationships	179	1.82	8.9	41	3.12	17.1
Fatigue						
Fatigue	186	2.48	21.9	40	3.58	43.9
Loss or lack of energy	186	2.47	15.6	40	3.2	12.5
Fear-uncertainty						
Fear of disease progression	187	2.68	27.8	40	3.68	34.1
Unknown future	185	2.59	16.8	40	3.38	7.3
Fear of making symptoms worse	187	2.53	16.0	41	3.12	4.9
Unknown prognosis	185	2.48	12.4	41	3.34	17.1
Anxiety about advanced aspect	187	2.42	19.3	41	3.56	17.1
Fear of dying	185	2.28	18.9	41	3.63	26.8
Future perspective	186	2.19	7.5	41	3.24	9.8
Independence						
Needing help from family children	187	2.37	13.4	41	3.15	4.9
Loss of independence	187	2.03	10.2	39	3.31	30.0
Dependency on others	186	2.02	12.9	41	3.24	17.1
Musculoskeletal pain						
Back pain	187	2.28	13.9	41	2.98	12.2
Muscle aches pains	186	2.26	15.6	41	3.24	19.5
Joint aches pains and stiffness	187	2.2	15.5	41	3.12	29.3
Bone pain	187	2.1	16.0	40	3.28	26.8
Physical symptoms (side-effects)						
Hair loss	184	2.45	28.6	40	3.38	42.5
Treatment side effects	186	2.41	25.1	40	3.33	36.6
Numbness tingling burning in hands feet	185	2.12	19.4	41	3.24	24.4
Hot flush	187	2.11	17.1	41	3.15	19.5
Feeling unwell	186	2.09	5.9	41	3.05	14.6
Decreased grip strength	186	2.03	14.0	40	2.53	9.8
Sore mouth*	186	1.66	8.6	41	2.9	9.8
Fever	185	1.32	1.1	40	2.83	17.1
Infections	186	1.31	3.8	41	3	14.6
Sexual issues						
Decreased sexual interest	180	2.21	15.0	40	2.9	17.1
Decreased sexual activity	178	2.16	14.0	41	2.9	19.5
Decreased sexual enjoyment	177	2.07	11.9	41	2.76	7.3
Vaginal dryness	187	1.98	10.2	41	2.8	14.6
Treatment (disease) impact						
Health instability caused by treatment and symptoms	186	2.41	17.2	41	3.1	14.6
Impact of cancer symptoms	184	2.4	14.1	39	3.28	25.0
Medicalised lifestyle	182	2.27	19.8	40	3.05	12.5

Mean = mean relevance score. Priority = proportion of participants selecting the issue as important for inclusion.

Green = mean relevance ratings ≥ 2 (patient and HCP) and importance ratings ≥ 15% (patient and HCP). *- added following expert panel review.

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Data statement

Data can be made available upon reasonable request to the EORTC Quality of Life Group.

Ethical approval

All procedures were performed in compliance with relevant laws and institutional guidelines and approved by the Health Research Authority, UK (10.12.2019 – Ref:19/YH/0350). Privacy rights have been observed and informed consent was obtained.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Galina Velikova reports financial support was provided by European Organisation for Research and Treatment of Cancer. Katarzyna Pogoda reports a relationship with AstraZeneca, Gilead, Roche, Novartis, Eli Lilly, Pfizer, MSD, Sandoz, Swixx, Bayer, Astellas, Exact Sciences and Menarini that includes: consulting or advisory, non-financial support, and speaking and lecture fees. Monica Pinto reports a relationship with Becton Dickinson that includes: funding grants and speaking and lecture fees. Given their role as editors, Galina Velikova and Fatima Cardoso had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229–63.
[2] Morgan E, et al. Metastatic recurrence in women diagnosed with non-metastatic breast cancer: a systematic review and meta-analysis. Breast Cancer Res 2024;26(1):171.
[3] Malmgren JA, et al. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990–2010. Breast Cancer Res Treat 2018;167(2):579–90.
[4] Tao L, et al. Occurrence and outcome of de novo metastatic breast cancer by subtype in a large, diverse population. Cancer Causes Control 2016;27(9):1127–38.
[5] Fuentes JDB, et al. Global stage distribution of breast cancer at diagnosis: a systematic review and meta-analysis. JAMA Oncol 2024;10(1):71–8.
[6] Gogate A, et al. Projecting the prevalence and costs of metastatic breast cancer from 2015 through 2030. JNCI Cancer Spectr 2021;5(4):pkab063.
[7] Palmieri C, Owide J, Fryer K. Estimated prevalence of metastatic breast cancer in England, 2016-2021. JAMA Netw Open 2022;5(12). e2248069-e2248069.
[8] Fallowfield L, et al. Gaps in care and support for patients with advanced breast cancer: a report from the Advanced Breast Cancer Global Alliance. JCO Glob Oncol 2021;7:976–84.
[9] Cardoso F, et al. Knowledge in motion: a decade reviewed, A future defined–the ABC Global alliance 2015-2025 decade report and 2025-2035 Global charter. Breast 2025:104601.
[10] Ghislain I, et al. Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. Lancet Oncol 2016;17(7):e294–304.
[11] Clarijs ME, et al. Measuring quality of life using patient-reported outcomes in real-world metastatic breast cancer patients: the need for a standardized approach. Cancers 2021;13(10):2308.
[12] Bjelic-Radisic V, et al. An international Phase IV field study-psychometric properties of the updated module on assessing quality of life of patients with breast cancer EORTC QLQ-BR42. Breast 2025;80:103890.
[13] Danesh M, et al. Informational needs of patients with metastatic breast cancer: what questions do they ask, and are physicians answering them? J Cancer Educ 2014;29(1):175–80.
[14] Bjelic-Radisic V, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. Ann Oncol 2020;31(2):283–8.
[15] De Ligt K, et al. International development of a patient-centered core outcome set for assessing health-related quality of life in metastatic breast cancer patients. Breast Cancer Res Treat 2023;198(2):265–81.
[16] ABC Global Alliance. ABC global charter and decade report 2025-2035 [cited 2026 1st August]; Available from: https://www.abcglobalalliance.org/abc-global-charter-report; 2025.
[17] Cardoso F, et al. 6th and 7th international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). Breast 2024;76:103756.
[18] Johnson C, et al. EORTC quality of life group guidelines for developing questionnaire modules. Brussels: EORTC QoL Group; 2011.
[19] Department of Health UK. Generic choice model for long term conditions. London: Department of Health; 2007 [cited 2025 Nov]; Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20130104184944/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081105.
[20] Tacconelli E. Systematic reviews: crd's guidance for undertaking reviews in health care. Lancet Infect Dis 2010;10(4):226.
[21] Arksey H, O'malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19–32.
[22] Kulis D, et al. The use of the EORTC item library to supplement EORTC quality of life instruments. Value Health 2017;20(9):A775.
[23] Giesinger JM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol 2016;69:79–88.
[24] Webster K, Cella D, Yost K. The F unctional A ssessment of C hronic I llness T herapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcome 2003;1(1):79.
[25] Piccinin C, et al. Flexibility in patient-reported outcome and health-related quality of life measurement: the EORTC Quality of Life Group measurement strategy. Eur J Cancer 2025;220:115392.
[26] Bjelic-Radisic V, et al. Abstract P4-01-04: adaptation of the EORTC quality of life breast cancer module for male breast cancer–results of the phase I-II module. Clin Cancer Res 2025;31(12_Supplement). p. P4-01-04-P4-01-04.
[27] Schröder CP, et al. Quality of life in male breast cancer: prospective study of the international male breast cancer program (EORTC10085/TBCRC029/BIG2-07/NABCG). Oncologist 2023;28(10):e877–83.
[28] EORTC QOL Group. EORTC module guidelines fifth edition. 2021. Available from: https://qol.eortc.org/manual/the-module-development-guidelines-2021/.