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A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer

The International Consortium for Health Outcomes Measurement (ICHOM) Initiative

Wee Loon Ong, BMedSc, MBBS, MPhil, Epi; Maartje G. Schouwenburg, MD; Annelotte C.M. van Bommel, MD; Caleb Stowell, MD; Kim H. Allison, MD; Karen E. Benn; John P. Browne, BA, PhD; Rodney D. Cooter, MBBS, MD, FRACS; Geoff P. Delaney, MBBS, MD, PhD, FRANZCR; Francois P. Duhoux, MD, PhD; Patricia A. Ganz, MD; Patricia Hancock; Reshma Jagsi, MD, DPhil; Felicia M. Knaul, MA, PhD; Anne M. Knip, RN; Linetta B. Koppert, MD, PhD; Henry M. Kuerer, MD, PhD; Sarah McLaughin, MD; Marc A. M. Mureau, MD, PhD; Ann H. Partridge, MD, MPH; Dereesa Purtell Reid, MBA; Lisa Sheeran, RN, BN; Thomas J. Smith, MD, FACP; Mark J. Stoutjesdijk, MD, MSc, PhD; Marie Jeanne T.F.D. Vrancken Peeters, MD, PhD; Yvonne Wengström, PhD; Cheng-Har Yip, FRCS; Christobel Saunders, MB, BS, FRCS, FRACS

A major challenge in value-based health care is the lack of standardized health outcomes measurements, hindering optimal monitoring and comparison of the quality of health care across different settings globally. The International Consortium for Health Outcomes Measurement (ICHOM) assembled a multidisciplinary international working group, comprised of 26 health care providers and patient advocates, to develop a standard set of value-based patient-centered outcomes for breast cancer (BC). The working group convened via 8 teleconferences and completed a follow-up survey after each meeting. A modified 2-round Delphi method was used to achieve consensus on the outcomes and case-mix variables to be included. Patient focus group meetings (8 early or metastatic BC patients) and online anonymized surveys of 1225 multinational BC patients and survivors were also conducted to obtain patients' input. The standard set encompasses survival and cancer control, and disutility of care (eg, acute treatment complications) outcomes, to be collected through administrative data and/or clinical records. A combination of multiple patient-reported outcomes measurement (PROM) tools is recommended to capture long-term degree of health outcomes. Selected case-mix factors were recommended to be collected at baseline. The ICHOM will endeavor to achieve wide buy-in of this set and facilitate its implementation in routine clinical practice in various settings and institutions worldwide.

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Supplemental content

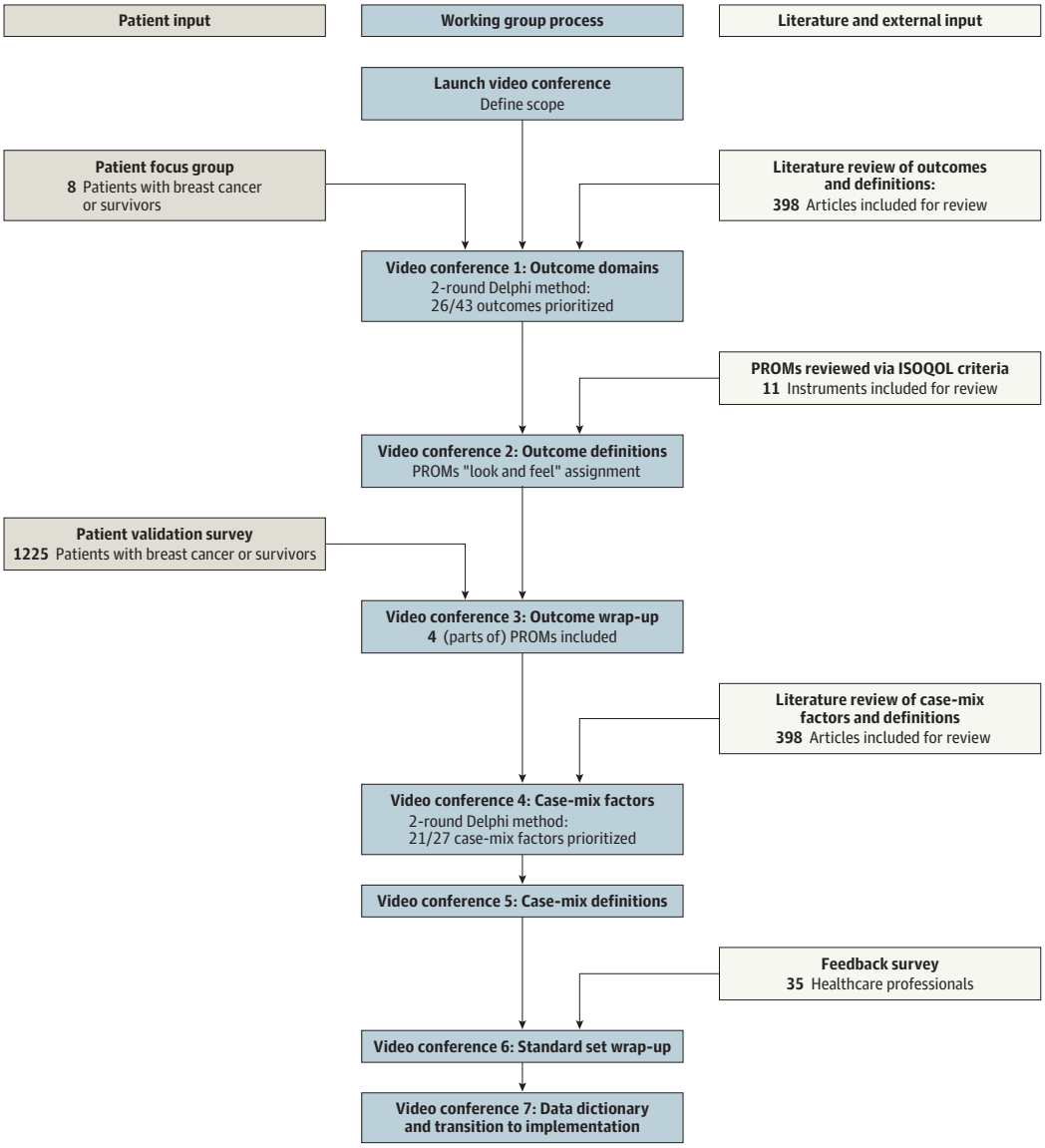
Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Wee Loon Ong, BMedSc, MBBS, MPhil Epi, Department of Epidemiology and Preventive Medicine, Monash University, Commercial Road, Prahran 3181 VIC, Australia (weeloonong@cantab.net).

Breast cancer (BC) is the most common cancer and the most common cause of cancer death in women worldwide.[1] Management of BC usually requires a multimodal approach, involving surgery, radiotherapy, chemotherapy, hormonal therapy, and survivorship care.[2,3] However, there is considerable variation in BC treatment across institutions, geographical regions and countries.[4-9] Multiple randomized trials have shown equivalent survival outcomes with different BC treatments,[10] hence the treatment decision often comes down to the value each patient places on the potential gains and losses associated with each treatment option.

While achieving high value—defined as health outcomes per dollar spent—for patients is the overarching goal of health care delivery,[11] often, defining and measuring health outcomes can be difficult. Outcome measurements need to encompass overall disease control, treatment complications, and quality of life (QOL) during and following treatment. Recognizing the lack of consistent outcome measurements, which hampers the monitoring of routine clinical practice, as well as quality of care and outcome comparison in a systematic and meaningful manner, the International Consortium for Health Outcomes Measures (ICHOM), a nonprofit organization, has initiated efforts to develop standard sets of patient-centered outcome measurements for various medical conditions, such as back pain,[12] coronary artery diseases,[13] cataract,[14] and cancers (eg, prostate cancer[15,16] and lung cancer[17]). Building on previous ICHOM experience and successes, an international multidisciplinary working group for BC was assembled to develop a minimal standard set of outcomes that matter most to patients with BC. The set can: (1) enhance clinician-patient shared decision-making, (2) provide quality outcome information to providers and institutions to drive transparency and improvement, and (3) increase the opportunity for comparative effectiveness research.

Figure 1. Summary of the Development of the ICHOM Breast Cancer Standard Set



PROMs indicates patient-reported outcome measurements; ISOQOL, International Society for Quality of Life Research.

Methods

The ICHOM Breast Cancer Working Group

The development of the set was initiated by ICHOM (http://www.ichom.org) (eTable 1 in the Supplement). The working group comprised 26 experts, including clinicians (breast and plastic surgeons, medical and radiation oncologists, pathologists, radiologists, and palliative care physicians), nurses, epidemiologists, patient representatives and advocacy groups, from Europe, North America, Latin America, Australia, and Asia. A smaller project team (W.L.O., M.S., A.V.B., C.S., and C.S.) guided the efforts of the larger working group.

Development of Breast Cancer Standard Set

The working group convened via eight videoconferences (August 2015 to April 2016), and worked through a similar process as previous ICHOM working groups.[15-17] Development of the set involved several phases (**Figure 1**).

Development of Potential Outcomes and Case-Mix List

The project team performed a structured PubMed literature review (January 1, 2005, to July 29, 2015) (eTable 2 and eFigure 1 in the Supplement) to identify relevant clinical and patient-reported QOL outcomes, treatment-related complications, survival measures, and case-mix factors. The literature review retrieved 1360 randomized clinical trials, and a total of 398 articles were included for

review. Existing BC registries were also reviewed, and working group experts were asked to identify additional relevant sources. To ensure patients' input in the outcomes selection, a focus group meeting with 8 early or metastatic BC patients was conducted (guided by W.L.O., M.S., and A.V.B.), to explore patients' perspectives on the importance of different outcomes, and what affected them, or other patients, the most during their day-to-day lives.

Modified 2-Round Delphi Method

After each videoconference, a survey was circulated, requiring each working group member to vote on the proposed outcomes, case-mix variables and PROMs. A modified 2-round Delphi approach (eTables 3 and 4 in the Supplement) was used to reach consensus. In brief, the proposed outcomes or variables needed to be voted as very important (ie, score of 7-9 on a 9-point Likert scale) in either voting rounds by more than 70% of the working group members for inclusion in the set.

Outcomes Validation

The final list of outcomes was validated in 1225 multinational BC patients and survivors, recruited via several international patient organizations (eTable 5 in the Supplement). Participants were asked to complete an anonymized survey, rating the importance of each outcome on a 9-point Likert scale, with an option of including additional outcomes in text form (eTables 6 and 7 in the Supplement).

Selection of PROMs

After finalizing the list of outcomes, the corresponding PROMs were identified. The PROMs were evaluated by the project team, based on psychometric quality according to the International Society for Quality of Life Research (ISOQOL) criteria[18] (eTable 8 in the Supplement) and the domain coverage (eTable 9 in the Supplement). Prior to the voting, working group members were asked to complete the different PROMs, from a patient's perspective.

External Input

The final draft was presented to key stakeholders and others with an interest in outcome measurement for review and to provide feedback via online survey. They were asked to rate their confidence on several elements of the set (eg, completeness of the outcome list, implementation feasibility) on a 9-point Likert scale, with an open field for comments.

Results

Condition and Treatment Scope

The set was designed for all pathologically confirmed American Joint Committee of Cancer (AJCC) patients with stages 0 to IV BC, including ductal carcinoma in situ (DCIS), in both men and women. Rare tumors such as Phyllodes tumors and lobular carcinoma in situ were excluded, given the difficulty in defining a standard of care for these tumor subtypes.

Outcomes

After consolidating the findings of the literature review and focus group meeting, a proposed list of 43 outcomes was identified for voting (eTable 3 in the Supplement), of which 26 were voted for inclusion in the set (**Table 1**). Outcomes were grouped into 3 tiers[11]: (1) survival and cancer control, (2) disutility of care (eg, acute treatment complications), and (3) degree of health (QOL and functioning, and long-term adverse effects). In the validation surveys involving 1225 multinational patients with BC and survivors, 81% agreed with the set of included outcomes (eTables 6 and 7 in the Supplement).

Survival and Cancer Control

The working group unanimously recommended the inclusion of overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS). Although progression-free survival (PFS) is another commonly reported endpoint in clinical trials, it was excluded because it depends on the frequency and intensity of surveillance, and is not considered the most relevant patient-centered outcome.

Disutility of Care

While most clinical trials collect complication data using the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE),[19] the collection of an exhaustive list of CTCAE complications is deemed infeasible in routine clinical practice, and may not be of great patient interest. The working group adopted a more patient-centered approach, and recommended collection of acute complications leading to additional major interventions, as described in the Clavien-Dindo classification[20] and CTCAE (Table 1) (eTable 11 in the Supplement). The working group also recommended collection of data on reoperation owing to involved surgical margin. We recognized that there is no universally accepted consensus on surgical margin status necessitating reoperation,[21] and the decision is often at the discretion of the surgeon and/or multidisciplinary team; however, any additional procedure after the primary surgery is considered to have an impact on patients' overall cancer treatment experience.

Degree of Health

The working group identified a minimal set of cancer-specific, and treatment-specific outcomes that have an impact on patients' long-term QOL (Table 1). Cancer-specific outcomes include overall functioning level, as well as body image and satisfaction with breast. Financial impact was frequently raised in patient surveys (eTable 7 in the Supplement) and was voted for inclusion in the final voting round (eTable 3 in the Supplement). Satisfaction and confidence in decision-making is another outcome that was raised frequently by patients. It is deemed to be an important component in a patient's journey through BC treatment; however, it did not meet the predefined voting criteria for inclusion. Among the main reason for exclusion was the ambiguity in identifying the many factors that may influence a patient's perspective of satisfaction and confidence in decision-making through the whole treatment process. Treatment-specific outcomes were also included (eg, breast and arm symptoms from surgery and radiotherapy), as well as neuropathy, vasomotor, and vaginal symptoms from systemic therapy.

It is well-recognized that these QOL outcomes are often underestimated by physicians,[22] and PROMs are increasingly being used to more accurately characterize these outcomes.[23] Given that no single PROM adequately captures all outcomes included in the set

Table 1. Summary of Outcomes for the ICHOM Breast Cancer Standard Set

Patient Population	Measure		Data Sources[a]
Survival and Disease Control			
All patients	Overall survival		Administrative
	Death attributed to breast cancer		
Patients with curative intent	Recurrence-free survival (local, regional, or distant)		Clinical
Degree of Health			
All patients	Overall well-being	Tracked via EORTC QLQ-C30	Patient-reported
	Physical functioning		
	Emotional functioning		
	Cognitive functioning		
	Social functioning		
	Ability to work		
	Anxiety		
	Depression		
	Insomnia		
	Financial impact		
	Pain		
	Fatigue		
	Sexual functioning	Tracked via EORTC QLQ-BR23	
	Body image		
Patients with surgery and/or radiotherapy	Satisfaction with breast(s)	Tracked via BREAST-Q-Satisfaction With Breasts domain	Patient reported
	Arm symptoms	Tracked via EORTC QLQ-BR23	
	Breast symptoms		
Patients with systemic therapy	Vasomotor symptoms	Tracked via EORTC QLQ-BR23	Patient reported
	Peripheral neuropathy	Tracked via EORTC QLQ-LMC21-one item	
	Vaginal symptoms	Tracked via ES of the FACT-6 items	
	Arthralgia		
Disutility of Care			
Patients with surgery	Reoperations owing to involved margins		Clinical and/or patient reported
All patients with treatment	Severity of acute complications based on the Clavien-Dindo and CTCAE		Clinical
	Name of acute complication		

Abbreviations: BR, Breast Cancer module; C, Core module; CTCAE, US National Cancer Institute Common Terminology Criteria for Adverse Events; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ES, Endocrine Subscale; FACT, Functional Assessment of Cancer Therapy; LMC, Colorectal Liver Metastases.

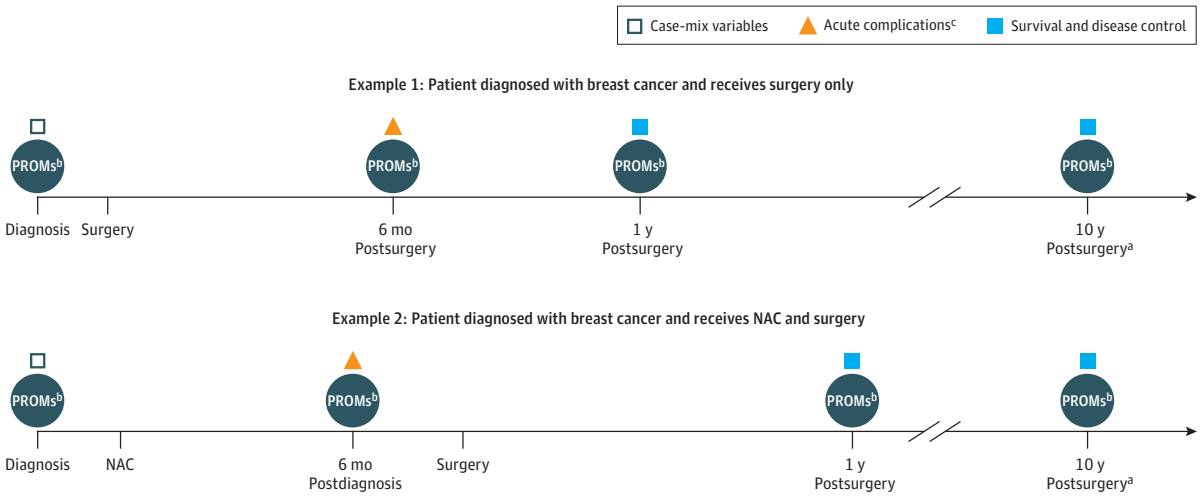
[a] The data source reflects the way outcomes are collected and was determined as clinical (eg, physician report), patient-reported (eg, EORTC QLQ C-30), and administrative (eg, death registry), in some cases a combination.

(eTable 9 in the Supplement), the working group recommended the use of a combination of multiple PROMs (Table 1). The working group recognized that selection and recommendation of PROMs for inclusion in the set can be contentious given that there are multiple available PROMs of high psychometric quality (eg, European Organization for Research and Treatment of Cancer Quality of Life [EORTC-QLQ] and Functional Assessment of Cancer Therapy [FACT] questionnaires) that are already being used in different institutions. The PROMs were evaluated based on the outcomes coverage, psychometric quality, clinical interpretability, and feasibility of PROMs implementation in daily practice (eTables 8 and 9 in the Supplement). After extensive discussions and a "look-and-feel" assignment, the use of EORTC-QLQ-Core (C30)[24] and EORTC-QLQ-Breast Cancer (BR23)[25] was eventually recommended by the working group to capture the core cancer-specific and BC-specific outcomes. The working group also recommended additional questions from other PROMs to capture outcomes not encompassed by the EORTC questionnaires. These included the BREAST-Q[26] subscale for breast satisfaction, a single item from EORTC-QLQ-Liver Metastases (Colorectal) (LMC21)[27] for peripheral neuropathy, and 6 items from the FACT-Endocrine Subscale (ES)[28] for vaginal symptoms and arthralgia. The assessment of degree of health outcomes was recommended at baseline (ie, at diagnosis), 6 months after primary surgery, and annually thereafter (**Figure 2**). Follow-up was recommended up to 10 years in early BC patients to capture the period during which patients might still be on endocrine therapy.

Case-Mix Variables

The working group identified a minimal set of demographic, clinical, and tumor-related factors to be collected at baseline for meaningful outcome comparisons (**Table 2**). While socioeconomic status (SES) is an important demographic factor, accurate characterization of SES can be complex, involving multiple components such as occupation and income. As with previous ICHOM working groups, the BC working group recommended the collection of education level based on the International Standard of Schooling Classification[29] because it is reported to be a good surrogate for SES, easy to obtain, and globally comparable.[30] Relationship status is also

Figure 2. Sample Timelines Illustrating When Particular Outcomes and Baseline Factors Should Be Collected for Patients With Breast Cancer



These timelines are intended to represent the outcome data collection points for possible treatment paths a patient could take, and do not advocate a particular treatment approach. Of note, a majority of baseline factors should be collected at the time of initiation of the Breast Cancer Standard Set, although several (eg, pathologic stage) are collected after treatment. NAC indicates neoadjuvant chemotherapy; PROMs, patient-reported outcome measurements.

[a] Collection of acute complications is recommended while the patient is undergoing treatment or within 90 days of treatment completion, except for complications of hormonal therapy which will be collected up to 1 year.

[b] All PROMs will be collected at baseline, 6 months after treatment, and then annually, except for the BREAST-Q-Satisfaction with Breasts domain, which will only be collected at baseline,1 year, and 2 years after treatment.

[c] Distinction for long-term follow-up: patients with local disease; follow-up up to 10 years, patients with advanced disease; follow-up annually for life.

included, because it is an indicator of available social support and is associated with survival and several functional outcomes.[31] Race and ethnicity did not meet the predefined voting criteria for inclusion in the set. However, because there is evidence suggesting its potential association with treatment decisions[32] and outcomes[33,34] for certain countries, it was decided to include this as optional.

Patients' baseline health status is another important factor influencing treatment decision-making and eventual treatment outcomes. However, the Eastern Cooperative Oncology Group (ECOG) performance status scoring is deemed to be an over-simplified representation of patients' health status, and is not commonly collected in patients with early stage BC. Likewise, collection of the Charlson Comorbidity Index (CCI) can be burdensome. Therefore, the working group recommended the use of the modified Self-administered Comorbidity Questionnaire (SCQ) to capture a list of relevant medical comorbidities,[35] and baseline health status as measured by the EORTC-QLQ-C30/BR23 (Table 1). It has been shown that SCQ predicts functional outcomes as well as the CCI.[36] Tumor factors to be collected are based on the AJCC TNM staging. Information on hormone and human epidermal growth factor receptor 2 status are recommended to be collected as a binary data ("yes" or "no"), recognizing variability in pathology reporting between institutions and countries.

Treatment Variables

To provide a standardized terminology of treatment options over heterogeneous, international health care settings, the most commonly used treatment modalities in daily practice were included (Table 2). Patients should also be asked to report on their ongoing treatments during follow-up because clinical data may be inaccurate, especially with endocrine therapy adherence.[37]

External Input

A total of 35 health care professionals from different specialties completed the survey. The respondents were confident (mean score, 6.7 on 9-point Likert scale) of the comprehensiveness of the outcome list, case-mix variables, and feasibility of data collection in routine clinical practice (eTable 10 in the Supplement). The main concerns raised were related to the lack of end-of-life (EOL) care outcomes, and the number of PROMs items, which could lead to noncompliance.

Data Collection and Implementation

The next crucial step after finalizing the BC set is the adoption and implementation of the set. To minimize variability and inconsistency in data collection, a reference guide including sample questionnaires and a data dictionary has been created by ICHOM (http://www.ichom.org/medical-conditions/breast-cancer/). This will cover the potential source of the data, including clinical records and patient-reported sources, as well as frequency for each data collection.

Discussion

With rising health care costs, and the options of multiple treatment modalities and prolonged survival among patients with BC, the importance of value-based health care is increasingly being recognized.[38] However, a major challenge in value-based health care

Table 2. Summary of Case-Mix Factors[a] and Treatment Approaches for the ICHOM Breast Cancer Standard Set

Patient Population	Measure	Data Sources[b]
Demographic Factors		
All patients	Sex	Patient-reported
	Date of birth	
	Body mass index	Clinical
	Ethnicity	Patient-reported
	Educational level[c]	
	Relationship status	
	Menopausal status	
Baseline Clinical Factors		
All patients	Comorbidities via the modified SCQ[d]	Patient-reported
	Laterality	Clinical
	Second primary tumor	
Baseline Tumor Factors		
All patients	Date of histological diagnosis	Clinical
	Histological type	
	Mutation status predisposing BC	
	Tumor grade (invasive)	
	Tumor grade (DCIS)	
Patients with NAC	Clinical TNM stage (AJCC 7th edition)	Clinical
Patients with surgery	Pathological TNM stage (AJCC 7th edition)	Clinical
	Size of invasive component of tumor (in millimeters)	
	Number of lymph nodes resected	
	Number of lymph nodes involved	
	Estrogen receptor status	
	Progesteron receptor status	
	HER-2 status	
Treatment Approaches		
All patients	(Reconstructive) surgery	Clinical and/or patient-reported
	(Neo)adjuvant radiotherapy	
	(Neo)adjuvant chemotherapy	
	Targeted therapy	
	(Neo)adjuvant hormonal therapy	
	No therapy	

Abbreviations: AJCC, American Joint Committee on Cancer; BC, breast cancer; DCIS, ductal carcinoma in situ; HER-2, human epidermal growth factor receptor 2; NAC, neo-adjuvant therapy; SCQ, self-administered comorbidity questionnaire.

[a] All case-mix factors include measures with corresponding patient populations, definitions or supporting information, timing for collection and source of data.

[b] The data source reflects the way outcomes are collected and was determined as clinical (eg, physician report), patient-reported (eg, EORTC QLQ C-30), and administrative, in some cases a combination.

[c] Level of schooling defined in each country according to the International Standard Classification of Education.

[d] Have you ever been told by a doctor that you have any of the following? I have no other disease, heart disease (eg, angina, heart attack, or heart failure), high blood pressure, leg pain when walking owing to poor circulation, lung disease (eg, asthma, chronic bronchitis, or emphysema), diabetes, kidney disease, liver disease, problems caused by stroke, disease of the nervous system (eg, Parkinson disease or multiple sclerosis), other cancer (within the last 5 years), depression, arthritis (select all that apply).

is the lack of standardization in outcome measurements meaningful to patients across different cultural and geographical settings.[38] The ICHOM has therefore convened an international multidisciplinary working group, from middle- to high-income countries, to develop a standard set of patient-centered outcomes that should be measured in all patients with BC.

The aim was to develop a set which can, and should be collected in routine clinical practice, even in resource-limited health systems. We acknowledge that randomized controlled trials remain the gold standard for treatment outcomes comparison; however, the measurement of outcomes in routine clinical practice will better reflect outcomes in a real life setting. Furthermore, the set can function as a core outcomes measurement to be collected in trial settings, and can be expanded to include additional outcomes, based on individual trial requirements.

We are cognizant of the need to collect minimal data to limit burden to both health care providers and patients, but at the same time recognize the need to encompass important outcomes for meaningful comparisons. More than 80% of the multinational survey respondents agreed with the set, providing support that the set captures the key outcomes relevant to patients with BC. The working group is aware that the recommendation of collecting (part of) multiple PROMs, ranging from 59 to 82 questions, represents significant patient burden. However, patient representatives in the working group did not find the PROMs too cumbersome, because they are all salient questions. The EORTC is currently developing computerized adaptive testing (CAT) versions, which should reduce respondent burden.[39] In addition, there is evidence suggesting clinical benefits in symptom-monitoring with PROM during routine cancer treatment.[40]

The primary PROMs recommended by the working group are based on the EORTC questionnaire. However, other PROMs, such as the FACT questionnaire, are also commonly used in many institutions. In fact there is no strong evidence to suggest that the psychometric properties of 1 PROMs are superior to the other.[41] However, the EORTC questionnaire was deemed to be less ambiguous by the working group (after having completed both EORTC and FACT questionnaires themselves), and has wider outcomes coverage, encompassing outcomes such as cognitive functioning and financial impact. The working group recognized that switching across to the EORTC questionnaire might cause disruption in longitudinal data collection in institutions not currently using it. Hence, future studies are definitely warranted in making commonly used PROMs comparable, to allow for transition into the implementation of the standardized measurement recommended by the working group.

To our knowledge, this is the first international set incorporating outcomes of almost a full cycle of BC care, from diagnosis to completion of treatment and long-term survivorship, with an emphasis on patient-reported outcomes. Other entities currently measuring BC care outcomes have largely been monodisciplinary, focusing largely on surgical treatments,[42,43] are more related to measuring and defining quality by processes and short-term outcomes of BC care,[44-46] or have been set up for a short research period.[47] It is also important to acknowledge that the BC set does not include outcomes measurement on EOL care. While EOL care was raised during several videoconferences, the working group felt that EOL care is often not BC-specific, and ICHOM will consider assembling a palliative care working group to develop a standard set encompassing EOL care across various cancers and medical conditions.

To facilitate the implementation and for practicality, the working group has developed a measurement timeline in such a way that the PROMs collection runs in conjunction with patients' follow-up visits, and so the data can be used as part of clinical consultation. Even so, ICHOM recognizes the challenges involved in implementation. Routine collection of this set in clinical settings will require investment in human resources and information technology, and will depend on the active involvement of clinicians, who must see the value of having such data at the point of care, as well as for retrospective and comparative analyses.

Initially, ICHOM aims to facilitate the implementation process in a number of pilot institutions. The experience and lessons learned from these institutions will be documented, and feedback to a steering committee comprising a subgroup of the current working group members, to refine the set and to prepare it for widespread adoption. This approach has been successfully adopted for the localized prostate cancer set, facilitated by the Movember Foundation.[48] The implementation process will involve 4 phases: (1) to engage clinical champions and establish proper governance process; (2) to identify current measurement audit practices and gaps, and suggest practical strategies for collecting structured clinical data and administrating PROM assessment at the indicated time points; (3) to use pilot sites to trial strategies including existing data sets collection; and (4) to establish how to feedback the data to the clinical teams (eTable 12 in the Supplement).

While this process can take a year or more, advancement in the capabilities of electronic health record (EHR) systems, and in third-party applications capable of integrating with those systems, are continuously reducing the time and complexity of implementation. Myriad tools are available today, and an increasing number of health care providers have demonstrated that outcomes sets like this can be implemented via EHR integration with automated data extraction and collection of PROMs.[49-51] While this may be challenging in low to middle income health care settings, where EHR systems are less prevalent and follow-up is often limited and fragmented, the recommended follow-up should ideally be the gold standard of care and what all institutions should strive for.

Conclusions

Through the use of literature review and extensive patient input, an international multidisciplinary team of BC experts has developed a minimal standard set of value-based patient-centered outcome measures, deemed to be most important to patients with BC, and generally applicable worldwide. It is recommended that the set is collected in routine clinical practice. This will allow for monitoring and meaningful comparison of BC treatment outcomes within, and across, countries, and in the longer term facilitate improvement in BC care worldwide.

ARTICLE INFORMATION

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Author Affiliations: Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (Ong, Cooter); Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne Australia (Ong); International Consortium for health outcomes Measurement, Cambridge, Massachusetts (Schouwenburg, van Bommel, Stowell); Dutch Institute for Clinical Auditing, Leiden, the Netherlands (Schouwenburg, van Bommel); Department of Pathology, Stanford University, Stanford, California (Allison); EUROPA DONNA, The European Breast Cancer Coalition (Benn); Department of Epidemiology and Public Health, University of College Cork, Cork, Ireland (Browne); Ingham Health and Medical Research Institute, South Western Sydney Local Health District, NSW, Australia (Delaney); South Western Sydney Clinical School, University of New South Wales (Delaney); King Albert II Cancer Institute, Cliniques Universitaires Saint-Luc, Brussels, Belgium (Duhoux); Department of Health Policy & Management, UCLA Fielding School of Public Health, California (Ganz); Breast Cancer Network Australia, VIC, Australia (Hancock); Department of Radiation Oncology, University of Michigan, Michigan (Jagsi); Miami Institute for the Americas, University of Miami, Florida (Knaul); Cáncer de Mama: Tómatelo a Pecho, Mexico City, Mexico (Knaul); Dutch Breast Cancer Association (BVN), Utrecht, the Netherlands (Knip); Department of Surgical Oncology, Erasmus MC Cancer Institute, University Medical Centre, Rotterdam, the Netherlands (Koppert); Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Texas (Kuerer); Department of Surgery, Mayo Clinic, Florida (McLaughin); Department of Plastic and Reconstructive Surgery, Erasmus MC Cancer Institute, University Medical Centre, Rotterdam, the Netherlands (Mureau); Department of Medical Oncology, Dana-Farber Cancer Institute, Massachusetts (Partridge); Hoag Orthopedic Institute, California (Reid); Breast Service, Peter MacCallum Cancer Centre, Melbourne, Australia (Sheeran); Department of Oncology and Palliative Medicine, Johns Hopkins Medical Institutions, Maryland (Smith); Department of Radiology, Ikazia Hospital, Rotterdam, the Netherlands (Stoutjesdijk); Breast Center ZuidHollandZuid, Rotterdam, the Netherlands (Stoutjesdijk); Department of Surgery, the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands (Vrancken Peeters); Division of Nursing, Karolinska Institutet, Department NVS, Stockholm, Sweden (Wengström); Department of Oncology & Pathology, Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden (Wengström); Department of Surgery, Subang Jaya Medical Centre, Malaysia (Yip); School of Surgery, University of Western Australia, WA, Australia (Saunders).

Author Contributions: Dr Schouwenburg had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. Drs Ong and Schouwenburg contributed equally to the work as co-first authors.
Concept and design: Schouwenburg, van Bommel, Stowell, Allison, Ganz, Knaul, Koppert, Kuerer, Mureau, Reid, Sheeran, Smith, Stoutjesdijk, Vrancken Peeters, Wengström, Yip, Saunders.
Acquisition, analysis, or interpretation of data: Ong, Schouwenburg, Allison, Benn, Browne, cooter, Delaney, Duhoux, Ganz, Hancock, Jagsi, Knip, Kuerer, McLaughlin, Partridge, Smith, Vrancken Peeters, Saunders.
Drafting of the manuscript: Ong, Schouwenburg, Browne, Reid, Sheeran, Saunders.
Critical revision of the manuscript for important intellectual content: Schouwenburg, van Bommel, Stowell, Allison, Benn, cooter, Delaney, Duhoux, Ganz, Hancock, Jagsi, Knaul, Knip, Koppert, Kuerer, McLaughlin, Mureau, Partridge, Smith, Stoutjesdijk, Vrancken Peeters, Wengström, Yip, Saunders.
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Study supervision: van Bommel, Stowell, Allison, Browne, Kuerer, McLaughlin, Vrancken Peeters, Saunders.

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