Patient-Reported Outcomes in the Translational Breast Cancer Research Consortium

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Abstract

Members of the Translational Breast Cancer Research Consortium conducted an expert-driven literature review to identify a list of domains and to evaluate potential measures of these domains for inclusion in a list of preferred measures. Measures were included if they were easily available, free of charge, and had acceptable psychometrics based on published peer-reviewed analyses. A total of 22 domains and 52 measures were identified during the selection process. Taken together, these measures form a reliable and validated list of measurement tools that are easily available and used in multiple cancer trials to assess patient-reported outcomes in relevant patients.

Keywords

INTRODUCTION

Patient-reported outcomes (PROs) are important measures of treatment benefit and toxicity for patients with cancer. The traditional medical provider-based collection of side effects and

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symptoms, such as those collected in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), now is recognized to be inadequate for understanding the full array and severities of cancer-related symptoms and treatment-related side effects.[1] For example, patient reports of certain symptoms (eg, fatigue) during clinical trials tend to occur earlier and be more severe than those reported by clinicians,[2–5] and presumably reflect more accurately how the patients truly feel. PROs provide an alternate method for reporting sensitive issues or particular symptoms that patients may not feel comfortable discussing with their medical team.

Understanding the patient experience during cancer treatment not only allows for optimal symptom management and the tailoring of cancer treatments to improve quality of life (QOL), but also may translate into disease-related benefits. For example, Basch et al recently published a trial randomizing timely communication of PROs to clinicians versus usual care for patients receiving chemotherapy for metastatic solid tumors. Among 766 participants, these investigators found that the median overall survival was 31.2 months (95% CI, 24.5–39.6 months) in the PRO group and 26.0 months (95% CI, 22.1–30.9 months) in the usual-care group $(P = .03)$, with an adjusted hazard ratio for death of 0.83 (95% CI, 0.70–0.99; $P = .04$). Patients in the PRO group tolerated chemotherapy on average 1.9 months longer compared with those in the usual-care group, most likely due to the improved symptom control that was facilitated by the communication of PROs to clinicians.

For years, patients and advocates have expressed the need and value of incorporating PROs into clinical trials. When new drugs are being studied in a clinical trial setting, PROs can provide crucial information regarding unexpected side effects. PROs can provide a useful measure of drug toxicities or declines in physical function, particularly within the setting of metastatic disease. The challenge is to consistently incorporate PROs into clinical trials without undue patient burden or considerable additional cost.

The Translational Breast Cancer Research Consortium (TBCRC) was established in 2005 to conduct trials in patients with breast cancer. In 2016, the TBCRC established a PRO interest group tasked with identifying a list of PROs used in TBCRC clinical trials, and since then all new trials are reviewed for consideration of the inclusion of PROs. It now is standard policy for all TBCRC trials to be reviewed for the inclusion of PROS before the trials are initiated.

One of the first activities of the PRO committee was to present the recommended selection of PRO measures regarding relevant domains for use in the trials associated with the TBCRC. This guide was meant to assist those less familiar with PROs to review options and select scientifically sound measures. The guide also was meant to help coordinate the measures across studies for easier comparison of effects. It is not an exhaustive review, but it is a selection of measures that exist in the literature. These measures all have been used in other trials, have at least some psychometric data behind them, and are free or of low cost to the investigators.

MATERIALS AND METHODS

The TBCRC is a national consortium of investigators working together to foster trial development and conduct clinical translational breast cancer treatment trials. The TBCRC was founded in 2005, and now includes 19 collaborative sites and subcommittee working groups organized around breast cancer phenotypes (eg, HER2 resistance, locoregional disease, etc). In 2016, a subgroup of TBCRC investigators with interest and experience in measuring PROs gathered to identify appropriate measures for inclusion in relevant TBCRC studies. This subgroup discussed a list of concepts that could form the basis of TBCRC measures for consideration in any relevant trial that was designed within the TBCRC.

Table 1 presents the eligibility criteria for the inclusion of PROs in the list. We used expert consensus to select domains relevant to the types of cancers targeted in TBCRC, that had measures existing in the literature, had been used in at least 1 previous trial, that were possible to obtain for broad use, and that had at least some psychometric data related to their reliability and validity. As we tabulated these measures, we discussed additional information that might be useful for measure selection. For each TBCRC trial, we recommended the inclusion of an overall QOL measure that could be compared across trials and cancer sites, as well as site-specific measures of symptoms unique to that type or site of cancer. We also recommended that a member of the PROs subgroup volunteer to work with each trial's team of investigators to help select measures and to support the analysis of the data.

RESULTS

Table 2[5–45] presents the selected measures, organized by domain, with the first listing within each domain being the choice recommended by the working group for common use in TBCRC trials. Each table entry includes the measure's name, its number of items, and the period of time for which the measure asks participants to provide data (recall period). We have briefly described the scoring method and scores provided by the measure and provided a source for permissions, if any are required for use. Finally, we have provided an estimate of the amount of psychometric work previously completed for investigators to consider. For each scale, we rated the psychometric work as "extensive" if reliability and validity were reported multiple times and the measure had been used in national or international projects, "moderate" if some of this work had been reported, and "minimal" if little of the psychometric work had been reported.

As seen in Table 2,[5–45] we identified 22 domains to form the basis of our guide. These ranged from health-related QOL, a very general measure that can be used for patients with multiple cancer sites and stages; to lymphedema, which often is used specifically with patients who have undergone breast surgery; to financial toxicity, a recently identified domain with which to assess the financial and resource-related difficulties experienced by patients with cancer. In general, the large number of measures in many of the categories, combined with the extensive psychometric research conducted on many of the measures, reflect the maturity of the field of PRO development. We rejected measures that could not be obtained for free or low cost because the expense of using these rejected measures often

would be beyond the budgets of many TBCRC trials. Measures in Table 2[5–45] are easy to score and use, with limited permission needed for use.

Table 3 provides examples of 3 TBCRC studies that can serve as examples of using PROs in the measurement battery. This is not an exhaustive list, but has provided specific examples of trials that included PROs. Within the TBCRC 022 trial, we collected neurocognitive function for the first cohort of 40 patients from baseline to the end of treatment. Values were compared for the Hopkins Verbal Learning Test–Revised Total and Delayed Recall, Hopkins Verbal Learning Test–Revised Delayed Recognition, Trail Making Test Parts A and B, and Controlled Oral Word Association. Change in QOL from baseline to the end of treatment was evaluated using 7 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) measures: health status, physical functioning, cognitive functioning, diarrhea, fatigue, nausea and vomiting, and emotional functioning. Because of the complexity and time required to administer these neurocognitive instruments, as well as the deterioration of health in many of the study participants with progressing brain metastases, the collection of data was incomplete, with paired data available for only 17 to 24 of the 40 enrolled patients, depending on the measure. Because it is likely that many of the sickest patients did not complete the end-of-treatment survey instruments, the data collected may not accurately represent the level of decline in cognitive function and deterioration of QOL among patients with rapidly progressing tumors. Nonetheless, the collection of detailed baseline data provides valuable neurocognitive information regarding this specific patient population that can prove useful in establishing meaningful measurement "anchors" and anticipated effect sizes for changes in QOL in future studies.

The Patient-Reported Outcomes Measurement Information System (PROMIS) QOL short form and the CTCAE and PRO-CTCAE, which to our knowledge are the recommended tools for evaluating QOL and symptoms, are being used within the trial entitled "Immunotherapy Combination Strategies to Treat Triple Negative Breast Cancer," which is a multicenter, multiarm TBCRC study. These questionnaires were combined with study-specific PROs, tools that evaluate a patient's social function and satisfaction with treatment decisions, to form the PRO battery for this multiarm, phase 2 study evaluating immunotherapy in combination with targeted therapy.

To reduce the burden of the distribution and collection of paper surveys, and to facilitate the central collection and ease of analysis of PRO data, multiple electronic platforms currently are available for the collection of PRO data. We selected the Research Electronic Data Capture (REDCap) as our system of choice for administration and data capture in TBCRC trials. REDCap is a cost-efficient, web-based, cross-platform data collection and management system supported by most academic research facilities and institutions. Study staff can program survey questions and response format into REDCap, thereby eliminating the need for costly custom database construction. Furthermore, REDCap can be easily programmed to send a link to REDCap questionnaires via email to all study participants at multiple time points with reminders if necessary. Once the participant has answered the REDCap questionnaire online, data automatically are stored in a database housed behind an institutional firewall that is accessible only to study staff for ready download in usable data

set formats. Regular downloads and reports generated by the REDCap system can be customized for this study to provide recruitment updates and data quality monitoring directly from the REDCap database. Survey programming can be transferred among institutions to support the collection of the same data in multiple sites for multiple studies.

DISCUSSION

Herein, we have presented a guide for the selection of PRO measures for translational breast cancer clinical trials. There were many measures to choose from in the literature, most with at least some psychometric data available to support their use. Through extended discussions, we selected measures based on patient burden, validity, cost, and breadth of use. This effort toward common tools will allow for comparison across trials and build experience with the use and interpretation of these measures. It will support clinical decisions regarding intervention efficacy from the patient perspective as well as from a treatment perspective.

PROs can be included in both early-stage and late-stage cancer-focused studies to better understand the patient perspective in these studied areas. Other investigators might be able to use this list as a starting point for building a similar guide for use in other cancer sites. Many choices exist for the method of administration, including paper administration, in-person administration, or electronic administration, depending on the response rate needed, the characteristics of the participants, and the budget and time available for administration. We selected to try for a more electronically administered method in general because of its simplicity and ease of administration. However, the choice of the method of administration will be left up to the investigator teams. For a discussion of the method of administration, please see Aday and Cornelis.[46]

Selecting and implementing measures for inclusion into translational research trials have some challenges. Increasing participant burden is one challenge. Ensuring that survey documents are easy to use in multiple platforms (eg, cell phone completion methods) reduces this burden. Based on our experience, we recognize that it is critical to consider both patient performance status and trial coordinator time burden in the selection of QOL instruments. It also is important to acknowledge that in a patient population with advanced disease, additional effort is required to collect at least a portion of off-study/ end-of-treatment data whenever possible. Last, statistical calculations must take into account missing data, recognizing that those patients who do not complete QOL surveys, especially at the end of treatment, may be likely to have worse QOL compared with those who do complete the surveys.

Limitations

There are several aspects to this article that limit its usefulness and generalizability to the larger field. First, this was an expert-driven review by a specific group of investigators within the TBCRC. Therefore, the recommendations in this review are limited to breast cancer research in academic medical settings and may not apply to other settings, such as community-based research. All investigators were based in the United States, and therefore this group contains a US-centric perspective. Future efforts to incorporate PROs in breast

cancer research should be applied across language and cultural barriers. One next logical step in PRO research would allow for the direct comparison of psychometric properties in several populations.

Conclusions

Incorporation of PROs is an important component of translational research and will become increasingly relevant as new discoveries are implemented into clinical care. We propose this list as a reference and summary of one group's approach to the measurement of PROs. We hope that it will stimulate discussion and enable the field to gather relevant data from the patient's perspective and thereby inform trial outcomes and clinical care improvement.

Acknowledgments

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TABLE 1.

Inclusion Criteria for the Selection of PROs Into the Study

Name of Criterion	Description
PRO relevance	Treatment of breast cancer; describes some element of the patient experience
Exists in the literature	Measures were published in a peer-reviewed journal
Used in at least 1 other trial	Cited in at least 1 trial
Some psychometric data published	Some information regarding validity and reliability available
Low or no cost; available online	No burden on studies

Abbreviation: PROs, patient-reported outcomes.

TABLE 2.

PRO Measures for Inclusion in TBCRC Trials

PRO Scale Name	No. of Items	Measurement Period[b]	Scoring Method	Permission	Psychometric Data
HRQOL					
PROMIS-10[a][5-8]	10	7 d	Patients are given 10 items to rate of 5 core domains; results (except pain rating) are averaged by 5 category response scales	Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Extensive
Functional Assessment of Cancer Therapy–Breast (FACT-B)[9-11]	44	7 d	Patients are given 0 to 4 items formatted as statements to rank. Some scores are summed to create subscale, some scores are summed for overall score	Free (http://www.facit.org/FACITOrg)	Extensive
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)[12-14]	30	1 wk	Average of all items, linear transformation to put scores from 0 to 100	Free (http://groups.eortc.be/qol/eortc-qlq-c30)	Extensive
EuroQol 5-Dimensions (EQ-5D)[15]	5	Today	Scored as 5 dimensions and also as summary score overall as well as visual analog scale for general health status	Free (https://euroqol.org/)	Extensive
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Breast Cancer Module (BR25)[16]	23	1 wk	5 multi-item scales and single items, and scores are transformed into a scale of 0 to 100	Free, but meant to be used only with QLQ-C30; permission details at http://groups.eortc.be/qol/why-do-we-need-modules	Extensive
Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[16]	12	4 wk	8 scaled scores that are weighted sums of individual items	Free (http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html)	Extensive
Functional Assessment of Cancer Therapy–Brain[17]	23	7 d	Patients are given 0 to 4 items formatted as statements to rank. Some scores are summed to create subscale, some scores are summed for overall score	Free (http://www.facit.org/FACITOrg)	Extensive
General physical symptoms					
Patient-reported outcomes version of the Common Terminology Criteria For Adverse Events (PRO-CTCAE)[a][18]	1–126	1–3 wk	Averaged across domains	Free (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Physical functioning					
PROMIS Adult Physical Function Short Form 1[19]	4, 6, 8, 10, and 20			Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	
Endocrine therapy side effects					
BCPT Symptom Scales[a][20]	42	4 wk	Participants rate the degree to which a symptom has bothered them on a 5-point or 6-point scale	Free; contact author to use	Moderate

Cancer. Author manuscript; available in PMC 2021 March 01.

PRO Scale Name	No. of Items	Measurement Period[b]	Scoring Method	Permission	Psychometric Data
PRO-CTCAE[21]	2	1 wk	Participants rate the severity of each symptom on 5-point scale; responses are scored from 0 to 4	Free (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Extensive
Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES)[22]	18	7 d	Participants rate the degree to which they experience each symptom on 5-point scale. The overall score is calculated from all items combined	Free (http://www.facit.org/FACITOrg)	Moderate
Sexual dysfunction[23]					
PROMIS Sexual Function and Satisfaction (PROMISSexF5)[24]	7	30 d	Average for subscores and overall scores	Free; no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Moderate
PRO-CTCAE dyspareunia, anorgasmia, and delayed orgasm items[22]	3	1 wk	Combined across items for overall score	Free, no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Female sexual function[3]	19	4 wk	Scores averaged across items for subscales and overall scales	Free, no permission needed; contact authors	Moderate
Pain					
PROMIS Pain Intensity–Short Form 3a[a,24]	3	7 d	Combined across items for overall score	Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Extensive
PROMIS Adult Pain Interference Short Form Version 1[24]	4, 6, and 8	7 d	Combined across items for overall score adjusted for number of questions answered (except for 4 items)	Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Extensive
PRO-CTCAE Pain items[24]	3	1 wk	Combined for overall score	Free; no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Brief Pain Inventory (BPI)[25]	7	7 d	The severity composite score was calculated as the arithmetic mean of the 4 severity items	Permission required; place request at http://www.mdanderson.org/BPI	Moderate
Fatigue					
PROMIS Cancer Fatigue Short-Form[a,8]	7	7 days	Summative scores across all items	Free, no permission needed; http://www.healthmeasures.net/explore-measurement-systems/promis	Moderate
Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)[26,27]	7	7 d	Combined to form subscales and overall scores	Free (http://www.facit.org/FACITOrg.)	Extensive
Brief Fatigue Inventory[8]	9	24 h	Combined into a single scale score	Permission required; place request at http://www.mdanderson.org/BFI	Moderate
Neuropathy					
EORTC CIPN-20[a,28]	20	1 wk	Combined across items for overall score	Permission required; place request to melodie.cherton@eortc.be	Moderate

PRO Scale Name	No. of Items	Measurement Period[b]	Scoring Method	Permission	Psychometric Data
PRO-CTCAE sensory neuropathy items[29]	2	1 wk	Combined for overall score	Free, no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Cognitive dysfunction					
PROMIS Applied Cognition Concerns[a],[30]	8	7 d	Overall score is represented as a T score, normalized against the US population	Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Moderate
PRO-CTCAE concentration and memory impairment items[31]	4	1 wk	Combined for overall score	Free, no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Functional Assessment in Cancer Therapy–Cognitive Function (FACT-Cog)[32]	50	7 d	Combined to form an overall score	Free (http://www.facit.org/FACITOrg)	Moderate
Aesthetics and breast satisfaction before/after surgery					
Functional Assessment in Cancer Therapy–BREAST[49]		2 wk	Combined into multiple modules	Complete user agreement at www.breast-q.org or WWW.PROCOLID.ORG	Moderate
Mental health					
PROMIS Emotional Distress–Anxiety and Depression–Short Form 4a[a],[5-8]	13	7 d	Items combined to form 2 subscales: anxiety and depression	Free, no permission needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	Moderate
PRO-CTCAE anxiety and depression items[21]	9	7 d	Combined to form overall scale	Free, no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Hospital Anxiety and Depression Scale (HADS)[33]	14	1 wk	Items summed within areas to form 2 subscores	http://shop.gl-assessment.co.uk/home.php?cat=417	Extensive
Center for Epidemiologic Studies Depression Scale (CES-D/CES-D 10)[34]	20	2 wk	Summed scores provide overall score	Public domain, free (http://cesd-r.com/)	Extensive
Sleep					
PRO-CTCAE[a],[5-8]	2	1 wk	Combined across subscales to provide overall score	Free, no permission needed (https://healthcaredelivery.cancer.gov/pro-ctcae/register.html)	Moderate
Pittsburgh Sleep Quality index (PSQI)[6]	19	1 mo	Summed by subscale to provide overall score	Free (buyssedj@upmc.edu for permission)	Moderate
PROMIS Adult Sleep Disturbance Version 1.0 Short Form[35]	4, 6, and 8		Items combined to form 2 subscales	Free, no permissions needed (http://www.healthmeasures.net/explore-measurement-systems/promis)	No data given
Comorbidities					

PRO Scale Name	No. of Items	Measurement Period[b]	Scoring Method	Permission	Psychometric Data
Adult Comorbidity Evaluation-27 (ACE-27)[36]			Combined to form overall score	Online version requires registration at http://www.medicalalgorithms.com/comorbidity-scores-cancer	Some
Cardiac toxicity					
MDASI-Heart Failure[37]	27	24 h	Combined to produce single overall score	Permission required; place request at http://www.mdanderson.org/MDASI	Moderate
Treatment satisfaction					
Treatment Satisfaction Questionnaire for Medication (TSQM)[2]	14	Now	Summation to form overall score	Request permission from http://www.quintiles.com/landing-pages/treatment-satisfaction-questionnaire-for-medication-tsqm	Moderate
Exercise					
International Physical Activity Questionnaire–Short Form (IPAQ-SF)[38]	7	7 d	Data summarized according to the physical activities recorded and estimated time spent sitting per wk	Accessible at www.ipaq.ki.se	Extensive
Social functioning					
Ability to Participate in Social Functions PROMIS Short Form[5–8]	8	7 d	Combined to form single overall score	Free, no permissions needed	Moderate
Adherence					
Measure of Nonadherence Part 1 (Extent of Nonadherence)[39]	3	7 d	Average of responses across the 3 items	https://sites.duke.edu/corrinevoils	Moderate
Adherence Estimator[40]	3	NA (questions in present tense)	Summed across 3 items to form trichotomous score	Free, permission needed; place request at Heather.black@merck.com	Minimal
Lymphedema					
LBCQ[2]	19	Now and during past y	Combined to form subscaies	Use is tracked via a form that can be obtained by armer@missouri.edu	Minimal
Financial toxicity					
COST[a,41–43]	11	NA (questions in present tense)	Participants rate importance a 4-point Likert scale	Free, no permissions needed (www.costofcancercare.org)	Moderate
Work productivity					
Work Productivity and Activity Impairment questionnaire in CD (WPAI:CD)[44]	6	7 d	Summation to obtain overall score	http://www.reillyassociates.net/WPAI_General.html	Minimal
Decision-making preferences and perception					
The Control Preferences Scale (CPS)[45]	5	Newly diagnosed	Cards sorted by patients using preference judgements	Free, no permissions needed; contact author	Minimal

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Abbreviations: BCPT, Breast Cancer Prevention Trial; COST, Comprehensive Score for financial Toxicity; EORTC-CIPN, European Organization for Research and Treatment of Cancer—chemotherapy-induced peripheral neuropathy; HRQOL, health-related quality of life; LBCQ, Lymphedema and Breast Cancer Questionnaire; MDASI, MD Anderson Symptom Inventory; NA, not applicable; PRO, patient-reported outcome, PROMIS, Patient-Reported Outcomes Measurement Information System; TBCRC, Translational Breast Cancer Research Consortium.

[a]Indicates preferred measure.

[b]Indicates the period of measurement embedded in the instructions for the measurement.

TABLE 3.

Examples of PROs in Use in Clinical Trials of the TBCRC

Name of Trial	General Measures Selected	Study-Specific Measures Selected
A Phase II Trial of Neratinib for Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases	Seven EORTC QLQ-C30 QOL measures	HVLT-R Total and Delayed Recall, HVLT-R Delayed Recognition, Trail Making Test Parts A and B, and Controlled Oral Word Association
Immunotherapy Combination Strategies to Treat Triple-Negative Breast Cancer	PROMIS QOL short form and the PRO-CTCAE	PROMIS Ability to Participate in Social Roles and Activities, Treatment Satisfaction Questionnaire for Medication
A prospective analysis of surgery in patients presenting with Stage IV breast cancer	PROMIS QOL short form and the PRO-CTCAE	Social function and satisfaction with treatment decisions

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HVLT-R, Hopkins Verbal Learning Test-Revised; PRO, patient-reported outcome, PRO-CTCAE, patient-reported outcomes version of the Common Terminology Criteria For Adverse Events; PROMIS, Patient-Reported Outcomes Measurement Information System; QOL, quality of life; TBCRC, Translational Breast Cancer Research Consortium.