



EFFECTIVENESS GUIDANCE DOCUMENT

Recommendations for Incorporating Patient-Reported Outcomes (PROs) into Clinical Comparative Effectiveness Research (CER) in Adult Oncology

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TABLE OF CONTENTS

TABLE OF CONTENTS	ii
EXECUTIVE SUMMARY	iii
PREFACE	v
INTRODUCTION	1
RECOMMENDATIONS	3
SELECTION OF MEASURES	3
IMPLEMENTATION METHODS	9
DATA ANALYSIS AND REPORTING	13
References	16
Appendix: MEMBERS OF THE TECHNICAL WORKING GROUP	19

EXECUTIVE SUMMARY

The Center for Medical Technology Policy (CMTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design and reporting of prospective clinical studies intended to inform decisions by patients, clinicians and payers. The recommendations are targeted to clinical researchers conducting studies of specific clinical interventions or health conditions. EGDs are intended to be analogous and complementary to Food and Drug Administration (FDA) guidance documents, but are focused on design elements that are particularly relevant to clinical and health policy decision-making. The recommended methods aim to balance validity with relevance and feasibility, in order to provide decision-makers with a reasonable level of confidence that the intervention improves net health outcomes. These documents are developed through an extensive consultative process involving a broad range of experts and stakeholders. A summary of the EGD development process is included in the preface, and is available on [CMTP's website](#), which describes the purpose of EGDs, target audiences, intended uses, topic selection, and related information.

The purpose of this EGD is to provide recommendations for the appropriate inclusion of patient-reported outcome (PRO) measures in the design and implementation of clinical CER in adult oncology. The principles and recommendations in this EGD were developed with input from patient advocacy groups, medical oncologists, pharmaceutical companies, US government agencies, public and private payers, drug compendia, clinical research entities, statisticians, and academics. The principles and recommendations in this EGD were formulated based on an a priori-defined multi-step process that involved semi-structured interviews conducted by CMTP staff, consensus meetings with a 13-member Technical Working Group (TWG), an in-person meeting hosted on December 8, 2010 with five subsequent telephone meetings to draft these recommendations.

The following statements summarize the recommendations of this EGD. Although these recommendations are not intended to be an all-inclusive set of recommendations for this aspect of clinical research, they are intended to improve the process by which studies in adult cancer patients are conducted to provide evidence that is helpful to patients and decision-makers.

Patient-Reported Outcomes EGD Recommendations

SELECTION OF MEASURES

1. Include patient-reported outcome measures in all prospective clinical comparative effectiveness research studies in adult oncology.
2. Include patient-reported symptoms that are appropriate to a study's population, intervention, context, objectives, and setting.
3. Include an assessment of health-related quality of life.
4. Consider a measure that enables cost-utility analysis.
5. Assure that measures have demonstrated validity, reliability, and sensitivity in a comparable patient population, as well as an appropriate recall period.

IMPLEMENTATION METHODS

6. Limit PRO data collection so that the average patient can complete the process as quickly as possible. This is ideally within 20 minutes at baseline and within 10-15 minutes at subsequent time points.
7. Collect PRO data as frequently as necessary to meet research objectives, without overburdening patients.
8. Collect PRO data via electronic data capture technologies whenever possible.
9. Consider whether measurement equivalence has been established when mixing modes of patient-reported data collection (e.g. web, telephone, handheld device, paper, tablet computers).
10. Employ methods to minimize missing patient-reported data including education of site personnel, training of patients, and real-time monitoring of adherence with backup data collection.

DATA ANALYSIS AND REPORTING

11. Conduct a power calculation for the key patient-reported endpoints when designing a study.
12. Include a plan for analyzing and reporting missing patient-reported data.
13. Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful for each measure, as well as mean group changes.
14. Consider evaluating the cumulative distribution of responses and including cumulative distribution curves in publications.
15. Analyze and publish results of PRO data collection simultaneously with other clinical outcomes.

PREFACE

The Center for Medical Technology Policy (CMTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies intended to inform decisions by patients, clinicians and payers. EGDs do not provide general methodological advice, but rather offer specific study design recommendations that are relevant to a defined clinical condition and/or category of clinical interventions. The purpose of EGDs is to better align the design of clinical research with the information needs of patients, clinicians, and payers. EGD recommendations will generally address one or more of the following elements of study design: patient inclusion/exclusion criteria, choice of comparators, research settings, selection of outcomes, duration of follow-up and other key elements of trial design that are most relevant to the topic of each guidance.

The primary audience for EGDs is clinical researchers who are developing research protocols for studies that are intended to be helpful to patients, clinicians and/or payers in making clinical or health policy decisions. This would include researchers from life sciences companies with clinical development responsibilities, or other clinical researchers receiving funding from public sources, foundations, etc. EGDs are intended to be analogous to FDA guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision-making. EGD recommendations are not intended to establish standards for research to be considered adequate with respect to coverage, payment or pricing decisions. They are likely, however, to be aligned with the expressed evidence preference of public and private payers, as they are developed with payer input.

The methods recommendations in EGDs are guided by the objective of achieving an acceptable balance across a number of desirable dimensions, including validity, relevance, feasibility and timeliness. Overall, the objective of EGDs is to offer study design recommendations that would give decision-makers a reasonable level of confidence that the intervention studies would improve net health outcomes.

The recommendations in an EGD are influenced, and sometimes limited by the available information. As new information about the epidemiology and natural history of a disease, or about the methods used to diagnose and/or treat that disease becomes available, the recommendations in an EGD may be modified.

There are a number of potential benefits of the creation and use of EGDs. First and foremost, they could help increase the consistency with which the body of clinical research that is reflective of the information needs articulated by patients, clinicians and payers. In addition, EGDs could contribute to greater consistency of trial design across studies of related treatments within specific clinical conditions, allowing for higher quality meta-analysis and systematic reviews due to reduced heterogeneity across multiple studies. By considering existing regulatory guidance in the EGD process, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making.

There are three primary features that distinguish EGDs from the majority of other methods guidance documents. First, EGDs focus on a specific clinical area or category of interventions, while most other available methods guidance documents are more general and apply across a broad range of clinical conditions or technologies. Second, a number of the other documents provide guidance on reviewing

Recommendations for Incorporating Patient-Reported Outcomes into the Design of Clinical Trials in Adult Oncology

the quality of existing studies, while EGDs provide recommendations for the design of future studies. Finally, we are not aware of any other documents that actively engage patients, clinicians and payers in the process of developing recommendations, with the goal of ensuring that the information needs of these decision-makers is given significant attention in generating methods recommendations.

Process and Development of this EGD

EGD recommendations are developed through an extensive consultative process involving a broad range of experts and stakeholders, including mechanisms for broad public review and comment. CMTP develops EGD recommendations with the support of a Technical Working Group (TWG) consisting of experts in clinical care and research methods specific to the clinical domain that is the focus of the EGD, and also includes patient, clinician and payer representatives. Draft EGDs are made available for public comment through targeted distribution to all key stakeholders, posting draft documents on the CMTP website, and meetings including one or more invitation methods symposia to address the most complex or controversial issues. All feedback on the draft EGD is reviewed by CMTP staff and the TWG in developing a “final” version of the EGD, which is posted on the CMTP website and widely distributed. Full details about EGDs are available at <http://www.cmtponet.org/effectiveness-guidance-documents/>.

The principles in this EGD were developed based on a series of semi-structured stakeholder interviews, followed by a multi-disciplinary stakeholder meeting hosted by CMTP in Baltimore, Maryland, on December 8, 2010. Participants in the interviews and the meeting included representatives from patient advocacy groups, medical oncologists, pharmaceutical companies, US government agencies, public and private payers, clinical research entities, statisticians, and academics. CMTP maintains full authorship and editorial control over this EGD and all other materials related to this initiative. Authors of this EGD received no compensation.

INTRODUCTION

Purpose

The purpose of this EGD is to provide recommendations for the inclusion of patient-reported outcome (PRO) data in prospective clinical comparative effectiveness research in adult patients with cancer. These recommendations are intended to set a minimum standard to ensure that studies examine patients' directly reported experiences. This patient-centered approach necessitates that the selection of outcomes for a particular study be based on input from representatives of a target population; that the measures used to assess these outcomes are meaningful to patients; and that results be analyzed and published in a rigorous, timely, and clinically useful manner. This EGD addresses these imperatives, within a broader context of emphasizing methodological rigor and the importance of employing endpoint models which are comparable across studies whenever possible.

Since the 1990s, the assessment of PROs has increasingly become recognized as important for those treatment- and/or disease-related consequences that are directly experienced by patients themselves, such as symptoms and health-related quality of life (HRQOL). The importance of incorporating PROs into cancer research and policy formation has been emphasized by major policy-making, standard setting, and regulatory entities¹ including the National Cancer Institute,² American Cancer Society,³ US Food and Drug Administration,^{4,5} U.S. Centers for Medicare & Medicaid Services,⁶ and National Institutes of Health.⁷

Systematic collection of PRO data is feasible and efficient, more reflective of underlying health status than clinician reporting, predicts meaningful clinical outcomes including survival, increases patient satisfaction with care, is valued by clinicians, and improves symptom management and patients' overall health status.⁸⁻¹⁶ Moreover, in the regulatory setting, patient self-reporting is the preferred method for collecting information about outcomes the patient knows best, as described in the FDA PRO Guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."¹⁷

The FDA PRO Guidance provides information for drug and other medical product manufacturers regarding FDA's thinking about clinical trials when an FDA-approved PRO-based labeling claim is desired. If a U.S. labeling claim is sought based on patient-reported data, which is beyond the scope of this EGD, then design and selection of measures in keeping with the FDA PRO Guidance is advised. The FDA PRO Guidance document does not specifically apply to CER or post-approval trials unless a sponsor is aiming to change the label. Thus, there is a need for guidance when selecting non-regulatory PRO endpoint measures for clinical research.

Recognition of the importance of integrating the patient perspective into CER is reflected in the creation of the Patient-Centered Outcomes Research Institute (PCORI) under the U.S. Patient Protection and Affordable Care Act.¹⁸ This legislation specifies that comparative clinical effectiveness research shall be designed to take into account patients' "quality of life" preferences. Moreover, the scope of PCORI's work includes identifying methods for incorporating the patient perspective into CER.

Presently, there is no evidence-based guideline or guidance document for the inclusion of PRO endpoints in CER in adult oncology. As such, these endpoints are variably included in studies. This EGD

offers guidance for improving the consistency and usefulness of PRO data in adult oncology studies. It aims to reflect the desires and needs of patients, clinicians, policy-makers, and payers by promoting the collection of PRO data that will enhance communication, education, decision-making, quality of care, and patient-centered outcomes.

Rationale and Scope of EGD

Patients' subjective experiences constitute information that is essential to any study examining the real-world outcomes of existing treatments or process interventions. PROs offer value added to standard clinical research and clinical care in several ways. First, they constitute research outcomes that, themselves, can serve as targets of study. Second, they provide a greater level of detail and comprehensiveness in descriptions of patients and populations, allowing for finer and/or new lines of distinction. Third, they enhance clinical care by improving communication between patients and providers, generating data that can be used to evaluate quality of care, complementing other data types in a rapid learning model of healthcare, and providing data to bolster reimbursement requests. Fourth, they allow systematic surveillance of treatment harms/toxicities when patients are subjected to available treatment regimens or care processes.

Inclusion of PRO assessments in research is particularly important in oncology, because it is common for the sequelae of cancer, its treatments, and associated psychosocial factors to impact patients' subjective experiences and function. There is a long history of assessing symptoms and health-related quality of life (HRQOL) in cancer research, but standards for collecting and reporting this information outside of the regulatory context are not widely accepted.

Although some aspects of this EGD may apply to diseases other than cancer, and to trials enrolling children, the focus of this EGD is specific to clinical studies in adult oncology. Through guiding the design and reporting of studies that adhere to its recommendations, this EGD is intended to generate a better understanding of the impact of treatments and care processes on patients. It will thus foster the generation of more clinically meaningful and valid evidence for post-regulatory decision-makers. The 15 recommendations that follow provide guidance for including PRO endpoints in the design of prospective clinical CER in adult oncology, spanning diverse interventions, populations, and study designs. We acknowledge that research issues, interests, and needs will vary across study types (i.e., registries, prospective observational studies, randomized controlled trials, studies for other purposes, and pragmatic clinical trials) and that investigators will tailor the PRO measurement approach to their specific study.

RECOMMENDATIONS

SELECTION OF MEASURES

RECOMMENDATION 1: Include patient-reported outcome measures in all prospective clinical comparative effectiveness research studies in adult oncology.

Rationale

Patient self-reporting provides the most direct measure of patients’ experiences with disease and treatment. Abundant evidence demonstrates that non-PRO data do not adequately reflect these experiences.^{9,19,20} Therefore, lack of inclusion of PROs misses important outcomes that reflect the impact of interventions or healthcare processes on patients. Although additional financial cost and effort is involved when PRO data are collected, not including direct measures of the patient experience is an omission of essential information that patients, clinicians, payers, investigators, and regulators need for decision-making.

Implementation

- Systematic collection of PROs should be incorporated into the design of registries, observational cohort studies, and controlled trials.
- If PRO measures are not included, a justification should be provided for their omission.
- PRO measures should be used to assess both the benefits and harms (toxicities) of treatments.

Challenges

- Including PRO assessments in research requires methodological expertise, infrastructure, training of site personnel and patients, and associated expense and effort. To overcome these challenges, investigators must think about integrating these endpoints early in study development, consider how PRO endpoints will complement other outcomes in a given context, engage appropriate experts, and understand the necessary resources.

RECOMMENDATION 2: Include patient-reported symptoms that are appropriate to a study’s population, intervention, context, objectives, and setting.

Rationale

Both cancer and its treatment can result in symptoms that impact patients’ functional status, general health perceptions, and quality of life.²¹ Measuring symptoms from the patient perspective is critical to understanding the burden of cancer on people’s lives. While numerous PRO measures have been used and evaluated in oncology, measure selection should be based on the needs of a study, psychometric properties of the PRO measure, and characteristics of the population.

TABLE 1. RECOMMENDED PRO MEASURES	
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FACT	Functional Assessment of Cancer Therapy
MDASI	M.D. Anderson Symptom Inventory
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROMIS	Patient-Reported Outcomes Measurement Information System

Implementation

- To understand what symptoms are prevalent and meaningful to patients in a given context, an investigator should conduct a literature review and/or qualitative and quantitative research with patients prior to conducting a study. This information, in addition to characteristics of the study's target disease and intervention, should guide selection of outcomes and measures.
- There are existing PRO measures that can inform what symptoms are prevalent and meaningful to patients. **Table 1** provides recommended measures based on the available evidence supporting their psychometric properties and past use in cancer research.
 - The EORTC QLQ-C30, FACT, and MDASI are questionnaires that include core modules with a static list of commonly experienced symptoms (as well as functioning and HRQOL measures), and offer optional context-specific modules with additional symptoms.
 - The PROMIS provides researchers access to short forms for a number of selected symptoms and HRQOL.
 - The PRO-CTCAE is an item library designed specifically for assessing symptoms related to treatment toxicity or tolerability, and may be used to complement other measures that are intended to assess the impact of interventions on symptoms related to disease, or in studies where the focus is on symptomatic toxicities (such as dose-finding, comparative tolerability assessments, or safety surveillance.)
- For measures with a static list of symptoms, studies should consider including a mechanism for collecting unsolicited symptoms from patients.
- The selection of measure(s) should depend on the context of the trial. If a longer HRQOL assessment is desired, investigators could administer the QLQ-C30 supplemented by additional items from its disease-specific modules or from one of the item banks. If a longer HRQOL assessment is not desired, then investigators could use the MDASI or PROMIS. PRO-CTCAE is the most appropriate approach if screening or assessment of symptoms felt to be related to treatment toxicity is of interest, or if comparative tolerability between study arms is a study aim.
- If a U.S. labeling claim is sought based on assessment of symptoms, which is beyond the scope of this EGD, then selection of measures in keeping with the FDA PRO Guidance is advised.
- **Table 2** lists 12 symptoms that are common across advanced cancers and clinical study contexts that frequently have a meaningful impact on the patient experience, as well as their availability in existing measurement systems. These symptoms can be related to disease, toxicities, or can be multifactorial. These and/or other symptoms should be selected for assessment in a study based on literature review and ideally feedback from patients, clinicians, and experts given the context and research application. This symptom list is based on prevalence and severity data from the development and implementation of several measurement systems (i.e. EORTC QLQ-C30, MSAS, MDASI, PCM, PRO-CTCAE, reported data from NCI's AdEERS and CDUS for all Phase II and III clinical trials sponsored by the NCI between 2005-2009, and from adverse symptoms reported by investigators in the clinical trials in the North Central Cancer Treatment Group.

Table 2. Common symptoms in advanced and metastatic cancers in adults for consideration in clinical comparative effectiveness research studies, and availability in existing instruments (listed alphabetically)

SYMPTOM	ESAS	FACT [†]	LASA	MDASI [†]	MSAS	PROMIS [†]	PRO-CTCAE [†]	PCM	QLQ-C30 [†]	RSCL	SDS
Anorexia	X	X ^c	-	X	X	-	X	X	X	X	X
Anxiety	X	X	X	X	-	X	X	X	X	X	-
Constipation	-	X ^c	-	X ^b	X	-	X	X	X	X	-
Depression	X	X	X	X	-	X	X	X	X	X	-
Diarrhea	-	X ^c	-	X ^b	X	-	X	X	X	X	X
Dyspnea	X	X ^c	-	X	X	-	X	X	X	X	X
Fatigue	X	X	X	X	X	X	X	X	X	X	X
Insomnia	X	X	X	X	X	X	X	X	X	X	X
Nausea	X	X	-	X	X	-	X	X	X	X	X
Pain	X	X	X	X	X	X	X	X	X	X	X
Neuropathy	-	X ^c	-	X	X	-	X	X	X ^a	X	-
Vomiting	-	X ^c	-	X	X	-	X	X	X	X	-

ESAS, Edmonton Symptom Assessment Scale; FACT-G, Functional Assessment of Cancer Therapy-General; LASA, Linear Analog Self-Assessment; MDASI, M.D. Anderson Symptom Inventory; MSAS, Memorial Symptom Assessment Scale; PCM, Patient Care Monitor; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS, Patient-Reported Outcomes Measurement Information System; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; RSCL, Rotterdam Symptom Checklist; SDS, Symptom Distress Scale. Most of these measurement systems include additional symptom items beyond these 12 symptoms.

[†] These PRO instruments are particularly recommended due to their evaluated measurement properties and past use in cancer clinical research.

^a Sensory neuropathy items are included in the QLQ-C30 LC13, OV28, MY20, LMC21, and OV28.

^b Constipation items are included in the MDASI-GI, MDASI-LC, MDASI-HN, MDASI-BT and MDASI-SP modules; diarrhea items are included in the MDASI-GI, MDASI-Thy, MDASI-BT and MDASI-SP modules.

^c Anorexia items are included in the FACT-Lym, FACT-Ga and FAFACT modules; constipation items are included in the FACT-Cx, FACT-En, FACT-Hep, FACT-V, FACIT-AI, FACIT-Pal; diarrhea items are included in the FACT-BI, FACT-C, FACT-Ga, FACT-ES, and FACIT-D modules; dyspnea items are included in the FACT-B, FACT-En, FACT-L, FACT-M, FACT-BMT, FACIT-AI, FACT-B+4, and FACIT-Pal modules and the FACIT-Dyspnea Scale 33 Item Bank; neuropathy items are included in the FACT/GOG NTX and FACT-Tax modules; vomiting items are included in the FACT-O, FAFACT, FACIT-AI, FACT-ES, and FACIT-Pal modules.

Challenges

- There are numerous available measurement approaches, each with strengths and limitations, making it difficult to select one over the other. Investigators should engage appropriate experts to assist selecting an appropriate approach for a given context, understanding these limitations.
- The specified symptoms in Table 2 may not all be applicable to a given population, and may be modified with justification depending on the context of a study.

RECOMMENDATION 3: Include an assessment of health-related quality of life.

Rationale

The patient’s global subjective experience with disease and treatment is essential to understand in real-world contexts. Although assessment of individual symptoms provides insights about specific impacts of disease and treatment, HRQOL reflects this overall patient experience and its multidimensional contributors, including non-symptom-specific areas. HRQOL measures can allow an investigator to understand how an intervention impacts physical, mental, social, and spiritual aspects of a patient’s life. Although measurement of HRQOL does not typically lead to drug product approval or labeling in the United States, such assessment has particular value in CER settings where understanding of the overall patient experience is valued by stakeholders including payers, guideline developers, clinicians, and patients themselves.

HRQOL can be measured using brief single items, or multi-item scales. The choice of approach depends on the context of a trial. An advantage of single item assessment is reduced patient burden whereas multi-item scales can be more precise and better elucidate the state of the patient's physical/functional, mental/emotional, social, and spiritual well-being. Single-item measures with robust psychometric properties include PROMIS global items and LASA items, while well-developed multi-item measures include the EORTC QLQ-C30, FACT-G, and PROMIS short forms.

Implementation

- If symptoms are assessed in a study by a non-HRQOL approach such as the MDASI, then a brief assessment of HRQOL via one or two single-item(s) is recommended. Single-item measures of HRQOL are available from the LASA (Linear Analog Scale Assessment) items developed by Sloan and colleagues.^{22,23} PROMIS also offers an assessment of quality of life.
- Greater details on sub-domains of quality of life (e.g., emotional well-being, social well-being, functional well-being) can be obtained via longer questionnaires such as the EORTC QLQ-C30²⁴ or FACT-G.²⁵ As noted above in Recommendation #2, these questionnaires contain some selected symptoms and can be supplemented with additional items to reach the full set of "Core" symptoms.
- Dedicated instruments for conducting cost-utility analyses include the EuroQOL EQ-5D and the Health Utilities Index (HUI).²⁶ The EQ-5D is frequently used in the preapproval setting by industry trials due to its widespread consideration by European regulatory authorities, and therefore is favored for use (particularly the recently updated version, the EQ-5D 5L).

RECOMMENDATION 4: Consider a measure that enables cost-utility analysis.

Rationale

Cost-utility analyses based on calculation of quality-adjusted life years (QALYs) can be valuable in CER and are enabled by instruments specifically designed for this purpose such as the EuroQoL EQ-5D and Health Utilities Index (HUI). These tools allow quantification in a single score of the impact of a disease or treatment on a patient's health status with weights derived based on a society or population's perspectives. Competing interventions can then be ranked against some baseline, or comparator, intervention in terms of cost per QALY gained.

Implementation

- Use of the EuroQoL EQ-5D is encouraged due to its common use in oncology clinical trials.
- Calculation of QALYs is increasingly feasible based on data generated by traditional HRQOL questionnaires.

Challenges

- Minimization of missing data via reminders and a backup data collection plan is advisable, particularly when repeat assessments in patients with declining performance status are expected in a clinical study. Imputation methods should be employed for missing data.
- A ceiling effect may occur with the EuroQoL EQ-5D in some contexts. A new version with additional response options called the "5L" is available and may reduce this effect but is not in wide use currently.

Recommendation 5: Assure that measures have demonstrated validity, reliability, and sensitivity in a comparable patient population as well as an appropriate recall period.

Rationale

Any measure used in clinical research – whether a serum biomarker, radiographic evaluation, or patient-reported outcome – should be valid, reliable, and sensitive in a given study context or in a closely related context. A unique first step in assuring the validity of PRO measurement is qualitative research with patients to assure that the terminology and information sought are understood and relevant. In CER, it is particularly important to represent the diversity of patients who might be included in “real-world” trials (i.e. beyond highly selected patients who might be included in a preapproval industry trial). Moreover, ensuring the construct validity, reliability, and the ability to detect meaningful change in patient status over time is essential. Conducting preliminary work with patient cohorts comparable to the target population (or selecting measures that have been previously evaluated in the target population or in a similar population) will assure that selected domains and measures are appropriate, and that score changes can be interpreted meaningfully. The general principles in the FDA PRO Guidance that pertain to including direct patient input as well as to assessing validity, reliability, and sensitivity to change should be considered in all clinical research, including CER.¹⁷ The Medical Outcomes Trust also provides guidance.²⁷

Implementation

- PRO measures should be selected, developed and/or assessed with direct input of patients from the target population or a similar population. This helps ensure understanding and acceptance of terminology, and to verify that items adequately represent concepts intended for assessment (i.e. content validity). Whenever possible, this should be based on qualitative research consistent with current methodological standards,²⁸ including the diversity of patients who might be included in a study in a “real world” context (e.g. with varying levels of education, age, cultural/racial-ethnic background, or geographic distribution).^{17,29} Moreover, selecting measures that evaluate constructs meaningful to patients may help ensure that study participants remain engaged over time and, consequently, continue to contribute to longitudinal data collection.
- Assessment of construct validity (i.e. assessment of the relationship of a PRO measure to an already established measure), test-retest reliability, sensitivity (including assessment of the meaningfulness of specific score changes, and ability to detect change over time) should be established for the target population or a closely related population prior to opening a study to enrollment. These measurement properties are described in the FDA PRO Guidance.¹⁷
- Selected measures should define a symptom recall period that is appropriate to the study-specific symptom, disease, and population. Memory degrades rapidly and variably by subjective experience and by symptom type and can degrade substantially after several days.³⁰ In general, no longer than seven days is recommended for recall of most symptoms. Selection of longer recall periods should be justified based on qualitative and quantitative data.
- When patients are unable to self-report, data may be collected from surrogates such as caregivers. For instance, a caregiver may report on behalf of patients with cognitive impairment or severely diminished performance status. In these cases, a pre-specified data collection and analysis plan should be followed. It is generally preferable to collect information from surrogates rather than to have missing data points or under-representation of the experiences of individuals who cannot report for themselves. Documentation of the individual reporting the PRO information should be retained in the study dataset when this approach is employed. Burden on surrogate/proxy reporters should be minimized. Systematic assessment of reasons for non-reporting by patients themselves is informative in this setting as well.
- Linguistic adaptations (i.e. translations) should be conducted using current standards, as described in a task force report issued by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).³¹

Challenges

- It is not always clear if a particular measure has the desired measurement properties or has been evaluated in a population/context of interest. Translations may not be immediately available in all languages pertinent to a given study. Therefore, early in a research program plan, investigators should engage experts in the design of PRO endpoints to assist with the selection, evaluation, or development of PRO instruments. This essential process requires time and effort up front which must be planned in advance.

IMPLEMENTATION METHODS

RECOMMENDATION 6: Limit PRO data collection so that the average patient can complete the process as quickly as possible. This is ideally within 20 minutes at baseline and within 10-15 minutes at subsequent time points.

Rationale

Patients with cancer may experience fatigue or other symptoms, psychosocial difficulties, and time demands which make it difficult or inconvenient to complete long questionnaires.³²⁻³⁴ Therefore, it is essential to minimize patient burden when designing patient questionnaires. Briefer questionnaires assure greater completeness of data and minimize missing data from those who experience the most impairment. An average of 10-15 minutes is selected as a rule of thumb for regular collection of PRO data, based on evidence of attrition of responses after this timeframe and an environmental scan of experiences of vendors providing electronic PRO data collection platforms to support industry trials.^{10,35} Therefore, it is incumbent upon investigators to carefully determine which data are essential, to focus on those data, and to avoid collecting extraneous information directly from patients. It is acknowledged that in some studies, longer interviews are conducted periodically to gather essential information from patients, and in such cases each item should be justified with an associated actionable hypothesis in the study protocol. The time to complete a given PRO assessment may decrease over time as respondents become accustomed to completing questionnaires.

Implementation

- The duration of completion of questionnaires should be assessed prior to initiating a study to assure an average duration within the recommended parameters.
- Use of questionnaires of longer duration should be justified in a study protocol with an associated actionable hypothesis stated for each item.
- The following prioritization for PRO measure selection is recommended:
 1. Specific symptoms (including symptoms focused on effectiveness as well as toxicities);
 2. Brief assessment of global health status or quality of life;
 3. Tool for cost-utility evaluation;
 4. Additional questionnaires pertinent to the population/context (such as functional status).
- Not all items need to be administered at all time points during a trial; therefore, the total number of items at any given time point can be minimized (e.g. assessment of symptoms related to adverse events may merit frequent administration, whereas assessment of symptoms related to effectiveness can be more sparsely administered).
- Consider methodologies that improve data collection efficiency, such as computer adaptive testing and skip patterns.

- Strategies to minimize respondent burden include staggering the time points at which each questionnaire or item set is administered (e.g. questionnaire #1 at week 6 and questionnaire #2 at week 8), or closely scrutinizing all included items to determine if they truly all will add value to the ultimate analysis.

Challenges

- In order to collect all information of interest in a given study, it is common for several questionnaires or item sets to be combined, which when administered together may exceed the recommended timeframe.

RECOMMENDATION 7: Collect PRO data as frequently as necessary to meet research objectives, without overburdening patients.

Rationale

In order to understand the patient subjective experience with disease and treatment, collection of PRO data at baseline and at selected follow-up time points (which are uniform across the study population), is necessary. If the goal of assessment is to understand how the patient experience changes from baseline to a particular time point (for example, symptom improvement following a particular intervention or period of observation), then a limited number of assessments may be reasonable. However, if the goal of assessment is to characterize toxicities or comparative tolerability of interventions from the patient perspective (e.g. to assess the impact of treatment on fatigue, nausea, diarrhea, sensory neuropathy, appetite, sleep, etc), then more frequent assessments (for example every 1-4 weeks) are necessary. This is because less frequent assessments may miss information about interim toxicities. Memory degrades after several days so respondents are likely to forget experiences predating a week, and recall periods longer than 7 days are discouraged for most symptoms.

Implementation

- Baseline assessments should always be conducted for PRO measures of symptoms and HRQOL.
- When using PRO data to measure treatment benefits, assessment after treatment completion (or study withdrawal) is recommended. Additional assessments, such as an intermediate assessment (i.e. prior to treatment completion), or assessment several months after treatment completion and at selected long-term time points, may be useful for characterizing the impact of treatment.
- When using PRO data to characterize toxicities or comparative tolerability of interventions, more frequent and regular assessments are recommended, for example every 1-4 weeks. If comprehensive capture of toxicity symptom data is desired, then the recall period of items should be identical to the frequency of administration (e.g. if administered weekly, then items should inquire about symptoms experienced over the prior 7 days). Following the period of treatment or observation of interest, selected long-term follow-up time points may elucidate late toxicities.
- It may not be clear if reported symptoms are related to disease, treatment, prior treatment sequelae, or comorbidities. Therefore, evaluation at baseline and comparisons between groups in controlled trials are essential.

Challenges

- It may not be clear prior to initiating a study which time points will be of greatest value in an analysis. A tension may therefore exist between desiring more time points of data vs. minimizing patient burden.

RECOMMENDATION 8: Collect PRO data via electronic data capture technologies whenever possible.

Rationale

Although many PRO measures were initially developed on paper prior to the advent of electronic data capture technologies, there are several advantages to using electronic modes of administration. Paper forms depend on distribution by research personnel, and often necessitate patients attending on-site, or taking a paper booklet home for in-between-visit reporting (thereby increasing the uncertainty for when and how the patient completed the form). Electronic forms can be automatically provided to patients, can be completed “in-office” or remotely, at the discretion of the patient, allow for time stamping, and have been widely shown as feasible in academic and community oncology as well as in industry settings.^{8,10,36-38} Recently developed PRO measures have been created specifically for electronic data capture, such as the Patient-Reported Outcomes Measurement Information System (PROMIS), the Patient-Reported Outcomes version of the Common Toxicity Criteria for Adverse Events (PRO-CTCAE), and Patient Care Monitor (PCM). These item libraries take advantage of electronic functionalities such as skip patterns or computerized adaptive testing (CAT), which can reduce the number of items patients have to complete. For patients or contexts without access to electronic interfaces, paper forms may be employed.

There are established guidelines for assessing whether a version of a measure originally created “on paper” has been faithfully converted to electronic form.³⁹ In general, paper to web migration yields between-mode equivalence comparable to the test-retest reliability of the original mode (i.e. paper questionnaire at time 1 and paper questionnaire at time 2)⁴⁰ and may lead to less missing data.^{35,41}

Implementation

- Usability testing in patients for any electronic interface should be conducted prior to implementation in a study.
- Data security and privacy must be assured for any selected software and hardware configuration.
- Skip patterns should be programmed into the data collection device so that patients do not need to answer irrelevant questions (e.g. if a patient does not report pain, then there is no need to answer a question about location of the pain). If the electronic interface involves conditional branching (or other skip patterns), the study protocol should include an analytic plan that imputes each skipped item.
- If a measure is intended for administration in a mode from which it was not initially developed (but reasonable measurement properties were demonstrated for the original mode of administration), then that measure should either have demonstrated reasonable equivalence with the mode or method for which validity, reliability, and sensitivity were previously demonstrated; or have demonstrated validity in the mode in which it is intended to be administered.
- For patients or contexts without access to electronic interfaces, paper forms may be employed.
- The specific mode(s) of administration should be documented.

Challenges

- Overseeing or subcontracting technology development, usability testing, and implementation requires effort and resources, and must be planned early in a research program plan.

RECOMMENDATION 9: Consider whether measurement equivalence has been established when mixing modes of patient-reported data collection (e.g. web, telephone, handheld device, paper, tablet computers).

Rationale

Modes may be mixed across patients in a study, where each patient selects a specific mode at baseline and continues to report via that mode throughout a study, or within patients (e.g., a patient reports by web until he or she becomes symptomatically ill, at which point IVRS becomes preferable). One mode may be preferred at a particular site, for example in multinational studies where IVRS or the web is variably accessible across countries. Mixing modes may be acceptable in clinical research if a reasonable level of between-mode equivalence has been demonstrated. The use of a PRO measure developed in one mode and subsequently used in another mode is referred to as “migration.” In general, it has been found that paper to web migration yields between-mode equivalence comparable to the test-retest reliability of the original mode.^{39,40}

Implementation

- Mixing modes of PRO data collection is acceptable when circumstances related to study conduct or population make the use of more than one delivery method desirable.
- When a study design calls for mixing modes, investigators should select measures that have reasonable equivalence across the selected modes.
- The format and wording of items and instructions provided to patients should be identical to how they were tested for mode equivalence.
- Evidence of measurement equivalence across modes should be referenced in the study protocol and in publications.
- Training is expected to be necessary for site personnel to enable them to teach patients to use the various data capture modes.

Challenges

- When multiple modes are included in a study, site personnel need to learn to use and teach patients to use each platform.
- Software should record which mode was used at each instance of reporting for potential sensitivity analyses.

RECOMMENDATION 10: Employ methods to minimize missing patient-reported data including educating local site personnel, training patients, and real-time monitoring of adherence with backup data collection.

Rationale

In real-world populations it is essential to employ methods to minimize missing data. Approaches used by vendors providing technologies to collect PRO data in preapproval industry clinical trials include real-time alerts to site staff or a phone bank, with a follow-up call to patients reminding them to complete items. Anecdotal accounts from vendors of electronic PRO data capture technologies studies estimate that such calls boost adherence by 10-15%. Site staff should reach out to patients who serially do not report, and ascertain reasons for non-adherence. This information should be recorded systematically on a form for use in subsequent sensitivity analyses.

Implementation

- Methods to minimize missing PRO data should always be used.
- A plan should be included in the protocol for systematically training and regularly contacting local site personnel to assure that they understand the importance of collecting PRO data. Ideally, this

- process will be centrally coordinated by a lead data manager who monitors patient adherence in real-time and communicates with sites when patients are non-adherent.
- Employ methods like electronic (text, email) or telephone messages that remind patients to report on time. Conduct follow-up telephone calls from a data manager or telephone bank to patients who do not report as scheduled. This is necessary to document the reason for non-compliance, and to allow verbatim administration of the missing items by an interviewer.
- When a patient is unwilling or unable to self-report, the reason (e.g. too ill/hospitalized, forgot, on vacation, technical difficulties, not interested) should be systematically collected and documented on a form for use in subsequent sensitivity analyses.
- When patients are too ill to self-report, collection of data from surrogates/proxies should be considered in the study design and the source of data should be documented for future subsequent sensitivity analyses.
- If a patient withdraws early from a study, a PRO assessment should be conducted at that time.

Challenges

- Patients may be less interested to participate in self-reporting if their PRO information is only used for research and not shared with providers to help guide clinical management. In cases when PRO information is not shared with providers, it can be noted to patients that the data will be used to benefit future patients, and patients should be instructed to inform their providers directly about concerning symptoms. An invitation to participate in the study from the patient's physician or nurse may help encourage participation.

DATA ANALYSIS AND REPORTING

RECOMMENDATION 11: Conduct a power calculation for the key patient-reported endpoints when designing a study.

Rationale

In order to understand the adequacy of a particular study design to ascertain meaningful information about the patient experience, a dedicated *a priori* power calculation for the PROs measures of greatest interest is recommended.

Implementation

- Study protocols should include a discrete statistical discussion about the planned analysis of PRO measures, with a power calculation included for the key measures.

Challenges

- Clinical protocols may include multiple endpoints meriting statistical discussion.
- Expertise in PRO endpoint design in addition to statistical training is beneficial for individuals designing PRO analyses for studies.

RECOMMENDATION 12: Include a plan for analyzing and reporting missing patient-reported data.

Rationale

Although the rate of missing data can be minimized in clinical studies, missing PRO data is still likely, especially in real-world populations and among patients with diminished performance status at

baseline. A plan for analyzing missing PRO data should be noted in a protocol, ideally including sensitivity analyses using imputation methods. This should include a plan for analysis when an entire measure has not been completed, or when item(s) within a multi-item composite instrument (e.g. a HRQOL questionnaire) are missing.

Implementation

- Methods for analyzing missing data should be included in the study protocol, including approaches based on imputation.
- Collecting information about why a patient missed a self-report via a standardized form should be considered.
- Use of surrogate/proxy reports should be considered in the study design for populations where patients are unlikely to be able to self-report at some point during the study (e.g. due to performance status or cognitive function limitations).
- In general, it is recommended that last observation carried forward not be used.
- Assessment for missing data not at random is recommended.
- Publications should include information about missing data and the analytic approach.

Challenges

- When there are large amounts of missing data, and particularly when the data are not missing at random, it may not be possible to interpret the results of PRO measurement. It is therefore essential to include methods to minimize missing data in near real-time during conduct of a study.

Recommendation 13: Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful for each measure, as well as mean group changes.

Rationale

Traditionally, analyses of PRO data have focused on comparisons of means between study groups. However, more granular and actionable information is provided by reporting the proportion of participants experiencing a specific change from baseline at a predetermined time point which is considered meaningful to patients in the study population (i.e. a “responder analysis”). Such information is particularly useful to individual patients and clinicians facing decisions, for whom information about mean group changes is less tangible.

Implementation

- Identify a score change that is meaningful to patients for each PRO measure, and compare the proportion of patients (in each study arm) attaining that change at predetermined time point(s) to baseline.
- Change may be reported as an absolute or percent change from the baseline score. The time points for analysis should be based on those that are meaningful to patients and relevant to the study setting, including long-term assessments for late toxicities. This approach can similarly be used for time to event analyses.

Challenges

- Establishing a score change that is meaningful in a population may require dedicated research. This can delay a planned study.

Recommendation 14: Consider evaluating the cumulative distribution of responses and including cumulative distribution curves in publications.

Rationale

In addition to a responder analysis, investigators are encouraged to report the cumulative distribution of responses (i.e., the proportion of patients who experience every magnitude of change in a specific measure at a time point of interest compared to baseline). Both improvements and decrements in scores from baseline can be shown. This approach permits reporting of the proportion of patients who experience an improvement or decrement at or above a specific percentage or absolute score change from baseline. Cumulative distribution curves are increasingly included in publications of PRO data and in drug labels, and are recommended in the FDA PRO Guidance.^{17,42} Responder analyses and cumulative distribution information can be useful to patients and clinicians at the point of care, where information about mean changes is less tangible.

Implementation

- Include a cumulative distribution function curve in analyses and publications, showing the percent change in PRO measure scores compared to baseline on one axis, and the proportion of patients in each study arm experiencing that percent change on the other.

Challenges

- Investigators may not be familiar with this technique, although it is increasingly common in the regulatory setting.

Recommendation 15: Analyze and publish results of PRO data collection simultaneously with other clinical outcomes.

Rationale

PRO data have often been analyzed and reported separately from other clinical trial outcomes, and presented in different journals if at all. As a result, important information about the patient experience has not been accessible to stakeholders reviewing the primary publication. Over time, it has become clear that stakeholders using information from CER studies value the patient perspective, and that this information is most accessible and meaningful when presented alongside other clinical outcomes. This means both including overall results of PRO data analyses in primary publications when PROs are not the primary endpoints, and publishing a dedicated PRO results paper simultaneously, ideally in the same journal.

Implementation

- When PROs are not the primary endpoints of studies, the PRO data should be analyzed simultaneously with other clinical data. A plan should be developed up front to include top-level results of PRO data analyses alongside other clinical outcomes in presentations and publications, and also to publish a dedicated paper with detailed PRO data analysis simultaneously. Ideally, these findings should be published in the same journal.

Challenges

- Investigators are often not oriented towards analyzing PRO data at the same time as other clinical outcomes such as survival, biomarkers, or radiographic indices. It is essential to plan analysis of PRO data at the same time as other clinical data.

- Journals are often not oriented towards publishing PRO data at the same time as other clinical endpoints. Authors as well as journal editors must change this orientation, with a default to include top-level results from a PRO data analysis in main publications from studies, with consideration of simultaneous publication of companion papers focused on PRO measurement findings.

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