Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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June 2021
Clinical/Medical

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I. INTRODUCTION

This guidance provides recommendations to sponsors for collection of a core set of patient-reported clinical outcomes (herein referred to as core patient-reported outcomes) in cancer clinical trials and related considerations for instrument selection and trial design. Although this guidance focuses on patient-reported outcome (PRO) measures, some of these recommendations may be relevant to other clinical outcome assessments (i.e., clinician-reported outcome, observer-reported outcome, performance outcome) in cancer clinical trials. Recommendations supplement previous guidance on use of PRO measures in clinical trials by providing additional considerations specific to the cancer clinical trial setting. Guidance specific to PRO endpoints and details of analytic methods are not comprehensively covered. FDA does not endorse any specific PRO measure and examples within this document are illustrative and should not be construed as endorsements.

This guidance is specific to registration trials for anti-cancer therapies intended to demonstrate an effect on survival, tumor response, or delay in the progression of a malignancy. Demonstration of a clinically meaningful improvement in patient-reported symptoms or functional impacts alone (i.e., in the absence of evidence of anti-tumor activity) would be more applicable to supportive care drugs and is outside the scope of this guidance. Refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (PRO guidance) for situations where the PRO endpoint will be used as the primary evidence of effectiveness.[2] PRO measurement may not be feasible in all cancer trial populations (e.g., in patients with significant cognitive impairment).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA

[1] This guidance has been prepared by the Oncology Center of Excellence, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research, in consultation with the Center for Devices and Radiological Health (CDRH) at the FDA.

[2] December 2009. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer, a performance-based assessment, or through other methods. A PRO is a type of clinical outcome assessment based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.[3] Additional definitions of patient-focused drug development terms can be found in the Patient-Focused Drug Development Glossary.[4]

Cancer trials typically employ standardized efficacy assessments using overall survival and tumor measures, and safety assessments provided by clinician reporting of adverse events. FDA acknowledges the potential added value of incorporating PRO measurement of symptoms and functional impacts into the benefit/risk assessment in appropriately designed trials; however, heterogeneity in PRO assessment strategies has lessened the regulatory utility of PRO data from cancer trials. Systematic assessment of a core set of PROs using fit-for-purpose[5] PRO measures can facilitate high quality data on patient-reported symptoms and functional impacts.

A core set of PROs including disease symptoms, symptomatic adverse events, and physical function, that may be important contributors to a patient's health-related quality of life (HRQOL) and that may be sensitive to the effect of the disease and treatment under study has been described.[6] This guidance expands on this concept, acknowledging that a core PRO set can provide a minimum expectation for patient experience data across cancer settings, but may not include all important patient experience outcomes to measure in specific disease contexts.

III. CORE PATIENT-REPORTED OUTCOMES

To maximize the utility of submitted PRO information, we recommend collecting and separately analyzing the following core PROs:

- Disease-related symptoms

[3] Throughout this guidance, FDA uses certain terms that appear in the FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK338448/ (accessed June 1, 2021).

[4] Available at https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary (accessed June 1, 2021).

[5] Fit-for-purpose is defined as a conclusion that the level of validation associated with a tool is sufficient to support its context of use. See BEST Resource.

[6] Kluetz PG, Slagle A, Papadopoulos E, et al., 2016, Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms, Clin Can Res, Apr 1;22(7):1553-8.

- Symptomatic adverse events
- Overall side effect impact summary measure
- Physical function
- Role function

Additional PROs that are important to patients, outside of the core concepts in this section, could be prospectively specified and collected in clinical studies based on the context of a given clinical trial. For instance, swallowing function and cognitive function may be outcomes of interest in addition to the core set in the context of advanced esophageal cancer and neuro-oncology, respectively. Selection of outcomes outside of the core PRO set should be carefully considered to minimize patient burden and improve the quality of data collected by focusing on the most meaningful and measurable outcomes.

IV. CONSIDERATIONS FOR INSTRUMENT SELECTION TO MEASURE THE CORE PATIENT-REPORTED OUTCOMES

For a PRO result to meaningfully contribute to a therapy's benefit/risk assessment, the PRO instrument used should be well-defined and reliable so that the results presented are accurate and not misleading. Sponsors should provide support for the selection of PRO instrument(s) with available data and/or published peer-reviewed literature guided by the principles laid out in the PRO guidance.[7] The FDA is also developing a series of Patient Focused Drug Development guidances, and specifically Guidance 4 of the series will address methodologies, standards, and technologies for the collection, capture, storage, and analysis of clinical outcome assessment (COA) data.

Some commonly used PRO instruments or measurement systems may have been developed prior to publication of the PRO guidance and may differ from some of the recommendations. In these cases, the sponsor should provide a rationale for why the endpoint measured by the PRO instrument is well-defined, relevant, and reliable. For example, there may be evidence from previous trials that the measure is sensitive to a disease- or treatment-related change. Some general principles to determine whether the PRO instrument is fit-for-purpose include the following:

- The PRO instrument is appropriate for its intended use (e.g., study design, patient population)
- The PRO instrument validly and reliably measures concepts that are clinically relevant and important to patients
- The PRO data can be communicated in a way that is accurate, interpretable, and not misleading

[7] See also the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

A PRO instrument can be used to assess a range of concepts of interest including single item symptoms (e.g., pain intensity), symptom scales (e.g., disease symptom scale consisting of multiple symptoms), functional scales (e.g., physical function), and multi-dimensional complex concepts (e.g., HRQOL). To allow for clear and accurate analyses and labeling, the PRO measure should be *well-defined*. One important aspect of a well-defined PRO measure is that the questions within the measure should all be related to the concept of interest. For instance, a well-defined physical function scale should include questions on a range of activities requiring physical effort and should not contain specific questions tied to or dependent on other concepts such as side effects or symptoms.[8]

In some cases, subscales or subsets of questions from existing PRO instruments may be used to inform the benefit/risk assessment and support labeling claims if prospectively defined and their measurement properties have been adequately evaluated. Early consultation with FDA is recommended regarding selection of appropriate instrument(s) for a particular cancer clinical trial context. Ideally, interactions with the agency would include discussion of the PRO instrument, trial design, and labeling considerations.

PRO instrument considerations and examples for the core PROs are:

- **Disease-related symptoms**: Where a group of common cardinal disease symptoms exist, disease symptom scales should be used. One example of a disease symptom scale is the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) that has gone through the FDA Drug Development Tool Qualification program.[9] In contexts where disease symptoms are heterogeneous in type and incidence, symptoms that patients have reported as being important across advanced cancer settings, such as pain, anorexia, and fatigue, can be measured either individually or within a symptom score with other important disease-related symptoms. Examples of patient-reported symptom severity assessments that may be fit-for-purpose include an 11-point (i.e., 0 to 10) numeric rating scale or verbal rating scale (e.g., none, mild, moderate, severe) that asks patients to rate their worst experience of a specific disease symptom over a specified recall period. Alternatively, a frequency scale for one or more of these items may also be considered (e.g., ranging from none of the time to all of the time).

- **Symptomatic adverse events (AEs)**: FDA recommends selecting a concise set of the most important symptomatic AEs that are expected to occur from an item library. In trials with active controls, symptomatic AEs expected to occur from both treatment regimens should be assessed for all patients in both arms. For example, if neuropathy is expected on active control only, an item assessing neuropathy should be included in both the active and control arms. FDA considers the National Cancer Institute's PRO version of the common terminology criteria for adverse events (PRO-CTCAE) to be an example of one acceptable item library for assessment of symptomatic adverse events.[10] Sponsors should provide a rationale for the selection of symptomatic AEs that will be

[8] Ibid.

[9] See https://www.fda.gov/drugs/development-approval-process-drugs/ddt-coa-000009-non-small-cell-lung-cancer-symptom-assessment-questionnaire-nsclc-saq (accessed June 1, 2021).

[10] See https://healthcaredelivery.cancer.gov/pro-ctcae/ (accessed June 1, 2021).

assessed, based on mechanism of action, early clinical data, and input from patients and healthcare providers. Sponsors should select only the most important and/or high frequency AEs to reduce question burden and consider a free-text question to mitigate concerns for missing important symptom items.

Importantly, PRO data describing symptomatic AEs are intended to complement, not replace, safety data.

- **Overall side effect impact summary measure**: A summary measure of the overall side effect impact can inform the tolerability of a treatment. Because individual patients may weigh some side effects as more important than others, one option to consider is a single global impression of severity item. For example, "Please choose the response below that best describes the severity of your **overall side effects from treatment** over the past week" (where 0 represents none and 3 represents severe). Examples of existing single item global side effect bother questions include the GP5 question from the Functional Assessment of Chronic Illness Therapy (FACIT) item library,[11] and the Q168 question from the European Organisation for Research and Treatment of Cancer (EORTC) item library.[12] Existing symptom libraries should consider developing such a global side effect item where one does not exist.

- **Physical function**: Sponsors should select scales that measure defined concepts and assess varying levels of ability to perform activities that require physical effort. One option to consider is the Patient-Reported Outcomes Measurement Information System (PROMIS)® physical function item bank.[13] Another commonly used physical function scale that can be considered is the EORTC Quality of Life of Cancer Patients QLQ-C30 physical function scale.[14]

- **Role function**: The impact of a treatment on the ability to work and carry out daily activities is important to patients and may also provide some information on other functional abilities such as cognitive function. One example of an existing tool that assesses this concept is the EORTC QLQ-C30 role function scale.[15]

Some of these instrument examples were developed prior to the PRO guidance and may not be suitable to address all clinical trial questions. For instance, using PRO measures to support a claim of equivalence or non-inferiority between two arms is problematic without sufficient support that the sensitivity of the measure is adequate.

[11] See https://www.facit.org/ (accessed June 1, 2021).
[12] See https://qol.eortc.org/questionnaires/ (accessed June 1, 2021).
[13] See http://www.nihpromis.org/measures/measureshome (accessed June 1, 2021).
[14] See https://qol.eortc.org/questionnaires/ (accessed June 1, 2021).
[15] Ibid.

V. TRIAL DESIGN CONSIDERATIONS

A. Assessment Frequency

The following should be considered when determining the frequency of PRO assessment for core PROs:

- A baseline assessment(s) should be included as a reference point for assessing change.
- Assessment frequency should be higher within the first few treatment cycles and depending on the trial may be less frequent in later cycles.
- Assessment frequency should take into account the administration schedule of the drug(s) under study.
- Different assessment frequencies can be selected for each core concept depending on the outcome and research objective.

It is acknowledged that other PRO concepts outside of FDA's core PRO set may be of interest to other stakeholders (e.g., international regulators, health-technology assessment bodies, etc.) and may include other functional domains (e.g., social function, emotional function) that comprise overall HRQOL. When using a modular approach where these elements are able to be assessed and analyzed separately, different assessment frequencies can be selected that can reduce the response burden to patients. A standard approach to assessment frequency over the first year of therapy would aid in consistency and interpretation across advanced cancer trials. An example of a PRO assessment strategy that assesses PRO more frequently in the first 8 weeks of treatment would be suitable across most drug administration schedules and is provided below:

Figure 1: Example PRO assessment frequency for first 12 months of advanced cancer trial

	Standard 6 month treatment period												Follow-up		
	BL	w2	w3	w4	w5	w6	w7	w8	M3	M4	M5	M6	M9	M12	*
Symptomatic AE[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Single Item Side Effect Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Function	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Role Function	X		X		X		X		X	X	X	X	X	X	
Disease Symptoms	X				X				X			X		X	
Other HRQOL	X								X			X		X	

BL – baseline, w - week, M - month, * - context dependent long-term follow-up

How a therapy is administered can affect the timing of assessments. For instance, intermittently administered intravenous (IV) cytotoxic chemotherapy often has the maximum intensity of

[16] Symptomatic AEs assessed by PROs are intended to complement, not replace, standard CTCAE safety data.

symptomatic AEs earlier in each cycle, whereas this may not be the case with an oral drug administered on a continuous daily schedule. Schedule of administration should be taken into account, and assessments and their analysis harmonized so as not to obscure the results of either arm. In the case where both arms have orally administered treatments on a daily schedule, assessments could be less frequent given the lack of cyclic variability surrounding administration schedules seen with IV chemotherapies.

B. Other Trial Design Considerations

The following should be considered to mitigate missing data and improve the interpretability of PRO results:

- Prospectively establish procedures for mitigating missing data, including training for investigators and patients, a completion monitoring strategy, and obtaining PRO data from patients at time of early withdrawal. Include these procedures in the protocol.

- Methods to lessen patient burden should be explored, including use of electronic PRO capture that may allow for assessments outside of the clinic. Sponsors should document how and where patients completed their PRO assessments (e.g., at home, in office, etc.).

- Reasons for missing PRO data should be documented and included in the analysis dataset.

- Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s), if relevant.

- Any deviation from the instrument's scoring manual should be noted and a rationale provided.

- Carefully record the use (including changes in dose) of concomitant medications or therapies that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain).

VI. LABELING CONSIDERATIONS

Inclusion of PRO data in the product label will depend on the adequacy of the design and conduct of the trial, the strengths and limitations of the instrument within the given context of use, and the quality of submitted data.

- Lack of statistical superiority is not suitable evidence for claims of "no meaningful difference." A claim of non-inferiority or equivalence should be supported by evidence that the sensitivity of the measure is adequate and the trial should be adequately designed, including justification for the selected non-inferiority margin, to make such a claim as documented in the statistical analysis plan.

- If a claim of superiority in a particular PRO endpoint is sought, pre-specify the PRO hypothesis and test it within the clinical trial. Control the overall type I error rate if multiple hypotheses are being tested. Prospectively define the statistical analysis methods, especially procedures for handling missing values and censoring rules if appropriate. Provide justification for the endpoint definition, including what constitutes meaningful change, for FDA review and comment in advance of initiating the clinical trial. This information should be included in the statistical analysis plan.

- Exploratory PRO findings (i.e., not included in the statistical hierarchy) are considered descriptive. FDA will review these data and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis, taking into consideration any factors that may affect the interpretability and reliability of the findings.

  For example, exploratory PRO results further describing the timing, frequency, and impact of visual disturbances were included in *Section 6 Adverse Reactions* of the USPI for XALKORI, in order to complement the safety signal of vision disorder reported by clinicians.

  Generally, exploratory PRO findings of a comparative treatment benefit are unlikely to support inclusion in product labeling if not prespecified and statistically tested.