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Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation

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Guidance for Industry and Food and Drug Administration Staff, And Other Stakeholders

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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff, and Other Stakeholders

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The U.S. Food and Drug Administration (FDA or the Agency) encourages the collection, analysis, and integration of patient perspectives in the development, evaluation, and surveillance of medical devices. Patients' perspectives on living with their health condition and its treatment or management are most useful in medical device evaluation when they are relevant to the regulatory decision and reliably measured.[1] **Patient-reported outcome (PRO)** instruments facilitate the systematic collection of how patients feel, function, and survive as valid scientific evidence to support the regulatory and healthcare decision-making process.[2] By integrating patients' voices throughout the total product life cycle (TPLC), concepts important to patients can be considered in the evaluation and surveillance of medical devices.

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[1] For more information, see FDA's guidance "Patient Preference Information-- Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

[2] For more information see FDA's guidance "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

The objectives of this guidance[3] are to:

1. Describe principles that may be considered when using PRO instruments in the evaluation of medical devices (Section IV);
2. Provide recommendations about the importance of ensuring the PRO instruments are fit-for-purpose (Section IV), and;
3. Outline best practices to help ensure relevant, reliable, and sufficiently robust PRO instruments are developed, modified, or adapted using the least burdensome approach (Section V).

This guidance is not meant to replace the Patient-Focused Drug Development (PFDD) guidance series, led by FDA's Center for Drug Evaluation and Research (CDER) and CBER.[4]

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 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

PRO instruments allow for the collection of certain data as valid scientific evidence of safety and/or effectiveness which is complementary to other evidence of clinical outcomes and/or biomarkers. Use of PRO instruments is generally voluntary but may be specifically recommended in certain standards and guidances. PRO instruments can include patient diaries, visual analog and numeric rating scales (e.g., measures of pain severity), symptom measures, as well as multi-item, multidomain questionnaires measuring aspects of health-related quality of life (HRQOL).[5] A PRO can be measured by self-report or by an interview, provided that the interviewer records only the patient's response.[6] Symptoms and unobservable concepts known only to the patient (e.g., pain intensity and anxiety level) can be measured using PRO instruments. A PRO instrument can be used in clinical studies to measure the effects of a medical intervention or changes in the health status of a patient.

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[3] This guidance is intended to improve the regulatory predictability and impact of PROs, as noted in the Patient Engagement and the Science of Patient Input section of the Medical Device User Fee Amendments (MDUFA IV). For more information, see the MDUFA IV Commitment Letter, pg. 16 Section 3a-c: https://www.fda.gov/media/100848/download. The term "bridging studies" listed in Section 3c refers to modification and adaptation of PRO instruments.

[4] For more information, please see the FDA Patient-Focused Drug Development Guidance Series website: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[5] It is important to note that HRQOL is a multidimensional measure of the health and treatment experience of the patient, generally involving physical, social, and emotional domains and should not be used interchangeably with the term PRO, which is broader.

[6] See Footnote 2.

FDA has produced several resources to assist the sponsor in selecting, modifying or developing a PRO instrument. These include the guidance entitled, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims;"[7] the series of guidance documents and other resources related to Patient-Focused Drug Development;[8] and the following resources that were posted to FDA's website as part of CDRH's 2016-2017 Strategic Priorities: "Value and Use of Patient-Reported Outcomes (PROs) in Assessing Effects of Medical Devices,"[9] "COA Case Studies,"[10] and "PRO Compendium."[11] The COA Case Studies include examples of PRO instruments used to support medical device regulatory submissions and the PRO Compendium lists some, but not all, of the PRO instruments that have been used and publicly reported in medical device premarket clinical investigations across a wide variety of devices and indications.

In addition, PRO instruments have been qualified under the Medical Device Development Tools (MDDT) program as tools that medical device sponsors can use in the development and evaluation of medical devices. Qualification under the MDDT program means CDRH has evaluated the tool and concurs with available supporting evidence that the tool produces scientifically-plausible measurements and works as intended within the specified context of use.[12]

With the development of novel technologies and novel uses for existing technologies, it is important that outcomes important to patients are measured and included in medical device submissions, when appropriate. As part of providing valid scientific evidence to assess the safety and/or effectiveness of medical devices, PRO instruments can measure the impact of medical devices on patient well-being and other concepts that may influence healthcare providers and patients when making decisions about potential treatments or management options.

FDA believes that information from well-defined and reliable PRO instruments[13] can provide valuable evidence for benefit-risk assessments, and can be used in medical device labeling to communicate the effect of a treatment on patient symptoms, functioning or HRQOL, when the use is consistent with the PRO instrument's documented and supported measurement properties. The Agency recognizes there are many ways PRO instruments can be used across the TPLC,

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[7] See Footnote 2.

[8] For more information see FDA's Patient Focused Drug Development website on the guidance and discussion guide series https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[9] https://www.fda.gov/media/109626/download

[10] https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/clinical-outcome-assessments-coas-medical-device-decision-making

[11] https://www.fda.gov/media/109629/download

[12] See FDA's guidance "Qualification of Medical Device Development Tools," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-medical-device-development-tools. See also FDA's website for a listing of qualified MDDT: https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt.

[13] For brevity, the text of this guidance does not distinguish between the PRO instrument and the score(s) that result from the administration and scoring of the PRO instrument. Instead, references to instructions, administration materials, content, formatting, and scoring rules should be interpreted as based on the instrument. References to the psychometric properties, such as reliability, should be interpreted as a properties of the score(s) they are based on.

including early feasibility, feasibilty, pivotal, and postmarket clinical studies. For example, PRO instruments may be used to help determine a patient's eligibility for inclusion within a study, to measure primary or secondary safety and/or effectiveness endpoints, either as a stand-alone or as a component of a composite endpoint. PRO instruments also may be valuable early in the design and development of a device and in postmarket surveillance efforts such as registries. When data from a PRO instrument is used in the evaluation of a medical device, FDA determines the validity evidence needed to support the PRO instrument's specified use for a regulatory purpose. FDA uses the term "fit-for-purpose" to describe this flexible approach.[14]

III. Scope

FDA intends the principles outlined in this guidance to apply to PRO instruments used in medical device evaluation across the TPLC. This guidance is intended to supplement the aforementioned resources by outlining recommended best practices for developing relevant, reliable, and sufficiently robust PRO instruments using the least burdensome approach. This guidance document does not detail the methods and steps of developing, modifying, or adapting a PRO instrument. Instead, it communicates what FDA believes are some of the best practices for selecting, developing, and modifying PRO instruments for use in medical device evaluation. A glossary is also included as an Appendix to clarify terminology.

IV. General Considerations for PRO Instrument use in Medical Device Evaluation

A. Key Principles

FDA believes the following principles are important to consider when incorporating PRO instruments into the evaluation of the TPLC of medical devices:

1. Establish and define the concept of interest (COI) the PRO instrument is intended to capture;
2. Clearly identify the role of the PRO (e.g., primary, secondary, ancillary, effectiveness, safety) in the clinical study protocol and statistical analysis plan;
3. Provide evidence showing that the PRO instrument reliably assesses the COI; and
4. Effectively and appropriately communicate the PRO-related results in the labeling to inform healthcare provider and patient decision making.

B. Importance of ensuring PRO Instruments are fit-for-purpose

[14] See Section VII for glossary. BEST Glossary, *FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Glossary. 2016 Jan 28 [Updated 2018 May 2]. Co-published by National Institutes of Health (US), Bethesda (MD).* https://www.ncbi.nlm.nih.gov/books/NBK338448/.

PRO instruments that are fit-for-purpose should be used for a specific context of use (COU). FDA believes three factors should be considered when selecting a PRO instrument that is fit for purpose:

1. Is the concept being measured by the PRO instrument meaningful to patients and would a change in the concept of interest be meaningful to patients?
2. What role (e.g., primary, secondary, ancillary, effectiveness, safety) will the PRO instrument serve in the clinical study protocol and statistical analysis plan?
3. Does the evidence support the PRO instrument's use in measuring the COI as specified in the clinical study protocol and statistical analysis plan?

A key consideration when assessing whether a PRO instrument is fit-for-purpose for a particular COU is the population in which the validity evidence was generated.[15] The population in which the validation work was performed should be consistent with the intended use population in the clinical study protocol. By assessing the similarities and differences between the population in the clinical study and in the development of the PRO instrument, FDA can determine whether the PRO instrument is fit-for-purpose.[16] For example, patients with late-stage disease may have different symptoms or perspectives than patients in the early stage. Hence, the items on the PRO instrument developed in early stage patients may not be applicable to patients experiencing later stages of the disease. Additionally, PRO instruments should not include items that could be misinterpreted or that are not applicable to the intended use population.

V. Best Practices for Least Burdensome Selection, Development, Modification and Adaptation of Patient-Reported Outcome Instruments

A. Measure Concepts Important to Patients

One purpose of using PRO instruments should be to assess outcomes that matter to patients; however, not all PRO instruments used in clinical studies accomplish this goal. Incorporating outcomes that reflect patient priorities in the clinical study protocol can help to seamlessly integrate factors included in a patient's decision-making process into FDA's benefit-risk determinations.[17] Assessing outcomes that patients find meaningful

[15] See Footnote 2.

[16] For more information on methods used to gather comprehensive input from patients, please see "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input. While the scope of this guidance is currently limited to drugs, we believe the recommendations are also applicable to medical device development and evaluation.

[17] FDA has several guidances on benefit-risk determinations. Please see "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-

may reduce the collection of less important PROs, thereby limiting the unnecessary burden on patients. Ultimately, including outcomes of importance to patients appropriately in the medical device labeling may help inform patient and healthcare provider conversations about treatment or management options.

During PRO instrument development or selection, effective engagement,[18] concept elicitation interviews, and cognitive interviews with patients can help ensure that the COIs intended to be measured by a PRO instrument are important to the daily lived experience of patients and could be useful to inform their future decisions regarding the use of the medical device. Concept elicitation interviews identify or confirm the concept(s) measured by the PRO instrument as well as what aspects of the concept are most important to the patients, such as the frequency, severity, and/or interference with daily life. For example, pain is a concept and the aspects that may be most important to patients are its severity and how it interferes with daily life.

B. Ensure Patient-Reported Outcome Instruments are Understandable to Patients

The elements of a PRO instrument include the instructions, items, recall period, and response options. FDA recommends that these elements be composed using plain language to help ensure that patients with varying levels of overall literacy and health literacy understand and are able to provide informed responses. In addition, using appropriate benchmarks (e.g., a point of reference against which things may be compared or assessed), activities, or symptom wording may facilitate patients being able to accurately report their health status. For example, a sponsor may be interested in assessing visual function. The concept may be measured with items assessing difficulties patients have with activities they may do in everyday life such as reading books, menus, and labels on medicine bottles. FDA recommends conducting cognitive interviews to generate evidence supporting the wording of these elements.

The response options to the items should be consistent with the wording of the item. For example, if the frequency of itching was identified through the concept elicitation interviews as important, then the response options should be measures of frequency (e.g.,

risk-determinations-medical-device-investigational-device. Please see "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de. Please see "Factors to Consider Regarding Benenfit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and. Please see "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

[18] See FDA's guidance "Patient Engagement in the Design and Conduct of Medical Device Clinical Studies," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-engagement-design-and-conduct-medical-device-clinical-studies.

never, rarely, sometimes, often, always) and the wording for the response options and items confirmed using cognitive interviews.[19] These interviews should be conducted prior to using a PRO instrument to collect outcomes in a clinical study. Technologies such as tele- or videoconferencing may facilitate conducting cognitive interviews, allowing diverse patient feedback on the interpretation of the PRO instrument elements. FDA encourages sponsor interactions through the voluntary Q-submission program[20] with the relevant review offices and the Patient Science and Engagement Program[21] to help determine the appropriateness of the cognitive interview approach.

FDA recommends that sponsors consider offering PRO instruments in different languages, where appropriate, in order to measure the patient experience in patients with limited English language proficiency. FDA believes that collecting PRO data from all patients, including those with limited English language proficiency and health literacy, can help ensure that the clinical study findings are generalizable to the intended use population. Moreover, adequate patient interpretation of the questionnaire items may help minimize missing data, improve the consistency of item interpretation, and potentially improve the data collected in the clinical study.

FDA recommends that sponsors also consider the impact on patients in responding to PRO instruments with the goal of reducing unnecessary burden. For example, sponsors may choose to use a well-developed short form version of a PRO instrument when available.

C. Be Clear About the Role of PRO Instrument in the Clinical Study Protocol and Statistical Analysis Plan

FDA determines the strength of evidence needed to support the measurement properties of a PRO instrument based on the role of the instrument specified in the clinical study protocol and statistical analysis plan. For example, a PRO instrument used to measure a secondary effectiveness endpoint may need different validity evidence[22] than a PRO instrument used to descriptively assess a safety endpoint.

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[19] See FDA's PFDD Guidance Public Workshop Discussion Guide 2 "Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments" available at https://www.fda.gov/media/116276/download

[20] The Q-Submission Program is used by sponsors and FDA to discuss certain questions relating to a submission (current or future) with review offices and/or broader device programs. For more information on the process for requesting feedback or meetings with FDA for medical device submissions, see FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[21] For more information, please see the CDRH Patient Science and Engagement Program website: https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-patient-science-and-engagement-program.

[22] Different validity evidence may refer to different types of evidence, different quality of evidence, and/or different amounts of evidence.

FDA believes the COI and COU in which a PRO instrument is used should be clearly conveyed in the clinical study protocol and the statistical analysis plan. As such, FDA recommends that the COI be clearly defined by a statement of what is being measured, how it is being measured and interpreted, and how the results will be communicated in the labeling. Similarly, FDA recommends that the COU describe the specific role of the PRO instrument in the medical device development and evaluation process, which includes defining what endpoint the PRO instrument is being used to capture in the clinical study (e.g., safety versus effectiveness, primary versus secondary versus ancillary) and an estimate of the amount of change measured by the PRO instrument that is clinically meaningful.[23] The sponsor should plainly state and clearly identify the PRO instrument's COU in the clinical study protocol and statistical analysis plan. For example, pain intensity as the concept, reduction in pain intensity as the primary effectiveness outcome with the endpoint being a specified reduction in the pain intensity scale score at three months compared to baseline.

FDA encourages sponsors to engage FDA throughout the TPLC of the device. During the study design stage, prior to the Investigational Device Exemption (IDE) submission or conducting of the pivotal study,[24] sponsors are encouraged to engage FDA regarding the relevance and suitability of a proposed PRO instrument to the benefit-risk assessment. The Q-Submission process should be used to obtain feedback per the FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[25]

When presenting results from a clinical study which includes a PRO instrument in a medical device submission, the sponsor should confirm that the concept measured by the PRO instrument matches the COI stated in the COU, and that the specified change in the PRO instrument is clinically meaningful. Sponsors should consider clearly identifying the location of this information within the application. Examples of the way PRO instruments have been used in FDA submissions can be found in the "COA Case Studies" resource on the FDA website.[26]

D. Leverage Existing PRO Instruments and Validity Evidence

Sponsors often choose to select from existing PRO instruments rather than develop a new PRO instrument. Existing PRO instruments can be used as-is, modified, or adapted, which is often less resource intensive than creating a new PRO instrument due to the

[23] See FDA's PFDD Guidance 3 Public Workshop Discussion Guide "Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments," available at https://www.fda.gov/media/116277/download.

[24] See FDA's guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

[25] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[26] See Footnote 10.

ability to leverage existing validity evidence. Modifying[27] or adapting an existing PRO instrument may be a least burdensome approach for a new COU. FDA encourages the modification or adaptation of existing PRO instruments where it is feasible and such an approach would still result in a relevant and reliable PRO instrument for the COU. When modifications are made to an existing PRO instrument for use in a clinical study, we recommend that the modifications be clearly described in the documentation accompanying the submission (e.g., PRO dossier or appendix). It would also be helpful to note existing publications or data demonstrating the use and/or supporting the validity of the modified PRO instrument. New evidence may be needed to support the validity, depending on the extent of modification made.

FDA recommends reviewing peer-reviewed literature as a starting point for identifying the validity evidence associated with the development, use, or evaluation of the PRO instrument of interest while keeping in mind that PRO instruments should reflect contemporary activities of daily life. Accordingly, PRO instruments historically used to assess patient functioning may not adequately reflect functioning in the present due to technological advances that may facilitate the performance of certain tasks. Modification of the items may be needed to ensure a given COI is still adequately being measured. To modify the PRO instrument, the sponsor may conduct supplementary cognitive interviews and construct new items as needed to adequately capture the COI. Sponsors are encouraged to engage in discussion with FDA through the Q-submission process regarding the approach to modifying or adapting an existing PRO instrument.

E. Consider Alternative Platforms and Parallel Development for Generating Validity Evidence for PRO Instruments

Real-world evidence derived from multiple sources outside of the clinical research setting (such as electronic health records, claims and billing activities, product and disease registries, or health-monitoring devices) may be used to generate validity evidence for PRO instruments. With the proliferation of real-world data (RWD), it is possible that PRO instrument development could be nested in a RWD source.[28] Professional organization and patient-driven registries may also help identify patients and facilitate generation of validity evidence. FDA encourages sponsors to consider these alternative approaches to generate validity evidence for PRO instruments as potentially less burdensome approaches.

Sponsors proactively developing or modifying PRO instruments for use in future product development may want to also consider using early feasibility, phased clinical studies, pivotal clinical studies, postmarket clinical studies, and/or real-world data platforms to collect and generate quantitative validity evidence. Such an approach of using the parallel

[27] Modification may change the properties of the PRO instrument such that new evidence would be needed to evaluate the properties of the modified PRO instrument.

[28] See FDA's guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

development work may be more efficient and cost effective than conducting a sequential, separate PRO instrument validation study. In addition, a separate study done in tandem with a pivotal clinical study may be needed to confirm particular measurement properties of a PRO instrument's score. It is possible that a tandem study may not support the intended use of the instrument. When choosing any of these options, sponsors should prospectively specify in the clinical study protocol and statistical analysis plan the intent to generate quantitative validity evidence for the PRO instrument.

Sponsors should note that generating validity evidence as part of the pivotal clinical study does not mean the PRO instruments can be used to support specific statements regarding safety and/or effectiveness in that pivotal study, in the labeling, or in public summaries. Instead, the validity evidence may support the PRO instrument's use in future clinical studies, including postmarket studies.

F. Collaborate with Others in the Pre-Competitive Space

Where possible and appropriate, FDA encourages sponsors and other stakeholders to work together in the pre-competitive space to develop, modify, or adapt a PRO instrument for use in regulatory submissions. Sponsors are encouraged to consider relevant stakeholders for potential collaborations, including but not limited to, patient organizations, health professional organizations, and research institutions with expertise in PRO instrument development. Collaborative development of a PRO instrument may also engender broader acceptance of results due to fewer concerns about bias in assessing the relevant aspects of the condition or its treatment or management of patients (compared to customized questionnaires developed by a single sponsor). Sponsors should consider submitting PRO instruments for qualification under the Medical Device Development Tools (MDDT) Program.[29]

VI. Summary

To further integrate patient voices throughout the TPLC of medical devices, it is important to consider concepts important to patients in the regulatory evaluation and surveillance of medical devices. Well-designed PRO instruments facilitate incorporating patient perspectives as scientific evidence to support regulatory and healthcare decision-making.

FDA believes that the recommendations outlined in this guidance will help ensure that PRO instruments are developed, modified, adapted, and used in the evaluation of medical devices in ways that generates relevant, reliable and sufficiently robust data to assess outcomes of importance to patients, regulators, and healthcare providers.

[29]See FDA's guidance "Qualification of Medical Device Development Tools," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-medical-device-development-tools. See also FDA's website for a listing of qualified MDDT: https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt. For more information, see Medical Device Development Tools available at https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt.

This guidance outlines flexible approaches to developing, modifying, or adapting a PRO instrument. FDA encourages sponsors and other stakeholders to explore other least burdensome approaches and discuss those approaches with FDA to help determine whether or how they can be applied to support regulatory submissions.

VII. Glossary

The following glossary is provided to clarify the meaning of terms used in this guidance document relating to patient-reported outcome instruments for medical device submissions. The terms used in this glossary have been defined in the BEST glossary, which was a joint FDA-National Institutes of Health (NIH) effort and the guidance entitled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," unless otherwise noted. These terms are not intended to be applied in any context beyond this guidance. Understanding that terminology in this field may change over time, we intend to publish this glossary on our website and update it periodically.

Adaptation – Any change made to the test that has been translated into the language of a target group and that takes into account the nuances of the language and the culture of the group.[30] Adaptation does not change the items comprising the PRO instrument but involves the transfer of a PRO instrument's content to another mode[31], language[32] or population.[33] Adaption studies are undertaken to confirm the properties of the PRO instrument in the new situation or language.

Cognitive Interview – A cognitive interview is a type of qualitative research method used to determine whether the concepts and items of a PRO instrument are understood by patients as intended by the instrument developers.[34, 35]

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[30] American Educational Research Association, American Psychological Association, National Council on Measurement in Education. *Standards for educational and psychological testing*. Washington, DC: American Educational Research Association; 2014.

[31] Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO good research practices task force report. *Value in Health.* 2009;12(4):419-429.

[32] Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value in Health.* 2005;8(2):94-104.

[33] Wild D, Eremenco S, Mear I, et al. Multinational Trials—Recommendations on the Translations Required, Approaches to Using the Same Language in Different Countries, and the Approaches to Support Pooling the Data: The ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force Report. *Value in Health.* 2009;12(4):430-440.

[34] See FDA's Patient Focused Drug Development Guidance 2 Public Workshop Discussion documents "Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments," available at https://www.fda.gov/media/116276/download and the "Public Workshop Legislation Background and Glossary" available at https://www.fda.gov/media/116280/download.

[35] Forsyth, B. H., & Lessler, J. T. (2011). Cognitive Laboratory Methods: A Taxonomy. In P. P. Biemer, R. M. Groves, L. E. Lyberg, N. A. Mathiowetz, & S. Sudman (Eds.), *Measurement Errors in Surveys* (Vol. 173): John Wiley & Sons.

Concept Elicitation Interviews – Concept elicitation is a process to collect a holistic set of relevant concepts that are important to patients. Concepts can be elicited using qualitative, quantitative, or mixed methods.[36]

Concept (also referred to as Concept of Interest [COI]) – In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical or functional state, or experience that the assessment (PRO instrument) is intended to capture (or reflect).[37] For a PRO, the concept represents aspects of how patients function or feel related to a health condition or its treatment.[38]

Context of Use (COU) – The context of use is a statement that fully and clearly describes the way the PRO instrument is used and the medical product-related purpose of its use.

Fit-for-Purpose – A conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use.

Item – An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept.[39]

Modification – A change in instrument content, format (including response formats), and/or administration conditions.[40]

Patient-reported outcome (PRO) – A type of clinical outcome assessment that is based on a report that comes directly from the patient about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else.[41]

Patient-reported outcome instrument – The measure or tool used to collect the PRO.

Questionnaire – A type of patient-reported outcome instrument that is a set of questions or items shown to a respondent to get answers for research purposes. Types of questionnaires include diaries and event logs.[42]

Recall period – The period of time patients are asked to consider in responding to a PRO item or question. Recall can be momentary (real time) or retrospective of varying lengths.[43]

Score – Any specific number resulting from the assessment of an individual, such as a raw score, a scale score, or a rating.[44]

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[36] See Footnote 34.
[37] For additional information see Patient-Focused Drug Development Glossary, available at https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary.
[38] See Footnote 2.
[39] See Footnote 2.
[40] American Educational Research Association, American Psychological Association, National Council on Measurement in Education. *Standards for educational and psychological testing*. Washington, DC: American Educational Research Association; 2014.
[41] See Footnote 2.
[42] See Footnote 2.
[43] See Footnote 2.
[44] Adapted from American Educational Research Association, American Psychological Association, National Council on Measurement in Education. *Standards for educational and psychological testing*. Washington, DC: American Educational Research Association; 2014.

Validation – The process to establish that the performance of a PRO instrument is acceptable for its intended purpose.

Validity – Validity is the degree to which evidence supports the performance of a PRO instrument result for its intended purpose.[45]

Validity Evidence – Data that supports the validity of a PRO instrument for its proposed uses.[46]

[45] American Educational Research Association, American Psychological Association, National Council on Measurement in Education. *Standards for educational and psychological testing*. Washington, DC: American Educational Research Association; 2014.

[46] Adapted from Kane, MT "Validation." In R. L. Brennan (Ed.), *Educational Measurement (4th edition)*. Westport: American Council on Education and Praeger, 2006.