Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

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

DRAFT GUIDANCE

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I. INTRODUCTION

A. Overview of FDA Guidances on Patient-Focused Drug Development

This guidance (Guidance 3) is the third in a series of four methodological patient-focused drug development (PFDD) guidance documents[2] that describe how stakeholders (patients, caregivers, researchers, medical product developers, and others) can collect and submit patient experience data[3] and other relevant information from patients and caregivers to be used for medical product[4] development and regulatory decision-making. When finalized, Guidance 3 will represent the current thinking of CDER, CBER, and CDRH on this topic. The topics that each guidance document addresses are described below.

[1]This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research, in cooperation with the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health, at the Food and Drug Administration.

[2] The four guidance documents that will be developed fulfill FDA commitments under section I.J.1 associated with the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) under Title I of the FDA Reauthorization Act of 2017 (FDARA). The projected time frames for public workshops and guidance publication reflect FDA's published plan aligning the PDUFA VI commitments with some of the guidance requirements under section 3002 of the 21st Century Cures Act (available at https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm563618.pdf).

[3] "Patient experience data" is defined for purposes of this guidance in Title III, Section 3001 of the 21st Century Cures Act, as amended by section 605 of FDARA, to include data that "(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers); and (2) are intended to provide information about patients' experiences with a disease or condition, including (A) the 'impact (including physical and psychosocial impacts) of such disease or condition or a related therapy or clinical investigation; and (B) patient preferences with respect to treatment of the disease or condition."

[4] For purposes of this guidance a "medical product" refers to a drug (as defined in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)) intended for human use, a device (as defined in such section 201) intended for human use, a biological product (as defined in section 351 of the Public Health Service Act (42 U.S.C. 262)).

- Methods to collect patient experience data that are accurate and representative of the intended patient population (Guidance 1)[5]
- Approaches to identifying what is most important to patients with respect to their experience as it relates to burden of disease/condition and burden of treatment (Guidance 2)
- Approaches to selecting, modifying, developing, and validating clinical outcome assessments (COAs) to measure outcomes of importance to patients in clinical trials (Guidance 3)
- Methods, standards, and technologies to collect and analyze COA data for regulatory decision-making, including selecting the COA-based endpoint and determining clinically meaningful change in that endpoint (Guidance 4)

Please refer to **Guidance 1** and other FDA guidances[6] for additional information on patient experience data.

In conducting research that involves accessing patient experience data or directly engaging with patients, it is important to carefully consider Federal, State, and local laws and institutional polices for protecting human subjects and reporting adverse events. For additional information about human subjects protection, refer to **section IV.A.2 of Guidance 1**.

FDA encourages stakeholders to interact early with FDA and obtain feedback from the relevant FDA review division when considering collection of patient experience data related to the burden of disease and treatment.[7] FDA recommends that stakeholders engage with patients and other appropriate subject matter experts (e.g., qualitative researchers, clinical and disease experts, survey methodologists, statisticians, psychometricians, patient preference researchers) when designing and implementing studies to evaluate the burden of disease and treatment, and perspectives on treatment benefits and risks.

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."

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[5] See the guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[6] See FDA guidance for industry *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* (August 2016), or subsequent guidances in the PFDD series, when available.

[7] In addition to the general considerations discussed in this guidance, a study may need to meet specific statutory and regulatory standards governing the collection, processing, retention, and submission of data to the FDA to support regulatory decisions regarding a marketed or proposed medical product. This guidance focuses on more general considerations that apply to many types of studies, and you should consult with the review division and applicable guidance regarding any other applicable requirements.

B. Purpose and Scope of the Guidance

This document provides guidance that is generally applicable to COAs, including patient-reported outcome (PRO), observer-reported outcome (ObsRO), clinician-reported outcome (ClinRO), and performance-based outcome (PerfO) measures. Appendices A, B, C, and D include additional considerations for each type of COA, respectively, and multiple illustrations of conceptual frameworks.

This guidance is intended to help sponsors use high quality measures[8] of patients' health in medical product development programs. Ensuring high quality measurement is important for several reasons: measuring what matters to patients; being clear about what was measured; appropriately evaluating the effectiveness, tolerability, and safety of treatments; and avoiding misleading claims. Such findings may help support regulatory decision-making in a variety of contexts. For example, findings measured by a well-defined and reliable COA in an appropriately designed and conducted investigation generally can be used to support a claim in required medical product labeling if the claim is consistent with the findings and the COA's documented measurement capabilities.[9]

The overall structure of this guidance is as follows:

- Overview of COAs in clinical trials, including:
  - Describing the four types of COAs
  - Specifying what a COA assesses (the concept of interest)
  - Specifying the purpose and context of the COA's assessment (the context of use)
  - Determining whether a COA has sufficient evidence to support its context of use, or is fit-for-purpose (BEST (Biomarkers, Endpoints and Other Tools) Resource 2016)
- A general process, referred to as a Roadmap to patient-focused outcome measurement, that sponsors and COA developers may consider as they select, modify, or develop a COA
- A discussion of components of a well-supported rationale to justify the COA's ability to assess the concept of interest for a specified context of use

[8] A measure is a means to capture data (e.g.., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding; a standard format for data collection; and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.

[9] The considerations addressed in this guidance may be relevant to a variety of regulatory decisions that require an assessment of benefit or risk, including but not limited to: drug approval decisions under the standards in section 505(d) of the FD&C Act and regulations in 21 CFR 314; device approval decisions under the standards in sections 513(a)(2) and 515(d) and regulations in 21 CFR part 814; device classification decisions under the standards in sections 513(a)(2) and 513(f) and regulations in 21 CFR parts 807 and 860; investigational new drug and investigational device exemption applications under sections 21 CFR parts 312 and 812; REMS and PMR requirements under sections 505-1 and 505(o)(3) and device post-approval requirements under 21 CFR part 814 subpart E; labeling decisions under 21 CFR parts 201, 801, and 809. Necessarily, this guidance does not attempt to capture all of the regulatory standards that might apply to a sponsor's intended plan of study; sponsors should consult the relevant review division(s) as necessary to discuss their study plans and are responsible for satisfying applicable requirements.

This guidance is informed by developments in research and applications of COAs to derive clinical trial endpoints that have occurred since the release of the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) (2009 PRO guidance):[10]

- Patients and caregivers have been increasingly integrated as stakeholders in the development and evaluation of medical products.
- Several best-practice publications have described recommendations for developing and evaluating COAs, as well as analyzing and reporting COA data. Readers are directed to relevant publications throughout this guidance.
- The growing need for FDA guidance regarding all types of COAs has motivated the broader scope of the PFDD guidance series compared to the 2009 PRO guidance.
- The framework discussed in this guidance for development of well-constructed measures is based on developing evidence-based rationales. Several publications have described the development of evidence-based rationales (American Educational Research Association et al. 2014; Kane 2013; Weinfurt 2021). This modern validity framework is useful for discussing the broad range of COAs addressed by this guidance and helps to clarify evidence that may be appropriate to support the rationale for using a particular COA.

This guidance distinguishes an endpoint from the COA, and the score produced by that COA. The COA includes any instructions, administration materials, content, formatting, and scoring rules. A COA score refers to any numeric or rated values generated by a COA through a standardized process. For example, a score could refer to:

- A response to a specific item (an individual question, statement, or task that is evaluated or performed by the patient to address a particular concept) on a PRO measure
- A rating assigned by a clinician (as part of a ClinRO measure) or observer (as part of an ObsRO measure) describing a patient's functioning
- The result from a performance test, such as grip strength measured in kilograms
- A combination of item responses assumed to measure some *domain* (a sub-concept represented by responses to a subset of items or tasks from a COA that measures a larger concept; such a COA would comprise multiple domains)
- A combination of scores from multiple domains to reflect some larger concept

A COA might produce more than one type of score, especially if the COA is designed to measure more than one concept. In contrast to a COA score, an endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A complete definition of an endpoint typically specifies the type of assessments made; the timing of those assessments; the assessment tools used; and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined (see Guidance 4, when available, for a discussion of COA-based endpoints).

[10]We update guidances periodically. 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.

II. OVERVIEW OF COAs IN CLINICAL TRIALS

A. Types of COAs

A COA is a measure that describes or reflects how a patient feels, functions, or survives. (Note that although clinical events, including death, require a clinician's judgment and might be considered ClinROs, they are not discussed further in this guidance. The remainder of this guidance focuses on COAs intended to provide insight into how patients feel and/or function.) COA scores can be used to support efficacy, effectiveness, and safety in the context of a clinical trial to determine the clinical benefit(s) and risks(s) of a medical product. There are four types of COAs and choosing which type(s) of COA to use is driven by the concept(s) of interest to be measured and the context in which it will be applied (the context of use). More than one type of COA can be used in a clinical trial to capture the patient experience and the status of the patient's disease or condition.

The following are the four types of COAs:

- **Patient-reported outcome** (PRO) measures (Appendix A)
  - Reports come directly from the patient
  - Useful for assessment of symptoms (e.g., pain intensity, shortness of breath), functioning, events, or other aspects of health from the patient's perspective
- **Observer-reported outcome** (ObsRO) measures (Appendix B)
  - Reports come from someone other than the patient or a health professional (e.g., a parent or caregiver) who has opportunity to observe the patient in everyday life
  - Useful when patients such as young children cannot reliably report for themselves, or to assess observable aspects related to patients' health (e.g., signs, events, or behaviors)
- **Clinician-reported outcome** (ClinRO) measures (Appendix C)
  - Reports come from a trained health-care professional using clinical judgment
  - Useful when reports of observable signs, behaviors, clinical events, or other manifestations related to a disease or condition benefit from clinical judgment
- **Performance outcome** (PerfO) measures (Appendix D)
  - A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

Another type of measure—a proxy-reported outcome measure—is discouraged by FDA. A proxy-reported measure is an assessment in which someone other than the patient reports on patient experiences as if the individual were the patient. FDA acknowledges that there are instances when it is impossible to collect valid and reliable self-report data from the patient. In these instances, it is recommended that an ObsRO measure be used to assess the patient's behavior rather than a proxy-reported measure to report on the patient's experience.

There has been a rapid evolution in digital health technologies (DHTs), which can be used to collect health care-related data from study participants in clinical trials. A DHT is a system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. This may include use as a measurement tool for COAs in clinical investigations. Refer to the FDA draft guidance for industry *Use of Digital Health Technologies for Remote Data*

Acquisition in Clinical Investigations (December 2021)[11] for more detailed discussion and recommendations on the use of DHTs in clinical investigations.

Sometimes composite measures are used that combine the scores from several COAs (or several COAs and biomarkers) into a single score. Discussion of these composite measures is beyond the scope of this guidance. For discussion of composite endpoints in CDER and CBER decision-making, see the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017).[12]

B. The Concept of Interest and Context of Use for a COA

To precisely describe a COA in the context of a clinical study, sponsors should propose to FDA how they intend to interpret scores from a COA (i.e., what they believe the score measures), how scores will be used, and the context in which scores will be used. In other words, the sponsor's proposal should explicitly reference the concept of interest and the context of use, which are discussed below. Each proposal should reference a specific score because a measure may produce multiple scores

1. The Concept of Interest

The concept of interest is the aspect of an individual's experience or clinical, biological, physical, or functional state that the assessment is intended to capture (reflect). Depending on the intervention, the intent of treatment may be to improve a symptom(s) or a specific function (e.g., ambulation); avoid further worsening of a symptom(s) or further loss of a specific function; or prevent the onset of a symptom or a loss of a specific function. Sponsors might also want to assess whether aspects of how patients feel and/or function could be negatively impacted by receipt of the intervention (i.e., harms). All aspects of health that might be meaningfully affected, positively or negatively, by the medical product could be concepts of interest. The identification of concepts of interest appropriate for a given target patient population in CDER and CBER decision-making is described in Guidance 2 of this series, the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (October 2019) (PFDD Guidance 2).[13] For some diseases/conditions, important concepts of interest might have already been developed and used in studies based on input from patients, caregivers, clinical experts, and other sources. In such cases, sponsors should reference and summarize the prior work done when justifying their choice of concept(s) of interest.

In a clinical trial, it is important to carefully select concepts that, when measured adequately:

- Reflect an aspect of health that is important to patients
- Have the ability to be modified by the investigational treatment
- Could demonstrate clinically meaningful differences between study arms within the time frame of the planned clinical trial

[11] When final, this guidance will represent FDA's current thinking on this topic for applicable medical products.
[12] When final, this guidance will represent FDA's current thinking on this topic for applicable medical products.
[13] When final, this guidance will represent FDA's current thinking on this topic for applicable medical products.

Often, a single disease or condition is associated with many concepts. For example, a condition that causes chronic pain may also be associated with fatigue and impact on physical and social functioning. To help focus a medical product development program, sponsors should identify the primary manifestations of a disease or condition (i.e., core concepts of a disease or condition). Other important concepts might represent the downstream impact of these core concepts on other aspects of how a patient feels or functions.

For example, when evaluating a treatment for the management of moderate to severe endometriosis-associated pain, it may be important to assess a core concept such as dyspareunia, defined as pain with intercourse. In addition, to further evaluate clinical benefit, a strategy to assess the impact of moderate to severe endometriosis-associated pain severity on daily activities could also be assessed.

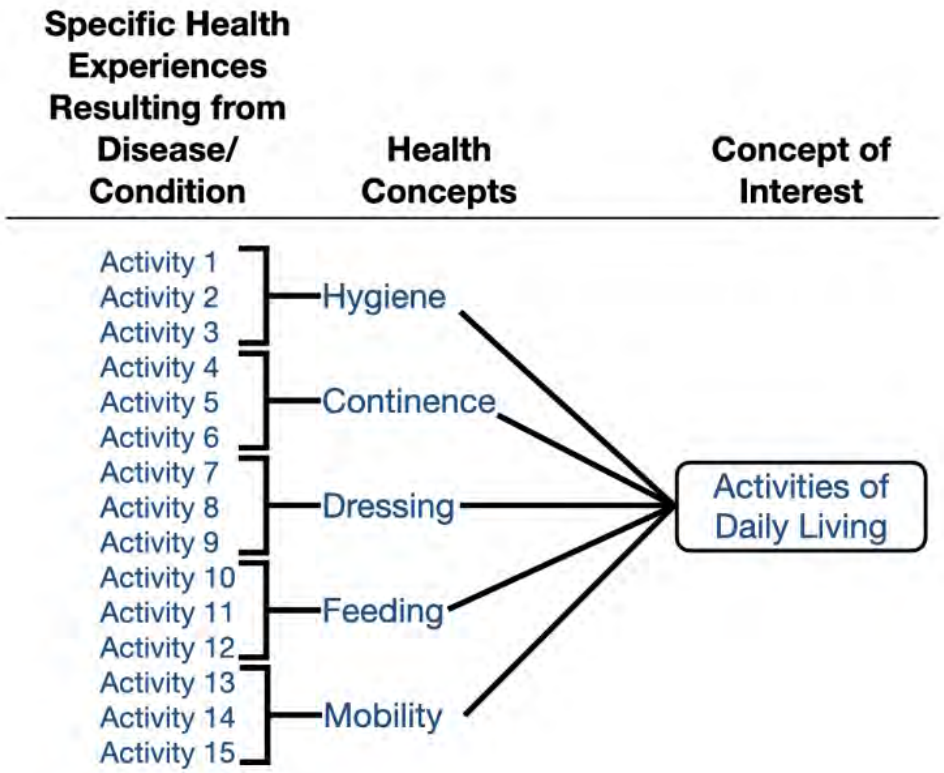
In addition to selection of the concept(s) of interest, the aspect(s) of the concept(s) of interest that will be assessed should also be considered. Aspects might include presence/absence, frequency, intensity, worst experience, and for concepts of interest reflecting a patient's functioning the amount of difficulty experienced or level of assistance needed. Patient and/or caregiver input can be used to identify which aspect(s) of a concept is most impactful for patients. This input will help sponsors in selecting or developing a COA that measures what is important to patients.

A conceptual model can be useful for representing patients' specific health experiences that result from their disease/condition, the health concepts that describe those specific experiences,[14]and the concept(s) of interest selected for assessment. For example, Figure 1 displays a hypothetical, conceptual model underlying activities of daily living (ADLs) as the concept of interest. In the figure, specific health experiences of the patient (Activities 1-15) are conceptualized in terms of five different health concepts—hygiene, continence, dressing, feeding, and mobility. For example, the activities collected under the concept "mobility" might include getting in and out of bed, being able to stand from a sitting position, and walking across a room. The five health concepts together make up a more general health concept known as ADLs, which the sponsor has selected as the concept of interest that will be assessed using a COA.[15] Such a conceptual model can be helpful to sponsors and FDA for communicating about the concept to be measured and for determining whether a proposed COA captures the entirety of a concept of interest.

[14] Note that what is referred to as a *health concept* in this guidance is the same as what Walton et al. (2015) refer to as a *meaningful health aspect*. The former term is used to avoid confusion that might arise from multiple uses of *aspect*.

[15] Here ADLs are both a higher-level health concept that includes the lower-level health concepts, such as hygiene, continence, as well as being the health concept chosen as the measured concept of interest.

Figure 1. Hypothetical Conceptual Model for Activities of Daily Living



2. The Context of Use

The context of use should clearly specify the way COA scores will be used as the basis for an endpoint, including the purpose for their use in a medical product development program. The appropriateness of a COA is evaluated within the proposed context of use.

Context of use considerations may include the following:

- **Use of the COA**: Clinical trial objectives and how the COA will be used to support COA-based endpoints (e.g., computing the mean COA score at 12 weeks)
- **Target Population**: Including a definition of the disease or condition; participant selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities); and expected patient experiences or events during the trial (e.g., that some patients will require assistive devices)
- **Study Context**: The clinical trial design in which the COA is to be used, including the type of comparator group and whether those providing responses or participating in the tasks for the COA (patients, observers, clinicians, trained raters) are masked with respect to treatment assignment and/or study visit)
- **Timing** of when assessment(s) of the COA is conducted
- **COA Implementation**: Including the site for COA collection (e.g., inpatient hospital, outpatient clinic, home); how the COA will be collected (e.g., DHT, paper form); and by whom (e.g., patient, study coordinator, investigator, parent/caregiver.)

C. Deciding Whether a COA Is Fit-for-Purpose

A COA is considered fit-for-purpose when "the level of validation associated with a medical product development tool is sufficient to support its context of use" (BEST (Biomarkers, Endpoints and Other Tools) Resource, 2016). Whether a COA is fit-for-purpose is determined by the strength of the evidence in support of interpreting the COA scores as reflecting the concept of interest within the context of use. Fit-for-purpose in the regulatory context means the same thing as *valid* within modern validity theory, i.e., validity is "the degree to which evidence and theory support the interpretations of test scores for proposed uses of tests" (American Educational Research Association et al. 2014).

Decisions about whether a COA is fit-for-purpose are based on two considerations:

1. *The Concept of Interest and Context of Use Are Clearly Described*

Section III.C describes what constitutes a clear statement of the intended interpretation of COA scores as measures of the concept of interest within the context of use. The statement should explicitly specify the concept of interest and the context of use in enough detail to describe clearly how the COA is intended to be used.

2. *There Is Sufficient Evidence to Support a Clear Rationale for the Proposed Interpretation and Use of the COA*

Regardless of whether sponsors propose to use an existing COA, a modified COA, or a newly developed COA, sponsors should present a well-supported rationale for why the proposed COA should be considered fit-for-purpose. The rationale is a set of reasons supported by evidence.

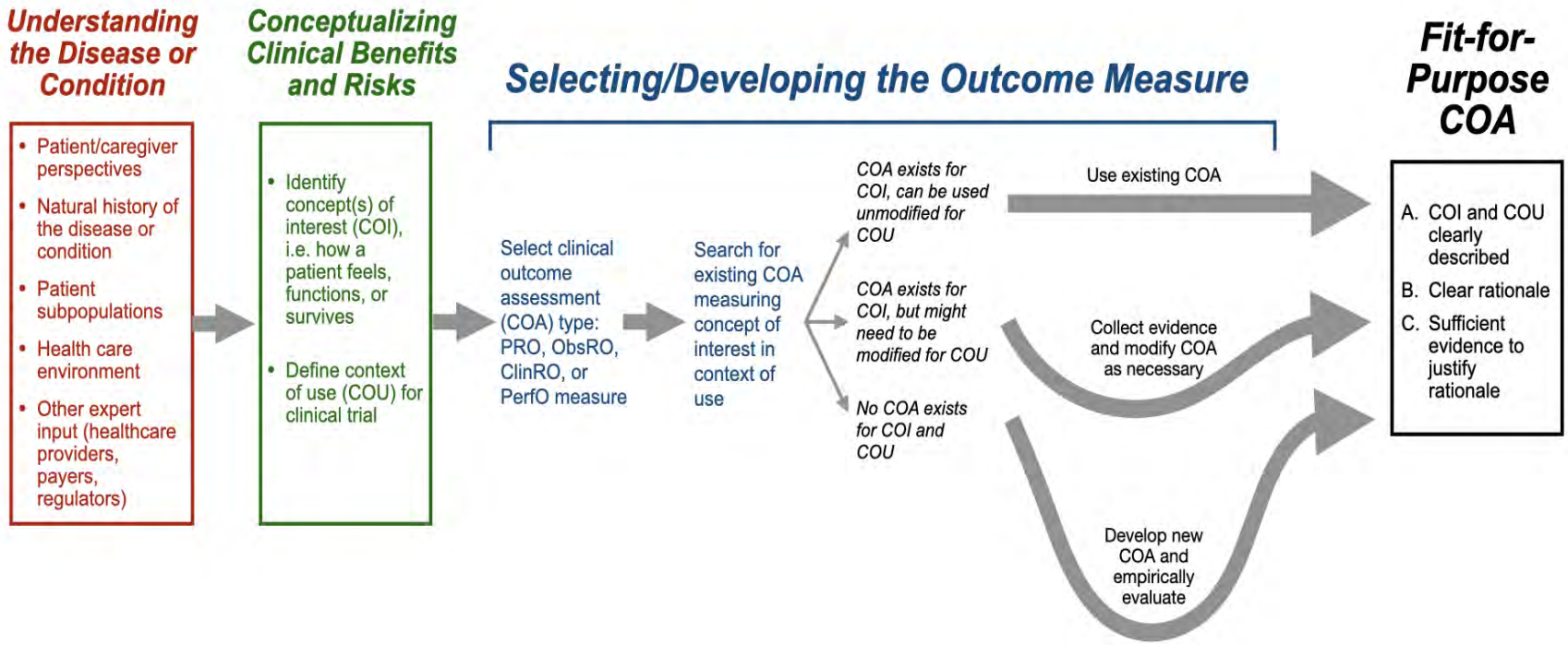
The rationale may have multiple components (see section IV, Table 1) and each component should be justified by one or more sources of evidence, including for example literature reviews; natural history studies; qualitative studies with patients, caregivers, or other stakeholders; and quantitative studies.

To determine whether sufficient justification has been provided for the rationale, FDA will review each part of the rationale and assess whether an appropriate type and amount of evidence has been presented. The evidence for a particular part of the rationale is weighed relative to the degree of uncertainty about that part. The greater the uncertainty, the greater the need for additional evidence to support that part of the rationale. In addition to the degree of uncertainty about each part of the rationale, FDA considers the context of use, and may consider the broader impact on the target patient population and medical product development of collecting additional evidence (Leptak et al., 2017), when determining whether a COA is fit-for-purpose. Section IV provides guidance about how to develop a clear rationale with supporting evidence.

III. A ROADMAP TO PATIENT-FOCUSED OUTCOME MEASUREMENT IN CLINICAL TRIALS

This section describes a general Roadmap to patient-focused outcome measurement in clinical trials (see Figure 2). Sponsors and COA developers are not required to use this approach, and it may not fit every development program, but it has worked well for a number of COAs. FDA recommends sponsors seek FDA input as early as possible and throughout medical product development to ensure COAs are appropriate for the intended context of use.

Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials



A. Understanding the Disease or Condition and Conceptualizing Clinical Benefits and Risks

1. Understanding the Disease or Condition

The first step involves considering the manifestations and natural history of the disease or condition; important patient subpopulations; the clinical environment in which patients with the condition seek care; and patient and/or caregiver perspectives on the disease, its impacts, and therapeutic needs and priorities. One important outcome of this step is understanding and summarizing the important signs, symptoms, and health impacts patients with the disease or condition might experience.

2. Conceptualizing Clinical Benefits and Risks

The next step involves considering which aspect(s) of the patient's experience with the disease/condition and/or its treatment will be targeted by the medical product. This consideration leads to identifying the concept(s) of interest (see section II.B.1) and context of use, including the population of interest, clinical trial design, and the trial objective and endpoints.

A conceptual model can be used to support the first two parts of the Roadmap. When little is known about a patient population and/or their health experiences, a hypothesized conceptual model can be developed based on literature review and/or expert clinical input. Then qualitative research with patients and/or caregivers can be conducted to evaluate and, if necessary, modify the conceptual model (see PFDD Guidance 2 and Patrick et al. 2011a). Note for relatively simple and narrow concepts, such as presence of itch, a simple definition might suffice without a more elaborate conceptual model. However, for more complex health experiences, we recommend a clear and detailed conceptual model for subsequent steps of the Roadmap. A conceptual model comprises one component of a conceptual framework (see section III.C).

B. Select/Develop the Outcome Measure

There are several steps involved in selecting or, if necessary, developing a COA to measure the concept of interest.

1. Selecting the COA Type

Sponsors and measure developers should consider what type of COA is most appropriate for assessing the concept of interest in the context of use. Considerations for selecting a specific type of COA are discussed in section II.A. and in Appendices A-D. Sometimes multiple COA types may be used to measure the concept of interest.

2. Evaluating Existing and Available COAs Measuring the Concept of Interest in the Context of Use

FDA recommends conducting a search to identify a COA that measures the concept of interest in the intended context of use and is available for use.[16] Existing COA measures for which there is already experience in the relevant context of use are generally preferred, particularly when measuring well-established concepts (e.g., pain intensity). Sponsors can identify potential measures by searching the scientific literature; repositories of measures, including item banks comprising previously developed and tested items; and other resources [FDA COA Qualification Program, 2021; FDA Medical Device Development Tools (MDDT), 2021]. When searching for existing COAs, the conceptual model for the concept of interest can be used to assess whether an existing measure addresses the full content of the concept of interest.

There are several possible outcomes of conducting this search.

a. An Appropriate COA Exists for the Concept of Interest in the Same Context of Use: Use Existing COA

If a COA exists to assess the concept of interest in the same context of use as intended in the sponsor's trial, the sponsor should assess its sufficiency; provide the rationale for selection of the COA; and summarize the evidence that supports that rationale (such as details on the prior experience with this COA, especially prior studies in which the COA was used, and evidence of how well it performed).

There are times when an existing COA may not have all the evidence recommended to support its use because the COA is still under development or was developed a long time ago, or for other reasons. For example, some types of studies (such as an assessment of test-retest reliability) may not have been conducted or some documentation may not be available for some steps in the development. Sponsors should summarize all existing information and evidence that supports the rationale for the use of the COA and assess how well the rationale is supported by the available information. In some instances, adequate evidence may be found in the literature or available clinical trial data, while in other instances, it may be necessary to collect additional evidence for the rationale before the COA can be considered fit-for-purpose.

COAs being used in registries, natural history studies, or observational trials may or may not be fit-for-purpose in other contexts of use. Sponsors should ensure that there is sufficient evidence to support the use of such COAs within the intended context of use in the planned clinical trial.

b. A COA Exists for the Concept of Interest for a Different Context of Use: Collect Additional Evidence and Modify COA as Necessary

If a COA exists that assesses the concept of interest but was not developed for the sponsor's context of use (e.g., was not developed for the same target patient population), then the sponsor should evaluate whether the COA can be used in the different context of use and provide supporting evidence or explanations supporting the new context of use. Evidence presented in prior work on the COA may suffice to support the rationale for its use in the new context of use.

[16] FDA encourages the sharing of COAs among sponsors and researchers to promote efficiency and to maximize the returns on the efforts made by patients who cooperated in their development.

Alternatively, if the existing evidence leaves too much uncertainty about the appropriateness of use in the new context of use, we recommend the collection of additional evidence.

A sponsor may also consider modifications intended to improve the COA's ability to reflect the concept of interest. Modifications could include, but are not limited to, changes to:

- Instructions/training materials
- Item or task content (e.g., omitting, adding, or modifying wording of items and/or response options; translating from one language to another; modifying the activity performed for a PerfO)
- Order of the items or tasks
- Recall period
- Format of the measure (e.g., paper or electronic device)
- Method of scoring, including changes to the scoring algorithm

The sponsor should carefully consider the impact of the proposed modifications to an existing COA. Any alteration of the COA could potentially constitute the creation of a new measure and result in altering the measure's scores and/or their interpretation. Some modifications are unlikely to alter the scores or their interpretation (e.g., changing the display on a tablet-based administration from one item per screen to three items per screen), whereas other changes are likely to affect scores and their interpretation (e.g., changing the recall period from 1 day to 7 days). In the latter case, the modification may, in effect, create a new measure. The type of evidence (qualitative and/or quantitative) to support modifications of a COA will depend on the type of changes that are proposed and the way in which the new context of use differs from the one for which the COA was originally developed. Sponsors should support their assessment, with appropriate evidence, that the modified measure adequately measures the concept of interest in the new context of use.

References are available that address considerations for modifying a COA (see Rothman et al. 2009 and Papadopoulos et al. 2019).

c. No COA Exists for the Concept of Interest: Develop a New COA and Empirically Evaluate

It is beyond the scope of this guidance to provide specific recommendations for developing all types of COAs, but helpful references that address measure development are provided at the end of this guidance (e.g., de Vet et al. 2011; Fayers and Machin 2016). There are general principles regarding the development process for any type of new COA:

- Clearly document all steps and data collected in the development process. For COAs involving multiple items, this includes an item tracking matrix that describes the history of the development and modification of all items.
- Develop and provide convincing evidence to support the rationale for interpreting COA scores as a measure of the concept of interest in the context of use (discussed in section IV). Support for the rationale includes evaluation of relevant measurement properties.

- Consider and evaluate potential limitations of the proposed COA. For example, could measurement of the concept of interest be affected by processes or concepts not part of the concept of interest (see section IV.D)?
- Create a user manual for the COA describing how to administer the measure. For most types of COAs, it is important to create training materials (e.g., for investigators, patients, observers, or clinicians) so that assessments are conducted in a consistent way.
- Document the method of scoring the COA, including how missing items or tasks should be handled. There should be clear justifications for the approach to scoring and addressing missing data.

When the sponsor is developing or significantly modifying a COA, FDA does not recommend evaluating measurement properties for the first time in a registration[17] trial, because it may be too late to learn that the COA is not performing as it should, potentially jeopardizing the success of a medical product development program. Earlier trials represent an opportune time to evaluate measurement properties of COAs and sponsors are encouraged to include prospectively planned analyses to inform subsequent trials.[18] If this is not a feasible option, FDA recommends conducting a standalone observational study prior to the initiation of a registration trial(s) to aid in the development of a fit-for-purpose COA measure(s). Furthermore, using data from the observational study to evaluate the psychometric properties and performance of a proposed COA measure prior to the registration trial will reduce the risk of using a COA that may not perform as expected, and therefore may not detect a treatment effect.

Early in the development process, sponsors are encouraged to request a meeting with FDA to discuss plans for newly developed COAs.

FDA encourages the sharing of COAs among sponsors and researchers to promote efficiency and to maximize the returns on the efforts made by patients who cooperated in its development.

3. Special Considerations for Selecting or Developing COAs for Pediatric Populations

If the concept of interest can be reliably measured across the age spectrum of the trial patient population, we recommend using one simple version of a COA for patients of all ages in a study. Including multiple versions of a COA for different age groups in the same trial is generally not recommended because it may introduce unwanted measurement variability. However, depending on the concept of interest, at times it may be necessary to use multiple versions of a COA and/or different COA types to measure a concept, because assessment of the target concept may differ substantially across the age and developmental spectrum (e.g., gross motor functioning in infants and adolescents). Using multiple COAs to measure a concept in a trial impacts statistical analysis plans and trial power (see Guidance 4, when available).

When pediatric self-administered COAs are feasible, the COAs should be completed by the child independently, without any assistance from caregivers, investigators, or anyone else, to avoid

[17] In this guidance, *registration trials* are used to stand for what different groups call pivotal trials, confirmatory trials, and clinical trials for marketing authorization.

[18] Sponsors should also use data from later clinical trials to confirm, to the extent possible, the measurement properties evaluated in earlier phase trials.

influencing the child's responses. Computer-administration, including automated reading of items, using a touch screen, or games, may make it easier for children to self-report. Self-administration and self-report may not be suitable with very young children and therefore might call for alternative approaches, such as interviewer-administration by a trained interviewer and/or different COA types.

Young children may be limited in their understanding of certain response scales used in a PRO measure (e.g., a 0 to 10 numeric rating scale, more/less comparison, references to periods of time). Simplified age-appropriate response scales (e.g., scales with few and simple response options, broadly culturally acceptable and interpretable pictorial scales) should be considered for use with young children and may be useful for all ages. Supporting evidence for the suitability of a COA for specific pediatric populations should address age-relevant vocabulary, language comprehension, comprehension of the target concept, and relevance of the recall period.

References are available that discuss measurement in pediatric patient populations (Arbuckle and Abetz-Webb 2013; Bevans et al. 2010; Matza et al. 2013; Papadopoulos et al. 2013). Also, refer to PFDD Guidance 2, section VI (Managing Barriers to Self-Report) for considerations on how to obtain input from pediatric patients.

4. Using DHTs To Collect COA Data

DHTs can be used to implement a COA, such as collecting responses to items from a PRO measure or assessing the patient's activity functioning in a PerfO. As in any COA development, the concept of interest and the context of use must be clearly identified. Early in the clinical development program, based on input from patients and/or caregivers, the sponsor should define and provide rationale to justify the use of the DHT for measuring important feature(s) of the concept of interest in the target population. See the DHT draft guidance *Use of Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2021)[19] for more information about specifying the minimum technical (e.g., operating system, storage capacity, sensors) and performance (e.g., accuracy and precision) specifications.

5. COA Accessibility and Universal Design

A portion or all of the target patient population may benefit from accessibility features and universal design[20] considerations. Usability testing is recommended for accessibility features for a selected COA, along with human factors testing (see Guidance for Industry and FDA Staff, Applying Human Factors and Usability Engineering to Medical Devices, 2016, for guidance on CDRH decision-making). The following resources should be reviewed to ensure the COA is accessible for patients with impairments (e.g., vision impairment/low vision, hearing impairment/deaf or hard of hearing):

- The World Wide Web Consortium (W3) has a Web Accessibility Initiative (WAI) with resources and recommendations for making electronically delivered material more

[19] When final, this guidance will represent FDA's current thinking on this topic.

[20] In the context of COAs, *universal design* is consideration for the design and composition of a COA so that it can be accessed, understood, and used to the greatest extent possible by all people, inclusive of people with disabilities.

accessible to people, see https://www.w3.org/WAI/ and https://www.w3.org/TR/low-vision-needs/.

- Section 508, a U.S. Government website, has resources addressing universal design, including color universal design, creating accessible portable document formats (PDFs), and other topics: https://www.section508.gov/.

Options including assistive technology that may be used by participants, such as screen readers or eye trackers, can allow patients and/or their caregivers to provide reliable reports. Consider which modifications and/or assistive technologies might be useful to assist broad inclusion in COA development, evidence generation, and trials.

C. Developing a Conceptual Framework

The Roadmap describes a recommended path sponsors can take to arrive at a fit-for-purpose COA. Sponsors can construct an illustration in the form of a conceptual framework[21] to demonstrate the results of each step along the Roadmap for the selection of COAs in the clinical trial; this framework is particularly helpful to FDA reviewers.

A conceptual framework summarizes (1) relevant experiences of patients in the target population, (2) specific concepts of interest targeted for assessment, (3) type(s) of COA proposed for each concept of interest, and (4) a representation of how the particular COA is intended to work in order to generate a score reflecting the concept of interest.

The conceptual framework includes two important representations:

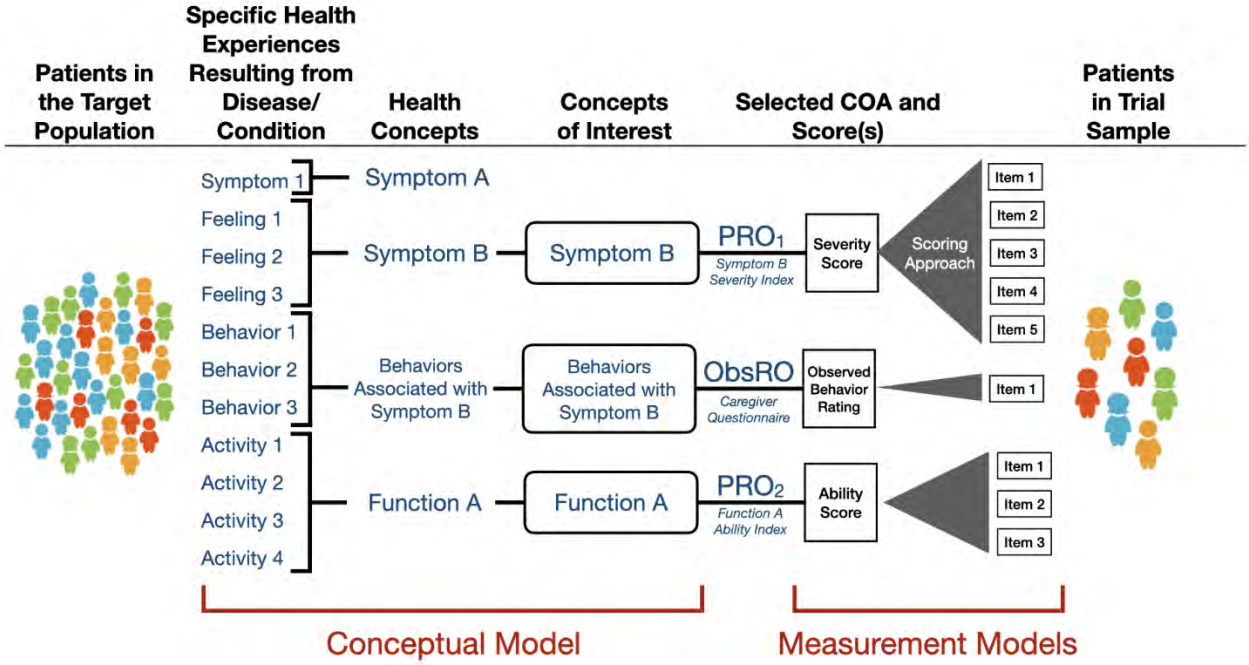
- The conceptual model, described in section II.B, which depicts the structure of a concept of interest, including the different aspects of the concept and how they relate to patients' experiences.
- The measurement model, which represents how a COA is intended to work to generate a score(s) that can be interpreted as a measure of the concept of interest in the context of use. How best to represent the measurement model for a specific COA will depend on the type and complexity of the measure, but most measurement models will include the parts of the COA (e.g., items or tasks) and how they are combined to result in a score(s).

A conceptual framework can be especially helpful when there is more than one concept of interest and COA. Figure 3 illustrates a generic conceptual framework for a clinical trial in which PRO and ObsRO measures are used to assess three related concepts of interest. Viewing the framework from left to right, the patients in the target population have a variety of specific health experiences that may be affected by their disease or condition, including different symptoms (e.g., feeling tired, dizzy, anxious); behaviors (e.g., scratching, waking up at night); and/or activities (e.g., walking up a flight of stairs, talking while walking). Through qualitative studies with patients and clinical expertise, these specific symptoms, behaviors, and/or activities can be

[21] In the 2009 PRO Guidance, the *conceptual framework* combined a representation of the concept and of the PRO instrument used to measure the concept in a single figure. To accommodate all types of COAs and more complex relationships between health experiences, concepts, and measures, the current guidance's conceptual framework separates the *conceptual model*, which represents the structure of the concept of interest, from the *measurement model*, which represents how the measure is intended to work in order to measure the concept of interest.

documented and summarized under one or more health concepts[22] that name the relevant symptoms, signs, and/or effects on functioning. From among these health concepts, sponsors select one or more concepts of interest to target for intervention and assessment based on the importance to patients; the target of the medical product (i.e., mechanism of action, targeted function); and the feasibility of observing intervention effects within the context of a clinical trial (e.g., trial duration). Note in Figure 3 that Symptom A is relevant for patients in the target population but was not chosen by the sponsor as a concept of interest for this trial. A specific type of COA is then selected to assess each concept of interest, generating a specific score(s) thought to reflect the concept of interest. Finally, the framework represents the way the measure is supposed to work to generate a score (i.e., the measurement model; see section IV.E). For example, a multi-item PRO measure would be represented by the specific items in the measure and some indication of how the items are combined to arrive at a score. Sponsors can consider the conceptual framework that best fits their specific development plan.

Figure 3. Illustration of a Generic Conceptual Framework Summarizing Which Patient Experiences Will Be Targeted and How They Will Be Measured



When reading from left to right, the representation provides a high-level view of the thinking behind the COA strategy—how the experiences of patients in the target population motivate the selection and measurement of the outcomes of interest. When reading from right to left, the representation provides an overview of the inference that stakeholders would like to make from the experiences of the trial participants, expressed as responses to one or more COAs, to the experiences that would be expected to occur among the larger target population of patients were

[22] Note that what is referred to as a *health concept* in this guidance is the same as what Walton et al. (2015) refer to as a *meaningful health aspect*. The former term is used to avoid confusion that might arise from multiple uses of *aspect*.

they to receive the investigational medical product(s). More examples of conceptual frameworks pertinent to each type of COA are found in the COA-specific appendices.

Section III describes a general Roadmap that sponsors might follow to arrive at a fit-for-purpose COA. The next two sections (IV and V) provide more focused guidance on how to construct and support a strong rationale for the proposed interpretation and use of a COA.

IV. DEVELOPING THE EVIDENCE TO SUPPORT THE CONCLUSION THAT A COA IS APPROPRIATE IN A PARTICULAR CONTEXT OF USE

Evidence collected in support of the use of a COA should support the rationale that explains how and why the specific COA is expected or intended to work. It is important for FDA to understand each part of a sponsor's rationale and the evidence being offered in support of each part. This understanding facilitates conversations between FDA and sponsors or measure developers.

This section describes eight components (see Table 1) that should be considered for inclusion in the rationale and supporting evidence or justification section of submissions to FDA. The discussion below also includes possible sources of evidence to evaluate each component. Different trials and contexts of use might call for different rationale components and/or evidence to support a COA as fit-for-purpose. Note that some types of studies might supply evidence to support more than one component. For example, a qualitative study using cognitive interviews involves asking patients how they understand items from a COA and arrive at their responses (Willis 2005 and Willis 2015) or asking patients and assessors how they interpret instructions for a PerfO. Data from such a study might be used to support components C, D, and F in Table 1.

Table 1. Eight Components Comprising an Evidence-Based Rationale for Proposing a COA as Fit-for-Purpose

A	The concept of interest should be assessed by [*COA type*] because . . .
B	The COA measure selected captures all the important aspects of the concept of interest.
C	Respondents understand the instructions and items/tasks of the measure as intended by the measure developer.
D	Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest.
E	The method of scoring responses to the COA is appropriate for assessing the concept of interest.
F	Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest.
G	Scores are sufficiently sensitive to reflect clinically meaningful changes within patients over time in the concept of interest within the context of use.
H	Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on patients' experiences.

Note: Listed components are those that are likely but not necessarily needed in the rationale for a specific COA, concept of interest, and context of use. Each rationale can be tailored to the proposed interpretation and use. Each component should be accompanied by comprehensive supporting evidence and justification.

A. The Concept of Interest Should Be Assessed by [COA Type], Because . . .

The sponsor should provide a clear rationale for the choice of type of COA (i.e., PRO, ObsRO, ClinRO, or PerfO) selected to assess the concept of interest. Considerations for selecting the specific type of COA are discussed in Section II.A and Appendices A-D. Note that more than one type of COA might be used to assess different aspects of a concept of interest. For example, a functional outcome could be assessed by a combination of a PRO measure and a PerfO measure for a particular context of use. In such cases, a separate rationale should be provided for each measure.

B. The COA Measure Selected Captures All the Important Aspects of the Concept of Interest.

All important aspects of the concept of interest should be covered by the chosen COA.[23] This includes the specific attribute(s) of interest, such as frequency, intensity, or duration. For narrow and simple concepts that can be assessed with a single item (e.g., asking patients to record how many times they woke up to urinate at night to measure nocturia), it is straightforward to see whether the item content covers the concept of interest. For more complex concepts of interest that include multiple aspects (for example, physical function), all important aspects should be reflected in the content of the COA, or else the concept of interest will only be partly assessed. Similarly, the tasks included in a PerfO should cover all important aspects of the function being evaluated as the concept of interest. The conceptual framework (section III.D) can show how the COA (represented by its measurement model) addresses all important aspects of the concept of interest (represented by its conceptual model).

C. Respondents Understand the Instructions and Items/Tasks of the Measure as Intended by the Measure Developer.

For PRO, ObsRO, and ClinRO measures, the most straightforward type of support for component C is in the form of cognitive interviews—individual qualitative interviews in which the participants discuss how they understand and respond to each of the components comprising the measure (e.g., their understanding and interpretation of instructions and items in a PRO measure) (Willis 2005, Willis 2015, and Patrick et al. 2011b). For PerfO measures, cognitive interviews with patients regarding task instructions combined with pilot testing tasks can confirm whether patients understand the task they are asked to do, and whether they are able to perform that task.

We also recommend that measure developers follow good practices in questionnaire design to avoid common pitfalls that could interfere with respondent understanding (e.g., avoiding double-

[23] How well a measure reflects all important aspects of a concept of interest was previously referred to as *content validity* in the 2009 PRO Guidance. The field of measurement, as reflected by the 2014 Standards for Psychological and Educational Testing, has moved from talking about different types of validity to specifying different sources of evidence. Validity is understood as a unitary concept and refers to the "degree to which evidence and theory support the interpretations of test scores for proposed uses of tests" (American Educational Research Association et al. 2014, p. 11), where tests in this case refer to COAs.

barreled items, which ask about more than one thing within a single item) (see section IV in PFDD Guidance 2).

D. Scores of the COA Are Not Overly Influenced by Processes/Concepts That Are Not Part of the Concept of Interest.

In a well-designed measure, it is the concept of interest that predominantly affects a patient's responses to items or tasks. Thus, sponsors or measure developers should consider the most likely interfering influences on responses to items or tasks and assess the presence and strength of those influences.

What follows are examples of some of the most likely sources of interfering influence. When a statement may only be relevant to certain COA types, those types are listed in brackets. Sponsors should consider whether there are additional factors (e.g., differences in use/access to health care related to location, income) not listed here that may influence scores on the COAs being used.

1. Item or Task Interpretations or Relevance Does Not Differ Substantially According to Respondents' Demographic Characteristics (Including Sex, Age, and Education Level) or Cultural/Linguistic Backgrounds.

Sponsors and measure developers should consider whether there are any demographic groups for whom items might be interpreted differently or tasks might have different relevance and, if so, evaluate potential differences between groups using qualitative (e.g., cognitive interviews) and/or quantitative methods (e.g., measurement invariance) as appropriate.

For some trials, COA instruments are used for patients with diverse linguistic and cultural backgrounds. Therefore, it is important to show that such differences are unlikely to influence response to COA items. It is recommended that translation, cultural adaptation assessment, and linguistic validation are conducted early in the COA selection and development process following good practice methodology (Eremenco et al. 2017; McKown et al. 2020; Wild et al. 2005). One approach is to describe in detail the process of language translation and/or cultural adaptation (including cognitive interviews) to support the quality of the resulting translation and/or adaptation. A robust process of translation and/or cultural adaptation increases confidence that all trial participants, regardless of their language and/or cultural backgrounds, understand the measure's instructions, items or tasks, and response options similarly.

For some types of multi-item measures, , one could also present evidence of measurement invariance, including differential item functioning (DIF) (Teresi et al. 2009). Such evidence could demonstrate that item responses provided by respondents from different demographic, linguistic, or cultural backgrounds can be interpreted and scored using the same statistical model. Such studies typically use larger sample sizes (e.g., at least 200 patients per group being compared (Scott et al. 2009)). Before embarking on a large DIF study, sponsors and measure developers might evaluate whether differences for particular items (considering the likely extent of demographic, linguistic, and cultural effects on the item response) will be large enough between groups to substantially change scores in a way that will affect the COA-based trial endpoint.

725
726 2. *Recollection Errors Do Not Overly Influence Assessment of the Concept of Interest.*
727 *[PRO, ObsRO, and ClinRO Measures]*
728
729 For COAs that involve a recall period (e.g., past 24 hours, past 7 days), sponsors should provide
730 support for the appropriateness of the recall period to be used. FDA recommends a clearly
731 specified recall period to help standardize reporting. The recall period should be shown to be
732 suitable for the intended context of use. Sources of evidence to support a given recall period
733 might include empirical study of the accuracy of different recall periods for the measure and/or
734 literature reviews of recall accuracy for the same or related concept of interests. Note that
735 cognitive interviews can provide justification that a given recall period is inappropriate (e.g., by
736 documenting that respondents generated their response thinking about a shorter period of time
737 than specified by the instrument). But cognitive interviews cannot provide evidence that
738 respondents can recollect with sufficient accuracy. The selected recall period should be short
739 enough to minimize the measurement error and/or potential bias (i.e., systematic inflation or
740 deflation of scores) due to recall error, while also minimizing respondent burden.
741
742 3. *Respondent Fatigue or Burden Does Not Overly Influence Assessment of the Concept*
743 *of Interest.*
744
745 Consider whether COAs may induce respondent fatigue and burden due to measure length,
746 complexity, and/or frequency of assessment. For data collected from patients during clinic visits,
747 the order in which COA data are collected (e.g., before or after blood draws and other data
748 collection) can influence respondent fatigue or burden. Respondents who feel fatigued or over-
749 burdened during an assessment might not provide data reflective of the underlying disease or the
750 impact of treatment. Evidence from cognitive interviews and/or usability testing may provide
751 insight as to whether a COA might lead to fatigue and/or burden. Sponsors may wish to explore
752 approaches to reduce burden, such as having patients complete assessments at home the day
753 before a clinic visit. Patient experience of burden might also be addressed by improving patients'
754 motivation through explaining the reasons for and importance of any lengthy, complex, and/or
755 frequent assessments.
756
757 4. *The Mode of Assessment Does Not Overly Influence Assessment of the Concept of*
758 *Interest.*
759
760 There are a variety of modes of administration for COAs, including paper-based forms and
761 electronic data capture using standardized devices (i.e., those used with all participants in a trial),
762 or participants' own mobile devices, computers, or other tools for assessment.
763
764 Using a mode of collection different from what was originally used for that COA (e.g., originally
765 used paper, now proposed to use a mobile device) may raise concerns about comparability of
766 assessment to prior experience. Similarly, using different collection modes in the same trial (e.g.,
767 different modes for different sites) would raise concerns regarding comparability of assessments
768 in the study. In both cases, part of the COA's rationale for using different modes is that
769 whatever measurement error or bias is created by changing mode of assessment will be too small

to affect the assessment of the concept of interest.[24] Whether this is reasonable will depend upon the situation and how the adaptation between modes was accomplished.

Sponsors can increase confidence that collection mode does not meaningfully influence measurements by following best practices for adapting measures to different assessment platforms (Critical Path Institute ePRO Consortium 2014a and 2014b; Byrom et al. 2019; Eremenco et al. 2014). FDA also recommends that sponsors conduct usability testing of the different data collection devices with a small number of respondents.

If a data collection platform has already demonstrated usability in a group of participants thought to be sufficiently similar to the target population and the content of the measure has already been evaluated using cognitive interviews, it may not be necessary to conduct a new equivalence study, especially if the COA uses typical response scales that have been well studied (Byrom et al. 2019).

Whether more extensive evidence is needed to support the comparability of scores between assessment modes will depend upon the specifics of each case.

5. Expectation Bias Does Not Unduly Influence Assessment of the Concept of Interest.

Responses to a COA may be influenced by the respondent's (i.e., patient's, caregiver's, or clinician's) or administrator's (for PerfO measures) expectations of how well the patient should be doing. Such expectations could be based on the patient's assignment to an experimental group in an unmasked trial and/or the duration the patient has been in the clinical trial (e.g., earlier versus later study visits). For ClinRO, ObsRO, and some PerfO measures, expectations might also be based on characteristics of the patient, such as their age or sex. An expectation bias could arise in at least two ways:

- For items that use a recall period, respondents may selectively recall those instances when symptoms or functioning were consistent with what the respondent expects. For example, a patient receiving a new medical product that the patient believes is effective provides self-reported assessments of functioning with a 7-day recall at both baseline and follow-up. The patient's expectations of benefit might make it more likely that the patient reports at follow-up based on recollections of more positive instances of functioning rather than negative ones.
- Expectations might influence how a respondent or an administrator interprets the meaning of items (Rapkin and Schwartz 2004). For example, consider two patients suffering from rheumatoid arthritis—one 49 years old and the other 82 years old. Relative to the 49-year-old, the older patient might expect that pain and discomfort are normal parts of aging. When asked about the impact of pain on daily functioning using response options of *None, Mild, Moderate, or Severe,* the older patient might interpret the response options differently from the younger patient. Thus, though both patients might have the same degree of pain and functional limitations, the older patient might select *Moderate* while the younger patient selects *Severe*.

[24] In some cases, a new mode of assessment may increase the accuracy or precision of scores.

Minimizing the influence of biases, including expectation bias, is very important and can be done by conducting randomized, placebo-controlled, and double-masked trials. Concealing the patients' assignment to study arms will also minimize the influence of patient expectations about whether a treatment will be beneficial.

6. Practice Effects Do Not Overly Influence the Assessment of the Concept of Interest. [PerfO Measures]

For PerfO measures, it is possible that patients' performance on the tasks could improve over time due to practice rather than to real improvements in the concept of interest. Practice effects may be minimized by using different tasks for each assessment whenever possible. Practice effects might also be reduced by administering a PerfO measure less frequently and/or separated by longer periods of time. Patients could also train on the tasks prior to randomization so that the patients' baseline status already reflects the effects of practice. Although randomization can reduce the impact of practice effects, it is still possible within a randomized trial for practice effects to (1) limit the ability of a COA to demonstrate the full magnitude of a treatment effect, and/or (2) differ by treatment arm when the intervention causes changes in cognitive function that facilitates practice effects. Evidence for or against the presence of strong practice effects could be obtained by examining the performance on PerfO measures over time among patients in a natural history or non-affected cohort outside of a trial, or by examining changes over time within a placebo group of a trial.

E. The Method of Scoring Responses to the COA Is Appropriate for Assessing the Concept of Interest.

Every COA provides some way for responses to be recorded or coded as an observed score for a prompt. For example, a PRO measure that assesses current nausea intensity might allow patients to record their responses on a verbal rating scale with four adjectives, producing an observed score between 0 and 3. A walking test might record the distance (or time) a patient walks for a specified time (or distance), producing an observed score in meters (or seconds).

1. Responses to an Individual Item or Task

For an individual item or task, response options should be non-overlapping and differences among adjacent response categories should reflect true differences in the concept of interest. The wording of the response options should be clear and concrete, and the instructions for making or recording the responses should be clearly understandable. Support for these considerations can come from cognitive interview data, demonstrating that respondents have no difficulty selecting an answer that matches their experience.

FDA generally does not recommend the use of a visual analog scale (VAS). There are known limitations with its administration (e.g., cannot be administered verbally or over the phone; photocopying or electronic rendering on different monitors or devices lead to different lengths of lines displayed at during a single trial) and interpretability (e.g., higher rates of missing data or incomplete data) (Dworkin et al. 2005 and Hawker et al. 2011).

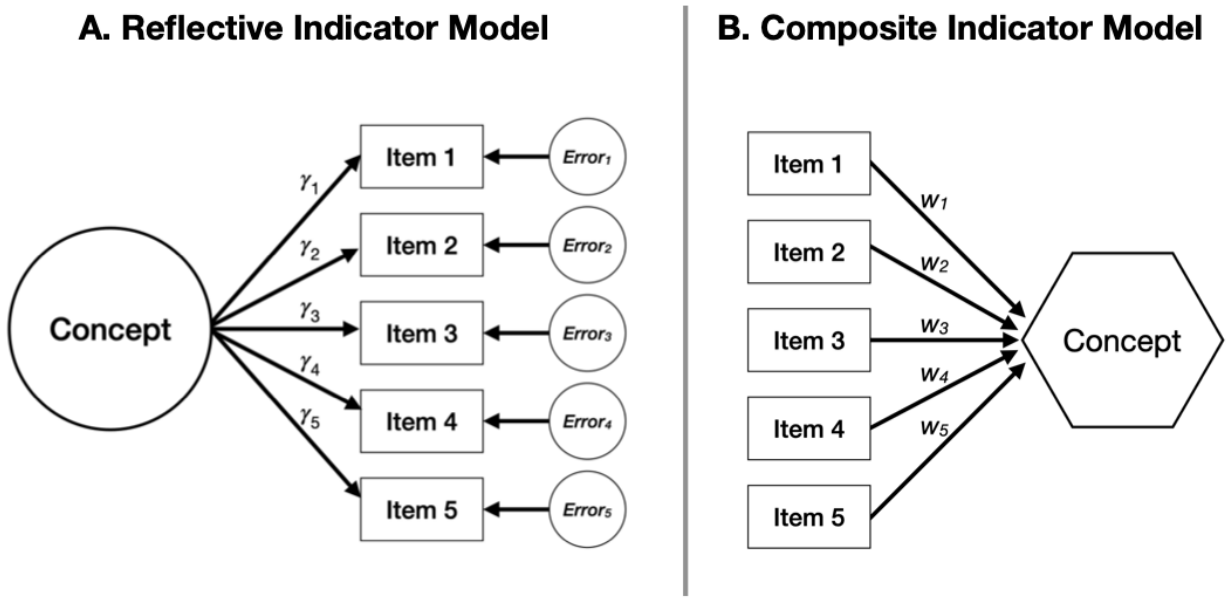
2. Rationale for Combining Responses to Multiple Items or Tasks

If multiple items or tasks are combined to generate a score on a COA, then the rationale for the method of scoring should be described and supported with evidence (Edwards et al. 2017). The approach for combining responses to multiple items/tasks is often expressed as a measurement model that relates responses to particular items/tasks to the score(s) thought to reflect the concept of interest. The rationale and justification for combining items or tasks will depend upon the particular measurement model chosen for the measure. Although there are many possible measurement models that might be appropriate for a COA, two of the more common models are the reflective indicator and composite indicator models.

3. Scoring a Unidimensional COA: The Reflective Indicator Model

The justification for combining responses across multiple items for a reflective indicator model is that all the item responses reflect, or are caused by, a single aspect of the patient described by the concept of interest (Fayers and Machin 2016)—an assumption known as *unidimensionality*. For example, a PRO measure might consist of multiple items that ask about lower limb-related mobility. Because the items are all reflections of, or effects of, lower limb-related mobility, the item responses should be consistent with a unidimensional measurement model (see Figure 4A). Statistical evidence including, but not limited to, confirmatory factor analysis can be provided to support the reasonableness of the assumption of unidimensionality. Sponsors or measure developers should also be clear about the psychometric model that is assumed (e.g., Classical Test Theory, Partial Credit Model, Samejima's Graded Response Model, Rasch Model) and supply statistical evidence in support of model assumptions and fit, as well as relevant model parameters. Note that FDA does not endorse any particular psychometric modeling approach but will review the strength of evidence in support of a model's use in specific cases.

Figure 4. Representations of Reflective (Panel A) and Composite (Panel B) Indicator Models.



Note: In panel A, the concept within a circle is conceptualized as a latent variable; the smaller circles represent measurement error that contributes to the responses of each item; γ denotes the causal effect of the concept on the item response. In panel B, the concept within a hexagon is conceptualized as a composite variable; *w* indicates the weight (may or may not be equally weighted) used for the item response in computing the calculated composite score that represents the concept.

Some PRO measures based on a reflective indicator model consist of multiple items assessing multiple domains. For such measures, if the multiple domains will be used to assess the concept(s) of interest, a rationale should be given supporting the conceptual distinctiveness of the different domains and psychometric analyses should be provided in support of the assumed dimensionality of the measure (e.g., demonstrating adequate fit of a confirmatory factor analysis model that includes the multiple domains).

When the assumptions are met, the sample size is large enough, and the model fit is acceptable, item response theory (IRT) models provide an approach to design, evaluation, and the scoring of COAs based on a reflective measurement model. Failure to assess assumptions such as unidimensionality, local independence of items, and measurement invariance may result in inadequate evidence of the properties of an IRT-based COA. When using IRT models to design, evaluate, or score a COA, additional information concerning the items and scale can be provided. In addition to estimated item parameters and corresponding standard errors, the functioning of response categories and DIF can be evaluated. For example, item characteristic curves can be used to examine for signs of redundant response categories for measures developed using IRT for polytomous items. Multiple IRT models and approaches exist. The chosen model or approach should fit with the characteristics of the COA and its items or tasks.

4. Scoring for a COA That Summarizes Across Heterogeneous Health Experiences: The Composite Indicator Model

Some measures assess a concept of interest using multiple items that, taken together, define the concept of interest. For example, the concept Basic Activities of Daily Living might be defined by a sponsor or measure developer as the degree to which the patient is able to accomplish everyday tasks that are necessary to live independently. The item content that defines *everyday tasks* might be determined through a consensus process with patients and their caregivers and could result, for example, in items addressing personal hygiene, dressing oneself, toileting, eating, and ambulation. Note that although it is likely that some of the item responses will be associated with one another, it is not necessary, because it is not assumed that all the items are reflective of or caused by a single, underlying thing as was the case for the reflective indicator model. Rather, these items, known as composite indicators, are like the ingredients of what is labeled Basic Activities of Daily Living (see Figure 4B) (Bollen and Bauldry 2011).[25]

For COAs based on a composite indicator model, sponsors or measure developers should describe and justify the process for selecting the items that make up the measure (e.g., by citing a consensus process with patients and others). A rationale should also be given for the way in which responses to the multiple items are combined to arrive at a score for the COA. For example, one might justify taking the sum of the item responses (which implies they are all weighted equally) based on qualitative or quantitative evidence that patients felt that all the activities described by the items are equally important for daily, independent living.

5. Scoring Approaches Based on Computerized Adaptive Testing

Some COAs make use of computerized adaptive testing (CAT) procedures, whereby the next item administered to a respondent depends upon a running estimate of the respondent's status based on the respondent's responses to prior items. The set of potential items to be administered is known as an item bank. With CAT, it is possible that fewer items will be needed to generate a sufficiently precise score for each patient, making the assessment more efficient and less burdensome to patients. Depending upon the concept of interest being assessed, a CAT may or may not be more efficient than administering the same items to every person.

FDA will consider well-justified approaches. To ensure changes in a patient's scores over time are not due to differences in the items administered, it is critical for sponsors to demonstrate, as for any COA, that (1) the item content aligns with the concept of interest; (2) all of the items are well understood by patients in the target population; (3) the items are well-calibrated in the context of a well-fitting IRT model; and (4) in the context of multinational or multicultural trial populations, all of the items in the item bank have undergone an acceptable process of translation and/or adaptation. FDA recommends not making changes to an item bank mid-trial; however, if

[25] It is important to distinguish between a composite indicator measurement model and a composite endpoint. Composite indicators are separate items or tasks, which may or may not be correlated, that are combined to create a new summary variable corresponding to a concept of interest. In contrast, a composite endpoint is a way of constructing an endpoint based on two or more individual clinical outcomes (components). The *composite endpoint* is then defined as the occurrence or realization in a patient of any of the specified components. For more discussion of composite endpoints, see the draft guidance for industry *Multiple Endpoints in Clinical Trials*. When final, this guidance will represent FDA's current thinking on this topic.

the item bank undergoes any changes (e.g., maintenance, updating, or addition of new items) during the clinical trial, it is important to demonstrate that the item bank remains well calibrated with respect to the original concept being measured. Sponsors should also describe and justify the stopping rule used for the CAT in terms of the minimum level of measurement precision desired. It is also suggested that stopping rules include considerations of patient burden (e.g., by stopping the CAT after some maximum number of items have been administered). Note that sponsors might consider different CAT stopping rules for different contexts of use.

As an alternative to full CAT administration, sponsors might also consider a hybrid CAT in which every patient is administered items by the CAT algorithm and a fixed set of items (if not already selected by the algorithm).

6. Approach to Missing Item or Task Responses

Missing item responses can create problems for interpreting and using scores from a COA with multiple items or tasks. The scoring algorithm should explicitly state the conditions under which a score can still be computed in the presence of missing item/task responses, e.g., specifying the minimum number of items/tasks responses to compute a score and/or how missing items are to be scored. Any rules for handling missing item or task responses should be justified sufficiently (e.g., through a missing data simulation study). A copy of the scoring manual should be provided to FDA so that reviewers can verify and replicate the sponsor's proposals according to the published scoring rules.

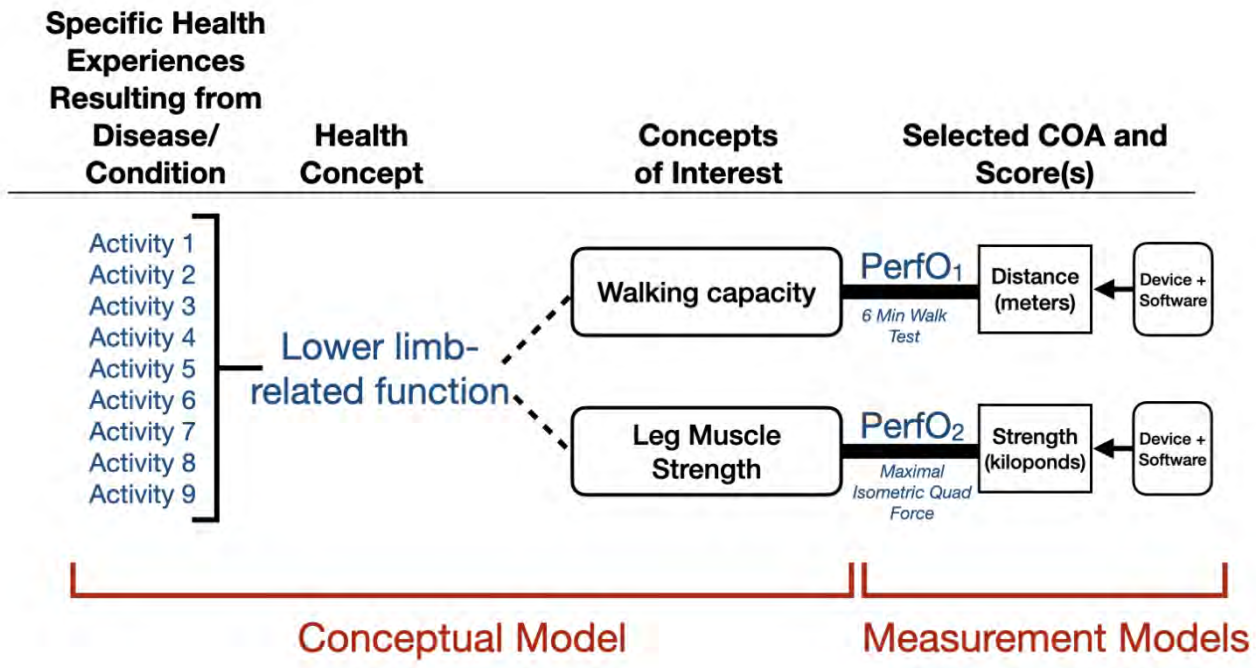
F. Scores From the COA Correspond to the Specific Health Experience(s) the Patient Has Related to the Concept of Interest.

Scores produced by a COA should correspond to important aspects of health in the patient's life that the medical product is targeting (Walton et al. 2015). Some measures assess a concept of interest that corresponds directly to the specific health experiences of the patient, such as ADLs (see Figure 1) or patient-reported pain intensity. For such measures, there might be little uncertainty that the scores correspond to the patient's experience. However, other measures might assess a concept of interest that is indirectly related to the specific health experiences that the medical product is targeting.

For example, an aspect of health that might be important to patients in the target population is lower limb-related function (Walton et al. 2015), which might include specific health experiences like walking from room to room inside a house and hiking outside on an uneven trail. A PRO measure might be used to assess this concept in a relatively direct way by asking the patient about the ease with which they have done a range of activities that require lower limb-related function (corresponding to Activities 1to 9 in Figure 5). Although measurement error might influence scores on the PRO measure, it is generally thought that those scores are directly related to the lower limb-related activities in the patients' usual lives. However, if there was significant heterogeneity among patients' physical environments and/or wide heterogeneity in the lower limb-related activities that patients undertake, a sponsor might decide instead to assess patients in a standardized environment via a PerfO measure. Under standardized conditions, one is no longer directly assessing lower limb-related function outside the test

environment. Instead, the concepts of interest being assessed are important subcomponents of lower limb-related function that are amenable to standardized assessment, but neither are sufficient alone to support an inference about the patient's overall lower limb-related function. Because of this, these measured concepts of interest could be considered more indirect reflections of patients' lower limb-related functioning in their daily lives. In this example, the sponsor might decide to measure in the test environment walking capacity and leg muscle strength, which are indirectly related to patients' lower limb-related functioning in their daily lives (reflected by the dotted line in the conceptual framework shown in Figure 5). But in the rationale for the use of each measure, it would still be important to evaluate how well scores are related to the patients' lower limb-related mobility activities in their usual lives outside of the clinical trial context.

Figure 5. Example Conceptual Framework for Measures of Two Concepts of Interest With Indirect Relationships to the Patients' Specific Health Experiences (Note: Dotted lines indicate an indirect relationship between the health concept and concept of interest.)



For measures such as these in which the relationship between the scores and the important aspect of health is less direct, more uncertainty exists. Thus, sponsors and measure developers might seek additional evidence by investigating the relationship between scores on the COA and other variables that are expected to be more directly related to the patient's experience. This is known as convergent evidence.[26] The other variables could include alternative measures of, or be related to, the measured concept of interest using different methods and/or sources (e.g., observer report

[26] *Convergent evidence* was referred to as *convergent validity* in the 2009 PRO Guidance.

or performance tests). For the example shown in Figure 5, the sponsor might assess patient-reported lower limb-related functioning in daily life along with measures of walking capacity and leg muscle strength in a phase 2 trial. The sponsor might predict a moderate correlation[27] between the PRO measure's scores and scores on the two performance measures and could test this using the phase 2 trial data.

When a sponsor is collecting convergent evidence, FDA notes that the correlation coefficient cutoffs based on Cohen (1988) may be too low to be considered as a moderate and/or strong correlation. FDA reminds sponsors that when prespecifying correlation coefficient cutoffs for the psychometric statistical analysis plan (SAP), it is important to take into consideration the *a priori* hypothesized relationship(s) among the concept(s) measured by any proposed reference measure(s) in the convergent evidence study and the concept(s) measured by the proposed COA measure. When interpreting correlation coefficients, sponsors should consider the size of the corresponding coefficient of determination and how the distribution of the variables might impact the magnitude of the correlation (e.g., attenuation due to restriction of range).

Sponsors and measure developers might also conduct empirical comparisons of scores for patient groups known to differ with respect to the concept of interest (i.e., known groups validity evidence[28]). When a sponsor is collecting known-groups evidence, FDA does not recommend dividing COA scores into groups based on the distribution(s) of reference measure scores (e.g., tertiles, quartiles, medians, or quintiles), because the percentile cutoff values are arbitrary and may vary across samples. Additionally, patient groups created based on the distribution of reference measure scores may not represent clinically distinct groups. Sponsors should propose and justify appropriate cutoff values that connote distinct levels of symptom severity and/or impact severity. In addition, sponsors should provide details of the proposed model and the hypothesis tests that will be performed.

G. Scores From the COA Are Sufficiently Sensitive to Reflect Clinically Meaningful Changes Within Patients Over Time in the Concept of Interest Within the Context of Use.

Though scores on the measure might correspond to the real experiences of patients (see section IV.F), the assessments might not have enough sensitivity to detect consequential[29] changes within patients over the duration of a clinical trial. Thus, it is important to show evidence that the scores are sensitive enough to detect such changes. Note that this assumption refers specifically to the ability to detect change, which reflects the signal-to-noise ratio of the COA's scores. Sensitivity to change could vary depending upon the target population, as when floor or ceiling effects limit the ability to observe change.

[27] It would be reasonable in this example for a sponsor to expect a moderate, but not large, correlation in this case. In the example, the sponsor chose PerfO measures rather than PRO measures out of concern for the heterogeneity in the patients' environments. That environmental heterogeneity is expected to reduce the magnitude of the relationship between patient-reported and performance tested assessments of lower limb mobility.

[28] The extent to which scores differed between groups known to differ on the concept of interest was referred to as *known groups validity* in the 2009 PRO Guidance.

[29] The Agency expects to address the concept of clinically meaningful changes in Guidance 4.

There are two general approaches to providing evidence on this point, with one providing more direct evidence than the other.

1. Evaluating Responsiveness to Change

One strategy for collecting relatively direct evidence for sensitivity to within-person change (i.e., responsiveness) is to examine the relationship between changes in the COA's scores and changes in some other measure(s) of the same or proximal construct, assessed over the same or comparable time frames, that would be expected to change for the same reason the COA scores should change (e.g., natural disease progression or response to an intervention). When changes in the COA scores track closely with changes in the other measure, there is increased confidence that the COA scores can reflect changes in the concept of interest. For example, a sponsor might examine how closely changes in a COA intended to measure the weekly headache pain severity with changes in the number of days with migraine. It is important to specify hypotheses about the expected direction and magnitude of the correlation(s) between changes in the COA scores and changes in the other measure(s) (Mokkink et al. 2011).

2. Evaluating Reliability/Precision

Before direct evidence of responsiveness to change is available, sponsors can evaluate a prerequisite for responsiveness to change—that there is minimal measurement error in COA scores.

When evaluating reliability, different types of consistency are relevant to various COAs in their context of use (see Table 2).

Table 2. Possible Assumptions About Consistency of Scores

		Potential Relevance for COA Type			
Scores are reasonably consistent . . .	**Type of Evidence**	***PRO***	***ObsRO***	***ClinRO***	***PerfO***
. . . over time within clinically stable patients	Test-retest reliability	X	X	X	X
. . . across different raters	Inter-rater reliability			X	X[a]
. . . within the same rater for the same patients (when the patients have not clinically changed)	Intra-rater reliability			X	X[a]
. . . across different but highly related or similar tasks	Evaluation of score differences between related tasks or sets of tasks				X

[a]Applies only if the PerfO measure requires a trained rater as part of the assessment process.

Test-retest reliability should be evaluated in the absence of any systematic intervening effects other than time. Sponsors should specify one or more criteria to define stable patients. FDA recommends that, in most cases, intraclass correlation coefficients be calculated using absolute-agreement, two-way mixed-effects model with the time as a fixed effect (McGraw and Wong 1996; Shrout and Fleiss 1979), as suggested by Shrout and Fleiss (1979) and Qin et al. (2019). Note that test-retest reliability evidence is only relevant for diseases or conditions in which a patient's health status can remain stable for some period of time (e.g., 1 to 2 weeks). In a disease in which symptoms can vary substantially during a single day, the assumption of consistency of scores over time may be irrelevant, and so it would not be useful or even possible to collect evidence of test-retest reliability.

For measures developed using IRT modeling, an alternative estimate of reliability can be generated based on the information function. The associated standard errors can provide another method of examining the variability and consistency of scores.

During the development process of a COA, evidence of good reliability might be obtained earlier in the process (e.g., using a cross-sectional study design). This evidence, along with other supporting material, might be enough to justify the exploratory use of the COA in prospective trials (e.g., phase 2).

H. Differences in the COA Scores Can Be Interpreted and Communicated Clearly in Terms of the Expected Impact on Patients' Experiences.

Because findings from clinical trials are used to inform decisions that patients, providers, and/or payers make, it should be clear what the COA scores reflect and how the magnitude of the difference(s) relates to patients' lives. This final component of the rationale includes any assumptions that might be involved in translating COA score differences into within-patient changes and why these within-patient changes are considered meaningful in patients' experiences. The Agency expects to address the concept of clinically meaningful changes and related justifications in Guidance 4.

For all the potential assumptions of a rationale, the specific versions will depend upon the type of COA.

V. ABBREVIATIONS

ADLs	Activities of Daily Living
CAT	Computerized Adaptive Testing
ClinRO	Clinician-Reported Outcome
COA	Clinical Outcome Assessment
DHTs	Digital Health Technologies
DIF	Differential Item Functioning
IRT	Item Response Theory
ObsRO	Observer-Reported Outcome
PerfO	Performance-Based Outcome
PFDD	Patient-Focused Drug Development
PRO	Patient-Report Outcome
SAP	Statistical Analysis Plan
VAS	Visual Analog Scale

VI. USEFUL REFERENCES FOR SELECTING, MODIFYING, AND DEVELOPING CLINICAL OUTCOME ASSESSMENTS

Please note that the citation of a scientific reference in this guidance does not constitute FDA's endorsement of approaches or methods presented in that reference for any particular study. Study designs are evaluated on a case by case basis under applicable legal standards.

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APPENDIX A: PATIENT-REPORTED OUTCOME MEASURES

I. INTRODUCTION

A PRO is a measure 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 others. A PRO measure may be the best COA type to assess a concept of interest when the concept of interest is any of the following and the patient is able to provide reliable self-report:

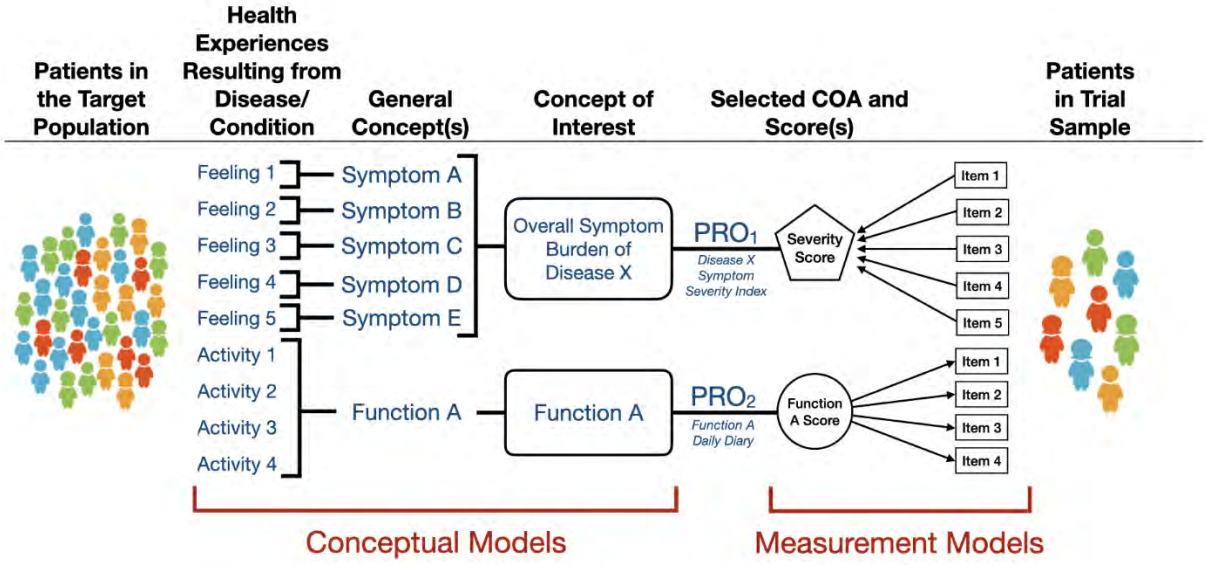
- A feeling or experience known only to the patient, such as pain, itch, shortness of breath as no one else has direct access to feelings except for the patient
- Any type of functioning or activity that is part of the patients' day-to-day life
- The patients' satisfaction or dissatisfaction with their treatment and/or functioning
- Degree of impact on day-to-day life associated with one or more symptoms

Note that a PRO measure cannot be completed by a proxy reporter, i.e., someone reporting on behalf of the patient (see Appendix B ObsRO and Appendix C ClinRO for further discussion).

II. CONCEPTUAL FRAMEWORK EXAMPLE WITH PRO MEASURES

Figure A illustrates a conceptual framework for a study in which two concepts of interest are assessed using PRO measures. In the example, Disease X can produce multiple symptoms A to E. One concept of interest is the overall symptom burden of Disease X, and it is assessed using a multi-item PRO measure, the Disease X Symptom Severity Index. The measurement model indicates that the five items, corresponding to each of the five symptoms, are combined to create a summary index (i.e., a composite indicator model). Disease X can also compromise Function A, which is the other concept of interest. It is measured by a single-item daily diary measure. The responses to the items by patients in the trial population are used as the basis for an inference about what patients in the target population might experience if they were given one treatment versus another.

Figure A: Illustration of Conceptual Framework for Concepts of Interest Assessed by Two Patient-Reported Outcomes Measures



APPENDIX B: OBSERVER-REPORTED OUTCOME MEASURES

I. INTRODUCTION

An ObsRO measure is a type of COA that assesses observable signs, events, or behaviors related to a patient's health condition and is reported by someone other than the patient or a health professional (e.g., parent, caregiver, or someone who cares for the patient the most or spends significant time with the patient during the relevant observation window in daily life). An ObsRO measure does not rely on medical judgment or interpretation[30] and can be particularly useful for patients who cannot report for themselves.

Example ObsRO Measures for Use in Clinical Trials
• Rating scales completed by a caregiver, such as: – Acute Otitis Media Severity of Symptoms scale, a measure used to assess signs and behaviors related to acute otitis media in infants • Counts of events recorded by a caregiver (e.g., observer-completed log of seizure episodes)

ObsRO versus proxy-reported measures

A proxy-reported outcome instrument is not an ObsRO instrument; it is an assessment in which someone other than the patient reports on patient health experiences as if they are the patient or on the patient's behalf. Proxy-reported outcome instruments are discouraged because they measure concepts known only to patients and do not necessarily reflect how patients feel and function in daily life. Concepts that are only known by the patient (e.g., symptoms, feelings) should be measured by a PRO. FDA acknowledges there are instances when it is impossible to collect valid and reliable self-report data from the patient. In these instances, it is recommended an ObsRO instrument be used rather than a proxy-reported outcome instrument.

[30] A measure that relies on medical judgment or interpretation is a ClinRO.

Examples of ObsRO Versus Proxy-Reported Item Stem Phrasing

ObsRO items

- "Based on what you observed (saw or what another observer saw), please rate the severity of your child's abdominal pain-related signs today (such as crying, holding stomach or abdomen)."
- "How frequently did they do household chores (e.g., laundry, washing dishes) in the past week?"
- "Based on what you observed (saw or what was told to you), how often did your child show presence of itch (such as rubbing or scratching) from the time your child woke up today until now?"

Proxy-reported outcome items

- "How severe was your child's pain from the time your child woke up until right now?"
- "Rate the difficulty they had when shopping for groceries."
- "Please rate your child's tiredness over the past 24 hours."
- "My child felt wheezy and out of breath because of their asthma."
- "My child felt sad when they had pain."

ObsRO Selection and Implementation Considerations

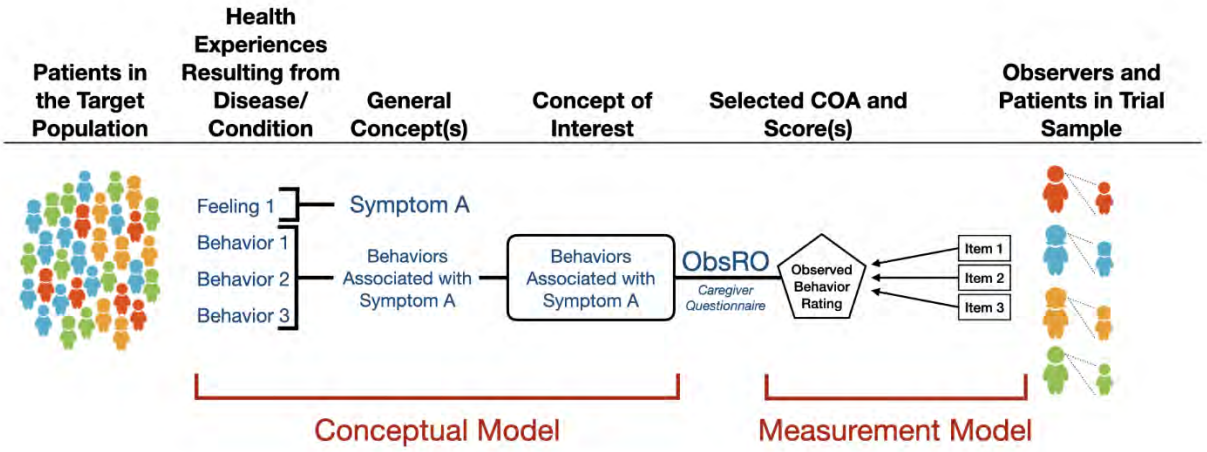
Below are key considerations and recommendations for selecting and implementing an ObsRO measure in a clinical study:

- Conduct qualitative research to explore and define whether a target concept of interest can be reported and observed by someone other than the patient. Such research could include researcher observation of patients along with interviews with caregivers and experts.
- Submit proposed protocols and, as appropriate, interview scripts or observation checklists for FDA review and comment prior to beginning the qualitative research.
- When implementing an ObsRO measure in a clinical study, to the extent feasible, the same observer should complete the assessments throughout the trial to minimize unwanted variability due to different reporters.

II. CONCEPTUAL FRAMEWORK EXAMPLE OF AN ObsRO MEASURE

Figure B illustrates a conceptual framework for a multi-item ObsRO measure in the context of young children with a disease who are unable to reliably and validly self-report. In the example depicted, Symptom A of the disease causes various behaviors that can be observed by a parent or caregiver. Parents or caregivers cannot report directly on the symptom severity of their child, but they can report on these behaviors that are associated with Symptom A, which is the concept of interest assessed by the ObsRO.

Figure B: Illustration of a Conceptual Framework for a Concept of Interest Assessed by a Multi-Item Observer-Reported Outcome Measure



APPENDIX C: CLINICIAN-REPORTED OUTCOME MEASURES

I. INTRODUCTION

ClinRO instruments are typically used when clinical judgment is needed to assess some aspect of a patient's health. ClinROs can include reports of clinical signs or events, ratings of a sign, and clinician's global assessments of the patient's current status or of the change the patient undergoes (Powers et al. 2017).

Examples: ClinRO Instruments

- Reports of clinical findings, such as:
  - Counts of skin lesions
  - Presence of swollen lymph nodes
  - Presence or absence of fracture
- Rating scales, such as:
  - Psoriasis Area and Severity Index, a measure used to assess the severity and extent of a patient's psoriasis
  - Clinician global assessment of psoriasis severity, such as through a single-item verbal rating scale

ClinRO Selection and Implementation Considerations

Below are key considerations and recommendations for selecting and implementing a ClinRO in a clinical study:

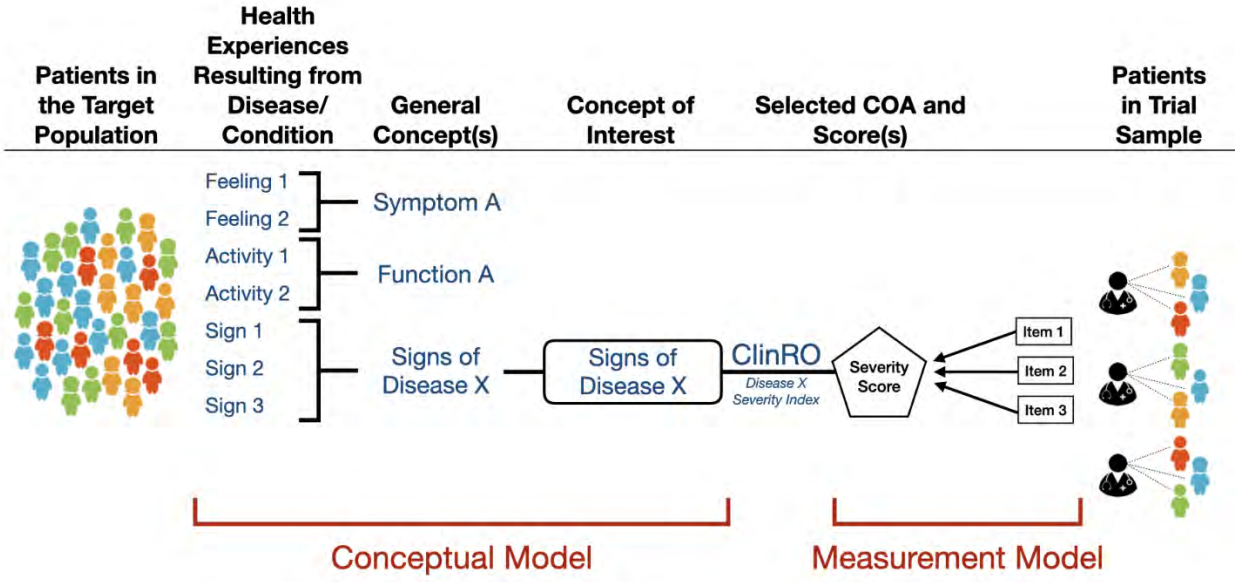
- Include a user manual with clear instructions and directions for standardized administration.
- Conduct a standardized training with all clinician raters in the study to help ensure that rating assessments are based on consistent criteria for the ratings to minimize unwanted variability.
- Scales should be developed and tested as they will be used in the registration trial (e.g., it is inappropriate to assume the measurement properties for a dermatology scale used to assess a patient's condition by photographs will be the same when the scale is used during an in-person (non-photographic) assessment)
- Implement standardized case report form for data collection
- Evaluate intra- and inter-rater reliability prior to using a proposed ClinRO measure in a pivotal study
- If visual aids (e.g., photo guides) are used, ensure that they cover a wide variety of patient, condition, and environmental characteristics and pilot test them with clinician raters to ensure they are well understood.

- Use a masked assessor for primary efficacy or effectiveness data collection; in some cases, a centralized blinded review and an adjudication process in the event of rating discrepancies may be necessary to ensure consistent assessment.
- To the extent feasible, the same clinician should conduct the assessments for the same patients throughout the trial to minimize unwanted variability due to different reporters.

II. CONCEPTUAL FRAMEWORK EXAMPLE OF A ClinRO MEASURE

Figure C illustrates an example of a conceptual framework for a ClinRO measure. In the example depicted, three clinical signs are associated with Disease X. These clinical signs are not direct measurements of how the patient with Disease X feels (i.e., Symptom A) or functions (i.e., Function A). Rather, there is an indirect association between the presence of the signs and worse feeling and functioning. Still, there might be interest in assessing treatment-related changes in the signs of Disease X, and so that becomes the concept of interest. Because clinical expertise is required to identify and quantify the signs appropriately, the concept of interest is measured by a ClinRO. In this case, the measure uses three items—one corresponding to each of the signs—and combines the responses in a way to generate an overall severity score. The Figure C also indicates that the items are combined, assuming a composite indicator model (see section IV.E.2).

Figure C: Illustration of a Conceptual Framework for a Concept of Interest Assessed by a Clinician-Reported Outcome Measure



APPENDIX D: PERFORMANCE OUTCOME MEASURES

I. INTRODUCTION

There are instances when patient experience data are best captured through performance tasks. A PerfO measure is a type of COA that is used to generate patient experience data through standardized task(s) performed by a patient. A PerfO measure is administered and evaluated by an appropriately trained individual or independently completed. PerfO measures are commonly used to assess patient physical or cognitive functioning, or perceptual/sensory functioning, through standardized tasks completed by the patient. The patient's performance on these tasks is then quantified and reported using defined procedures.

A PerfO measure can be considered for use when patient functioning is the concept(s) of interest (e.g., mobility, memory, attention, visual acuity) and the patient is able to follow the instructions to perform the required task(s). PerfO measures should not be used to capture information that is better assessed through other types of COAs, such as the severity of the symptoms of a disease or condition as captured through a PRO instrument.

Because PerfO instruments are based on patients' actual performance on a set of standardized tasks, they may be advantageous for the following reasons:

- When appropriately designed, PerfO measures may reduce the influence of culture and language variability on outcome assessment in multinational and multilanguage trials.
- By having patients perform standardized tasks in a controlled, standardized environment, PerfO measures are less influenced by variability between and within patients in the types and settings of daily activities performed by the patients in their natural environment (e.g., driving a car versus taking public transportation, living in rural area versus living in big cities).
- By assessing real-time functioning, PerfO measures are not vulnerable to errors of recall that can occur for some PRO, ObsRO, and ClinRO measures that use a recall period (e.g., during the past 7 days).
- PerfO measures may be less vulnerable to external changes in the patient's environment, such as seasonal impacts on daily routines.
- Results of PerfO measures can be communicated in units that are familiar and readily interpretable such as meters (e.g., distance walked in 6 minutes), seconds (e.g., time to climb a flight of stairs), and frequency counts (e.g., number of words recalled).

PerfO Selection and Implementation Considerations

Although using a PerfO measure can be beneficial in a clinical trial, the following are examples of unique challenges and recommendations:

- ***Potentially less direct relationship to a meaningful aspect of the patient's health.*** Each task usually assesses a specific function. Therefore, the patient's performance on the standardized task(s) may provide only limited information about the patient's overall functioning outside of the assessment setting.

- ***Potential interference of functions or abilities that are not part of the concept of interest.*** Some PerfO tasks require multiple functions to complete. For example, fine motor skills might be important in providing a response to a neuropsychological measure of memory functioning, and so someone with fine motor impairment might receive a score that does not reflect the person's true memory functioning. Care should be taken to ensure that functions other than the concept of interest do not unduly influence scores on the PerfO. If the patient's cognitive ability may interfere with the performance with the tasks, sponsors should consider whether the selected PerfO measure is fit-for-purpose.
- ***Potential for patient fatigue or burden.*** Because a PerfO measure involves assessing how well and/or how quickly a patient performs a task, it is important to consider how patient fatigue or burden may impact their performance. This is especially the case when PerfO measures are time- or effort-sensitive. When developing the clinical trial protocol, sponsors should consider the cumulative burden on the patient and the placement of the PerfO assessment. For example, in a trial for a disease in which fatigue is a primary concern for patients, it may be unwise to administer a 12-minute walk test at the end of a clinic visit day that included 3 hours of blood draws, other biological tests, and PRO measures.
- ***Voluntary.*** Patients might refuse to perform the task at the specified time for a variety of reasons. Consider gamification to make the task more appealing and ways patients can complete the task regardless of the severity of their condition. Also consider how to record the many different types of potential missing data.
- ***Standardization.*** If a specific published administrator's manual is selected for the test, it is important to conduct the test in accordance with the selected manual.
- ***Inaccessible equipment for task administration.*** Required equipment or assessment setup may not be available or feasible for certain clinical trial sites (e.g., a flight of stairs, air-conditioned rooms) or the materials may not be consistent across cultures (e.g., random words that are commonly used versus infrequent words, English words versus French words). Special attention should be paid to maintaining standardization of PerfO measures, especially in multisite and multinational clinical trials, to ensure that the assessment results are reliable, reproducible, and interpretable.
- ***Practice effects.*** There are some instances in which patients improve their performance after repeated exposure to the same tasks, even though their underlying disease state has not changed. Steps should be implemented in trials to minimize the practice effect so that it does not confound the assessment results, including increasing the time in between PerfO assessments and allowing all patients to practice the task prior to randomization. Sponsors should consider potential learning effects associated with the selected performance-based tasks. The study protocol should include plans and/or procedures that will be put in place to minimize potential bias contributed by the learning effects on the interpretation of the PerfO-based endpoint results.
- ***Standardized case report forms, assistive devices, and documentation.*** The use of a standardized case report form is recommended, which should include information on whether an assistive device was used during the test. The use of assistive devices should be standardized, and the type of device, if used, should be recorded. If the test was not completed, sponsors should collect the reason for not completing the test. These pieces of information should be part of the analysis data sets and may play a role in analysis and interpretation of the data.

II. CONCEPTUAL FRAMEWORK EXAMPLE OF A PerfO MEASURE

Figure 5 (shown in the body text) illustrates a conceptual framework for a PerfO assessment. In the example,[31] the disease impacts activities that are all instances of lower limb-related function. Perhaps because of the heterogeneity among patients in their activities and environments, the sponsor selects two subfunctions that are thought to be important to lower limb-related function—walking capacity and leg muscle strength. Note in Figure 5 dotted lines were used to represent the indirect relationship between the general health concept and the measured concepts of interest. Each of these two concepts of interest are then assessed using a PerfO measure.

[31] Example adapted from Walton et al., 2015.

APPENDIX E: EXAMPLE TABLE TO SUMMARIZE RATIONALE AND SUPPORT FOR A COA

Table A. Example Table To Summarize Rationale and Support for a [CHOOSE 1: PRO/ObsRO/ClinRO/PerfO] to Measure [FILL IN CONCEPT OF INTEREST] in [FILL IN TARGET POPULATION]

	Component	Support
A	**The concepts of interest, [FILL IN], should be assessed by a [PRO/ObsRO/ClinRO/PerfO], because . . .**	
A.1		
A.2		
A.3		
B	**The content of the [NAME OF MEASURE] includes all the important aspects of [CONCEPT OF INTEREST].**	
C	**[PERSON PROVIDING INFORMATION] understand the [e.g., INSTRUCTIONS, ITEMS, AND RESPONSE OPTIONS] as intended by the measure developer.**	
D	**Scores from the [NAME OF MEASURE] are not overly influenced by processes/concepts that are not part of [CONCEPT OF INTEREST].** *[Select and comment on appropriate rows for the type of COA]*	
D.1	[ITEM OR TASK] interpretations or relevance do not differ substantially according to respondents' demographic characteristics (including sex, age, and education level) or cultural/linguistic backgrounds or physical environment.	
D.2	Recollection errors do not overly influence assessment of the concept of interest. [PRO, ObsRO, and ClinRO measures]	
D.3	Respondent fatigue or burden does not overly influence assessment of the concept of interest. [PRO, ObsRO, ClinRO, and PerfO measures]	
D.4	The mode of assessment does not overly influence assessment of the concept of interest. [PRO, ObsRO, ClinRO, and PerfO measures]	
D.5	Expectation bias does not unduly influence assessment of the concept of interest. [PRO, ObsRO, ClinRO, and PerfO measures]	
D.6	Practice effects do not overly influence the assessment of the concept of interest. [PerfO measures]	
E	**The method of scoring responses is appropriate for assessing [CONCEPT OF INTEREST].** *[Select E.2 or E.3 if appropriate. E.1 and E.4 are likely appropriate for all COAs.]*	
E.1	Responses to an Individual [ITEM OR TASK]	
E.2	Rationale for Combining Responses to Multiple [ITEMS OR TASKS]	
E.3	Scoring Approaches Based on Computerized Adaptive Testing	
E.4	Approach to Missing [ITEM OR TASK] Responses	
F	**Scores from the [NAME OF MEASURE] correspond to the specific health experience(s) the patient has related to [CONCEPT OF INTEREST].**	
G	**Scores are sufficiently sensitive to reflect clinically meaningful changes within patients over [TIME] in the [CONCEPT OF INTEREST] within [CONTEXT OF USE].**	
H	**Differences in assessment scores can be interpreted and communicated clearly in terms of the expected impact on patients' experiences**	