U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

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

Guidance for Industry

What Is Recommended in This Guidance?

This guidance provides recommended approaches for selecting, modifying, developing, and evaluating measurements in clinical trials that evaluate outcomes important to patients.

Why Is This Guidance Important?

This guidance helps ensure that clinical outcome assessments (COAs) used during medical product development measure what matters to patients; are clear about what was measured; appropriately evaluate the effectiveness, tolerability, and safety of treatments; and avoid misleading claims.

Clinical Outcome Assessment Key Points

A COA is a measure that describes how a patient feels, functions, or survives. There are four types of COAs:

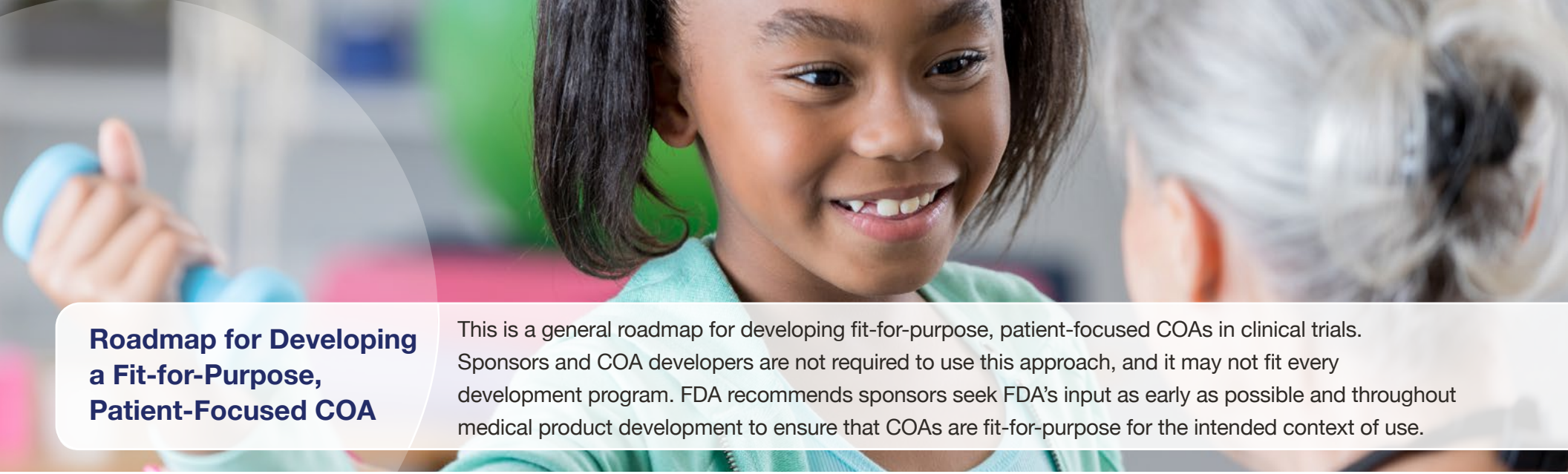
- Patient-reported outcome (PRO) measures
- Observer-reported outcome (ObsRO) measures
- Clinician-reported outcome (ClinRO) measures
- Performance outcome (PerfO) measures

The meaningful aspect of health (MAH), concept of interest (COI), and context of use (COU) should be explicitly defined:

- An MAH is some aspect of feeling or functioning in daily life that is important to patients.
- A COI is what is specifically measured by a COA to help understand how a medical product affects an MAH.
- A COU should clearly specify the way COA scores will be used as the basis for an endpoint, including the interpretation of the endpoint results in a medical product development program.

COA should be 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).



Roadmap for Developing a Fit-for-Purpose, Patient-Focused COA

This is a general roadmap for developing fit-for-purpose, patient-focused COAs in clinical trials. Sponsors and COA developers are not required to use this approach, and it may not fit every development program. FDA recommends sponsors seek FDA's input as early as possible and throughout medical product development to ensure that COAs are fit-for-purpose for the intended context of use.

Understanding the Disease or Condition

- Patient/caregiver perspectives
- Natural history of the disease or condition
- Patient subpopulations
- Proximate and distal meaningful aspects of health
- Health care environment
- Other expert input (healthcare providers, payers, regulators)

Conceptualizing Clinical Benefits & Risk

- Identify/define meaningful aspect(s) of health that are intended to be improved by the medical product
- Identify/define the concepts of interests to be measured that will alone or with other concepts of interest assess the meaningful aspect(s) of health
- Define context of use (COU) for clinical trial

Selecting/Developing the Outcome Measure*

Select clinical outcome assessment (COA) types: PRO, ObsRO, ClinRO, or PerfO measure

Search for existing COA measuring concept of interest in context of use

- COA exists for COI, can be used unmodified for COU → Use existing COA
- COA exists for COI, but might need to be modified for COU → Collect evidence and modify COA as necessary
- No COA exists for COI and COU → Develop new COA and empirically evaluate

Fit-for-Purpose COA

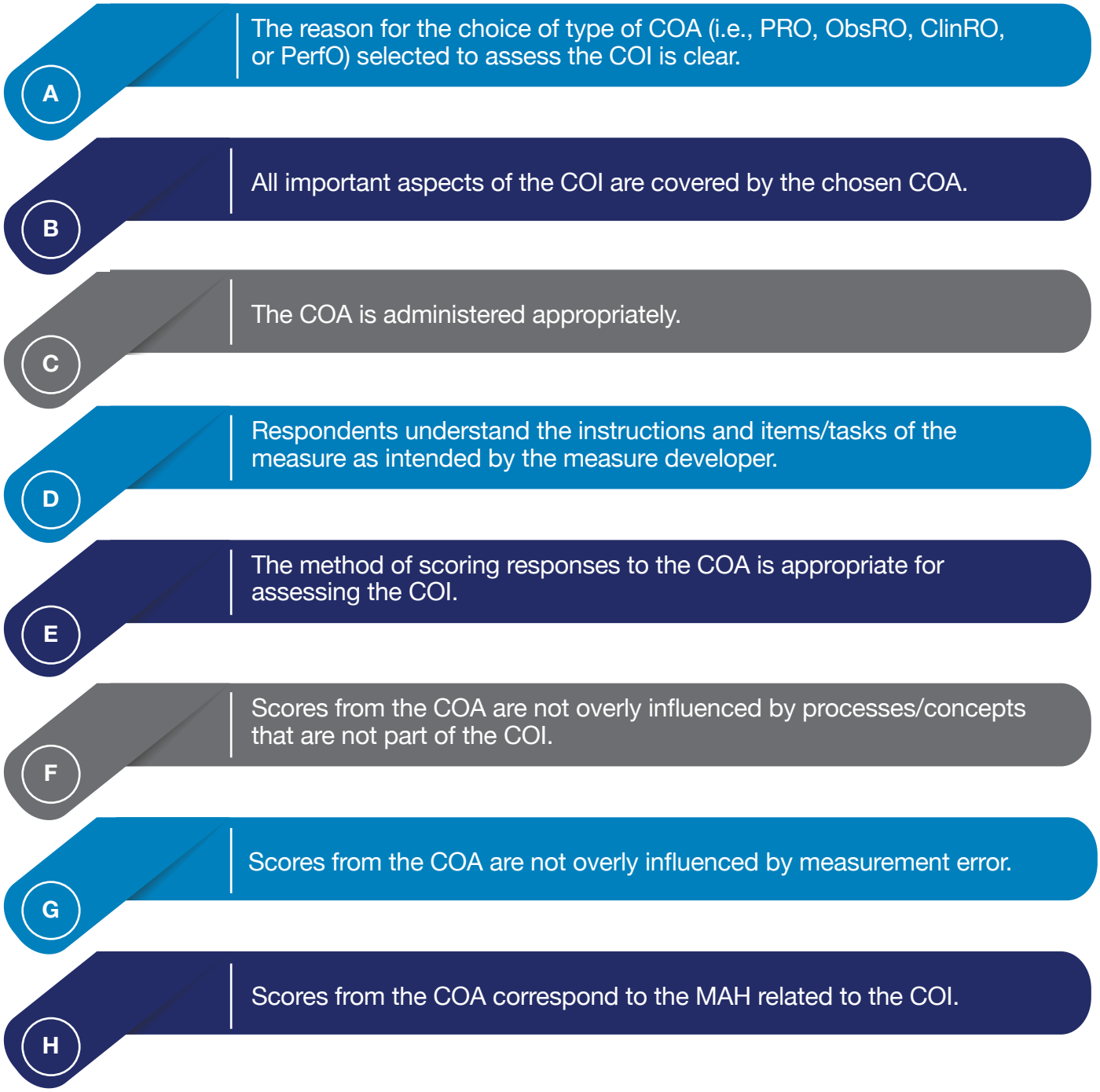
- COU clearly defined
- COI clearly defined
- Clear rationale
- Sufficient evidence to justify rationale

Construct COA-based endpoint that reflects the Meaningful Aspect of Health (See PFDD Guidance 4)

*This portion of the figure corresponds to a single COA. In some cases, multiple COAs might need to be used to capture a single MAH. In those cases, the path reflected here would be followed for each COA.

Eight Evidence-Based Considerations for Supporting a COA as Fit-for-Purpose

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. This table lists eight considerations that should be included in the rationale and supporting evidence or justification section of submissions to FDA. It is important for FDA to understand each part of a sponsor's rationale and the evidence being offered in support of each part. The considerations listed below are likely but not necessarily needed in the rationale for a specific COA, COI, and COU. Each rationale can be tailored to the specific situation.



What Is the Difference Between a COA, a COA Score, and an Endpoint?

This guidance differentiates a COA from a COA score and an endpoint in the following ways:

COA

A COA is a measure that is intended to describe or reflect how a patient feels or functions and includes any instructions, administration materials, content, formatting, and scoring rules.

COA Score

A COA score refers to any numeric or rated values generated by a COA through a standardized process. A COA might produce **scores** on different scales and/or multiple scores that correspond to a different concept.

Endpoint

An endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question (e.g., mean COA Score at 12 weeks post-randomization).

Medical Product Timeline: When to Apply the Guidance Recommendations?

During clinical development: Early phase trials conducted prior to the registration trial represent an opportune time to evaluate measurement properties of COAs, and sponsors are encouraged to include prospectively planned analyses to inform subsequent trials. 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 fit-for-purpose COAs.

Guidance Recap Podcast

Hear highlights straight from FDA staff

Speakers:

David Reasner, PhD,
Director of the Division of Clinical Outcome Assessment

Laura Lee Johnson, PhD,
Director for the Division of Biometrics III.

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