Biotechnology Innovation Organization

FDA – Sponsor Engagement Framework:

Clinical Outcomes Assessments

Table of Contents

Overview **2**

Meeting Planning **4**

FDA-Sponsor Engagement Framework: Clinical Outcome (COA)Assessments **4**

(1) Understanding the Disease or Condition **5**

Information/Data to share with FDA 5

Potential Questions / Topics for Discussion 5

(2) Conceptualizing Clinical Benefit and Risks – Identify concept of interest and context of use **6**

Information/Data to share with FDA 6

Potential questions/Topics for discussion 6

(3) Selecting, Developing, Modifying Outcome Measures **7**

Information/Data to share with FDA 7

Potential Questions/Topics for Discussion 8

(4) Assessment of Treatment Effect (COA implementation into clinical trials) **10**

Information/Data to share with FDA 10

Potential Questions / Topics for Discussion 11

(5) B-R Assessment and Approval Decision **12**

Information/Data to share with FDA 12

Questions / Topics for Discussion 12

Appendix A: Supporting Tables (From FDA PFDD Guidance 3: Selecting, Developing and Modifying Fit-for-Purpose COAs) **13**

Table 1: Summary of Rationale and Support for COA to Measure Concept of Interest in Target Population 13

Table 2: Evidence to Support Consistency of Scores 14

Appendix B: BIO Recommended FDA - Sponsor Engagement Timeline 15

Overview

Purpose

Sponsors often collect patient experience data (PED) to inform their understanding of a disease area and ensure that they are meeting the needs of patients. Although the FDA encourages Sponsors to engage with the Agency early and often regarding the collection and use of PED in development programs, sponsors are often unclear regarding when, how and who to engage with at FDA, and what information is needed to support PED discussions to elicit actionable feedback.[1] In addition, while FDA has issued guidance on FDA-Sponsor meetings, this does not address considerations for engagement on PED.[2] BIO believes that Industry and FDA would benefit from additional direction regarding how to optimize FDA-Sponsor interactions (when, how, and who to engage at FDA) to discuss PED specific development topics. To facilitate strategic and timely discussions on the collection and use of PED in product development and regulatory decision-making, BIO's PFDD taskforce built on prior work outlining the types and uses of PED throughout the product lifecycle to propose a detailed FDA-Sponsor Engagement Framework.

The goals of the Engagement Framework are to identify and enhance opportunities for meaningful interactions and meeting outcomes within or beyond the IND process, to ensure timely and actionable FDA feedback on PED, and to provide Sponsors with a tool to help facilitate internal planning and discussions on the value of FDA engagement with development teams.

Approach

There are many opportunities for patient input to inform medical product development and regulatory decision-making. In developing the FDA-Sponsor Engagement Framework, taskforce members focused on two key applications of PED that are most likely to impact regulatory decisions:

1. Selection, development, and implementation of fit-for-purpose clinical outcome assessments (COAs) for use as endpoints to support regulatory decisions
2. Use of patient preference information (PPI) (e.g., to inform benefit/risk, outcome selection, mode of administration)

For each, taskforce members identified key milestones at which Sponsors should engage FDA, what form of interaction would be appropriate, key questions to pose to the Agency, and what information Sponsors should provide to FDA to elicit detailed, actionable scientific advice. The taskforce also outlined overarching guiding principles for Sponsors to consider. The taskforce further divided each key application of PED into two separate Frameworks. The Framework in this document is specifically focused on the *Selection, development, and implementation of fit-for-purpose clinical outcome assessments (COAs) for use as endpoints to support regulatory decisions*. A separate framework to address PPI development is forthcoming.

[1] Eastern Research Group. "Assessment of the Use of Patient Experience Data in Regulatory Decision-Making." June 2021. Available from: https://www.fda.gov/media/150405/download. Accessed October 7, 2022

[2] Food and Drug Administration. "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft Guidance for Industry." Dec. 2017. Available from: https://www.fda.gov/media/109951/download

BIO's 2022 FDA-Sponsor Engagement Framework: Clinical Outcome Assessments (COAs)

Guiding Principles

- Recognizing that FDA resources are limited, Sponsors should aim to discuss patient-focused activities and collected PED with FDA when it is necessary to de-risk subsequent activities, such as when FDA feedback or agreement is needed on the proposed approach (e.g., because of a novel proposed methodological approach, or work in a new disease area that lacks established endpoints), or when insights from patients might otherwise inform FDA thinking on the analysis of the condition and therapeutic context. Specifically with respect to COA development and implementation, FDA-Sponsor engagement will likely be needed when:
    - developing novel or modifying existing COA
    - using COAs as endpoints to support labeling
    - using PROs or other COAs to optimize dosing and characterize treatment tolerability
- The frameworks developed (e.g., COA, PPI, etc.) are **not intended to be prescriptive or exhaustive**. Rather, they are intended to **guide development teams** by capturing key concepts, recognizing that different contexts (e.g., different therapeutic areas, need to modify vs. develop de novo tools) will factor into how different elements of the framework can be applied. Therefore, they should be tailored based on the users' needs. For more details regarding the concepts in the framework, development teams should reference additional resources (e.g., FDA guidance documents, literature).
- FDA-Sponsor interactions on collection and use of PED should be iterative, building on early discussions to inform FDA of Sponsors' learnings from patients and plans for incorporating PED into development programs.
- BIO believes that if Sponsors and FDA can collaborate to meet the following expectations for all FDA-Sponsor interactions, regardless of the specific meeting type, the interactions will result in more meaningful outcomes achieved with greater efficiency:
    - **Pre-mtg** – mutual clarity on meeting purpose and what information should be shared in advance, to ensure productive discussion regarding PED
    - **During-mtg** – informed collaborative dialogue that results in detailed and actionable scientific advice that enhances the quality of a PED activity and increases the certainty that the final negotiated study design or planned activity is acceptable to FDA, or identifies what aspects are considered at risk and potential changes that could mitigate that risk
    - **Post-mtg** – development of joint Sponsor-FDA meeting minutes highlighting agreements, open issues, and actions. If FDA asks for additional pre-submission information during a meeting, provide a clear timeline and path for providing and receiving feedback on the acceptability of that material once provided (ideally, without the need to request another formal meeting if the material submitted is limited in scope, size, and complexity). One option to facilitate joint meeting minutes could be development of live meeting minutes.

Looking Ahead

This FDA-Sponsor Engagement Framework is intended to be a foundational document to guide development teams and identify opportunities to improve FDA-Sponsor Interactions. We acknowledge that the Framework does not address all questions relevant to the use of COA or PPI data. For example, while the task force recognized the value of digital health technologies (DHTs) for measuring some COA types, DHTs were generally considered to be out of scope for this topic. We refer teams to existing guidance on DHTs and look forward to more guidance from the Agency on any specific considerations for DHT-derived COAs.[3] In addition to this topic, the PFDD task force identified the following priorities for future efforts:

- Obtain FDA feedback on the proposed Engagement Framework to ensure better alignment between sponsors and reviewers.

[3] Food and Drug Administration. "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry." December 2021. Available from: https://www.fda.gov/media/155022/download

- Work with FDA to develop best practices on how new meeting types (i.e., INTERACT and Type D) can be appropriately leveraged to discuss the specific PED topics and milestones addressed in this Framework.
- Cross-industry discussions on how to promote the precompetitive development of COAs and encourage making COAs publicly available once they are completed.

Meeting Planning

This Meeting Planning checklist should be consulted throughout the development program and tailored as needed for each specific meeting held to discuss the selection, development, and implementation of clinical outcome assessments to support drug development.

Types of meeting to request

☐ Type B (e.g., pre-IND meeting, EOP-1) for which PED will be one of several topics
☐ Type C (PED-specific)
☐ Application Orientation Meeting/Pre-submission meeting
☐ Portfolio meeting (if available)
☐ Type D (PED-specific; limited to no more than 2 focused topics)
☐ CDER Critical Path Innovation Meeting
☐ CBER INTERACT Meeting

FDA participants to consider

☐ FDA Center Review Division
☐ FDA Center Division of Clinical Outcome Assessment
☐ FDA Center Office of Biostatistics
☐ FDA CDER Patient-Focused Drug Development Staff
☐ Oncology products – FDA OCE Patient-Focused Drug Development Staff
☐ CDRH Staff, as appropriate (e.g., digital health, eCOA, devices)

Industry participants to consider

☐ Regulatory
☐ HEOR / Value and Access
☐ Patient-Centered Outcomes or related staff
☐ Clinical
☐ Safety
☐ Biostatistics
☐ Policy

Other stakeholder participants (when appropriate)

☐ Patient, caregiver, and/or patient advocacy group representatives
☐ Disease specific experts

FDA-Sponsor Engagement Framework: Clinical Outcome (COA) Assessments

This COA-specific framework is separated into the typical phases on the Roadmap to COA Selection/Development for Clinical Trials, as adapted from FDA Draft Guidance: *Selecting, Developing and Modifying Fit-For-Purpose Clinical Outcome Assessments.*[4] Additionally, *Appendix B: BIO Recommended FDA - Sponsor Engagement Timeline* highlights timepoints during drug development when sponsors should consider engaging FDA to discuss their COA development strategy and implementation.

Reminder: The frameworks developed are not intended to be prescriptive or exhaustive. Rather, they are intended to guide development teams.

(1) Understanding the Disease or Condition

Information/Data to share with FDA

Collecting patient experience data to inform COA strategy

For details, refer to FDA PFDD Guidances: Collecting Comprehensive and Representative Input[5] *and Methods to Identify What is Important to Patients*[6]

☐ Research objective and research questions
☐ Preliminary conceptual disease model
☐ Natural history of the disease
☐ Target population
☐ Intended use and relevance to target population
☐ Type of patient experience data collected, as indicated in FDA's Patient Experience Data Table[1]
☐ Purpose of collecting patient experience data (e.g., disease/treatment burden, meaningful benefit)
☐ Source of patient experience data (e.g., literature or other publicly available sources, survey, qualitative research, social media)
☐ Method of collection (e.g., patient advisory boards, ethnographic research, concept elicitation for COA selection, patient preference study)
☐ Flow diagram and timeline of completed/ongoing/planned activities and studies

Potential Questions / Topics for Discussion

- Discuss initial plans to collect any type of PED to solicit feedback on methods and data sources proposed
    - Obtain feedback on whether proposed data sources and sampling strategy will yield patient input that is considered sufficiently comprehensive and representative of the target patient population
    - Obtain feedback on novel approaches or trial designs being considered (e.g., use of DHTs, DCT, eCOAs)
- Discuss and obtain feedback on how insights from PED that has already been collected will be applied to inform the program COA strategy and endpoint selection
- Discuss how prior/pre-existing data can be leveraged to shape the design of the COA program. (e.g., Can we leverage and combine prior data from sponsors' other programs?

---

[4] Food and Drug Administration. "Patient-Focused Drug Development: Selecting, Developing and Modifying Fit-for-Purpose Clinical Outcome Assessments; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders." June 2022. Available from: https://www.fda.gov/media/159500/download.

[5] Food and Drug Administration. "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input; Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders." June 2020. Available from: https://www.fda.gov/media/139088/download

[6] Food and Drug Administration. "Patient-Focused Drug Development: Methods to Identify What Is Important to Patients; Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders." February 2022. Available from: https://www.fda.gov/media/131230/download

(2) Conceptualizing Clinical Benefit and Risks – Identify concept of interest and context of use

Information/Data to share with FDA

Information to Support Concepts of interest (COI) Relevant to Patients

☐ Identified key patient-relevant disease signs/symptoms & symptom impacts, disease burden, and unmet needs
- Supporting evidence from qualitative and quantitative data sources (e.g., literature review, patient journey/story studies, social media scans, observational studies, patient preference studies)
- Detailed summaries of relevant patient input (e.g., description of diagnosis, quality of life impacts, concept-specific patient perspectives)
- Treatment goals or unmet needs to be addressed as identified by patients

☐ Target patient population

☐ Conceptual model, updated based on any additional information gathered since preliminary model

☐ At minimum submit study report, protocol, and other relevant information i.e., primary data capture from the qualitative/quantitative PED studies that informed identification of COI

☐ Plans to publish or share data if any

Additional information to support selection of COI to target for intervention

☐ Any information to support putative mechanism of action or intended drug effect

☐ Target product profile (TPP)/Target product label (TPL)

☐ Draft claims/Target Value Proposition

Potential questions/Topics for discussion

- Obtain feedback on proposed COA strategy, including alignment on:
  - key concepts that will be measured,
  - appropriate type of COA to consider
- Review TPP/TPL
- Does the Agency agree that the evidence provided supports that the <identified concepts> are important concepts of interest and relevant to patients with <condition> that should be assessed in the proposed clinical trials?
- Does the population studied in the PED research represent the target population and condition?
- Does FDA agree that concept saturation in concept elicitation is reached and does research support comprehensive evaluation of target COA endpoint?

(3) Selecting, Developing, Modifying Outcome Measures

Information/Data to share with FDA

Select/Modify/Develop COA and Evaluate Content Validity and Cross -sectional and Longitudinal Measurement Properties

For details, refer to FDA Draft Guidance: Selecting, Developing and Modifying Fit-For-Purpose Clinical Outcome Assessments[4]

Consider the following:

- Use existing COA, if an appropriate COA exists for the concept of interest in the same context of use
- Collect additional evidence and modify COA as necessary, if a COA exists for the concept of interest for a different context of use
- Develop a new COA and empirically evaluate, if no COA exists for the concept of interest

Description of COA instrument(s)

☐ Clearly defined Concept of interest and Context of Use

☐ Conceptual framework for each COA instrument

- ☐ Conceptual model
- ☐ Measurement model

☐ Rationale for selection of each COA instrument

- Supportive evidence (e.g., patient input collected through qualitative research, and how it informed selection of COA instrument)

☐ Method of data collection

- timing of assessments, frequency, and mode of administration (of COA instrument)
- plans for COA measurement after discontinuation from treatment

☐ Copy of COA instruments (i.e., current draft version or exact copy of final version)

☐ Statement that describes how/what eCOA best practice recommendations were followed (as per section D.4 of FDA Draft Guidance: Selecting, Developing and Modifying Fit-For-Purpose Clinical Outcome Assessments[4]).

☐ Scoring algorithm

Documentation that COA is Fit-for-Purpose (FFP) for Proposed Context of Use (may be context dependent)

☐ Evidence to support that COA is FFP

- ☐ Documentation of Evidence to support rationale
- ☐ Evidence to support concepts of interest (e.g., input from patients and/or caregivers, disease-specific experts, literature review)
- ☐ Qualitative study summary with evidence to support item relevance, comprehensiveness, clarity, item stems and response options, recall period
  - Specify if concept elicitation was spontaneous or endorsed
- ☐ Quantitative study summary with evidence to support item retention and item scoring
- ☐ Interview Transcripts, available on request
- ☐ Interview guides
- ☐ Evidence of concept saturation (saturation table or matrix)
- ☐ Item (question or task) tracking matrix (based on cognitive interviews)
- ☐ If relevant, provide evidence of appropriateness of DHT and establish that the DHT is fit-for-purpose in the target population

☐ Complete table to Summarize Rationale that COA is FFP (Appendix A, Table 1)

Measurement properties – validity, reliability, and ability to detect change

☐ Protocols for instrument testing (e.g., observational study or clinical trial)

☐ Psychometric analysis plan to evaluate instrument measurement properties, including the following:

- ☐ Item descriptive statistics including frequency distribution of item response and overall scores, floor and ceiling effect, and percentage of missing response
- ☐ Inter-item relationships and dimensionality analysis
- ☐ Item inclusion and reduction decisions, identification of subscales (if any), and modification to conceptual framework
- ☐ Preliminary scoring algorithm, including how missing data will be handled and interpretation of scores
- ☐ Evidence of test-retest, inter-rater, and intra-rater reliability and internal consistency, as appropriate (Appendix A, Table 2)
- ☐ Evidence of construct validity, including convergent and discriminant validity and known groups analysis
- ☐ Score reliability in the presence of missing item-level and if applicable scale-level data
- ☐ Final instrument, conceptual framework, provisional scoring algorithm for exploratory use, and plans for further revision and refinement

☐ Psychometric Analysis Summary Report with summary of descriptive statistics, reliability, construct validity, ability to detect change for each domain or summary score proposed as support for claims

☐ Quantitative and Qualitative support for meaningful change thresholds is encouraged but not required

- Describe what constitutes a clinically meaningful change and /or treatment-effect for patients as measured by instrument
- Description of how within-patient change and/or between-group thresholds for meaningful change will be characterized (e.g., cumulative distribution curves) and how they will inform interpretation of treatment effect

☐ Respondent burden

☐ Translation or cultural adaptation availability for all languages in which the instrument will be used. Refer to ISPOR principles for translation and cultural validation process.[7]

Modifications to existing COA

☐ Provide rationale for modifications and evidence that modified instrument is valid and reliable and that instrument's instructions, concepts, and items are relevant, meaningful, appropriate, and comprehensive, relative to its intended measurement, use, and target population

☐ Letter of permission from instrument developer to use/modify instrument as proposed

Potential Questions/Topics for Discussion

- Obtain feedback on proposed COA measurement strategy, including alignment on:
  - methods/instruments/items chosen are appropriate to measure the key concepts,
  - whether the schedule of assessment and analysis plan are appropriate including chosen meaningful change estimates
  - whether the PED data will be considered supportive to inform the Benefit-Risk
  - the viability of the data generated from the endpoints to support labeling claims.
- Discuss approach to evaluate psychometric properties and validate new or modified measures derived from the PED or to leverage existing measures based on PED findings

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

BIO's 2022 FDA-Sponsor Engagement Framework: Clinical Outcome Assessments (COAs)

- Does the Agency agree that this approach provides adequate support for the domain structure of selected COA instruments?
- Does the Agency agree that item content of instrument is consistent with concepts of interest from qualitative studies?
- Do qualitative and quantitative research findings, including cognitive debriefing of the COA instrument, support content validity?
- Does the Agency agree that measures are fit-for-purpose to assess <proposed domains> in patients with <condition>?
- [Company]proposes the use of <instrument> to assess <primary/secondary/exploratory endpoint>. Does the Agency agree with the endpoint, the selected instrument, and the planned statistical analysis approach?
- Additional questions, if applicable:
    - Does the Agency agree with the proposed recall interval for the <instrument>?
    - Does the Agency agree with the proposed timing of assessments for the <instrument>?
    - Does the Agency agree with the proposed use of digital health technology to collect patient data? Does the Agency have any advice in proceeding with using the device as planned?

(4) Assessment of Treatment Effect (COA implementation into clinical trials)

Information/Data to share with FDA

For details, refer to Patient-Focused Drug Development (PFDD) Public Workshop: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making Discussion Document[8]

Clinical SAP and Data analysis

☐ Describe methods to define within-patient meaningful change threshold in statistical analysis plan

☐ Describe any modifications to statistical analysis plan to address missing data. If method of imputing missing data is based on precedent, provide detailed rationale and evidence

☐ Proposed methods to summarize and analyze data (e.g., landmark analysis, ordinal data analysis, time-to-event analysis) to generate "substantial evidence"

☐ Scoring information, including detailed information on how COA scores will be analyzed as part of an endpoint

Psychometric Analysis report (Baseline from pivotal expansion) -- Updates to ongoing COA development

☐ List of studies in support of instrument including status of study, study synopsis, final or summary report, and results of analyses for observational psychometric studies

☐ Identify product benefits from patient perspective to identify potential COA endpoints based on exploratory COA data analysis from ongoing trials

COA-specific plans within Clinical Protocol

☐ Description of plans for blinding, frequency, and timing of COA assessments

☐ Description of procedures for patient or rater training or COA administration

☐ Description of plans for handling and documentation of missing data

☐ Description of plans for cumulative distribution function comparison among treatment groups

☐ Description of procedures for data collection, data storage, data handling and transmission

Estimand Framework

☐ Target Population of Interest

☐ Endpoint definition

- ☐ Intercurrent events
- ☐ Population Level Summary

Endpoint Model

☐ Updated proposed endpoint hierarchy based on emerging data

☐ Plan for derivation of clinically meaningful change threshold using longitudinal data () ––Psychometric validation of new or modified COA instruments

☐ Submit evidence to confirm measure is reliable, valid, and responsive to change

☐ Evidence to support definition of meaningful change for patients in COA score (e.g., exit interview evidence, rationale to support proposed anchor scales)

☐ Item analyses to inform item reduction

☐ Factor analyses to support conceptual framework

[8] Food and Drug Administration. "Patient Focused Drug Development Guidance Public Workshop. Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making." December 2019.

Proposed Labeling or Promotional claim

☐ Determine language and presentation of desired claim based on COA instrument

☐ Discuss results from new or modified COA instruments in relation to target claim (e.g., whether instrument score endpoints meet statistical significance and show clinically meaningful changes/difference in clinical trials)

Potential Questions / Topics for Discussion

- Does the Agency see any gaps in evidence that should be addressed prior to submission regarding suitability of proposed COA measures/selected domain(s) to collect data to support label claims and/or suitability of inclusion in patient experience data section?
- Does the Agency agree with proposed methods to develop and confirm preliminary responder/progressor definitions?
- Does FDA agree that evidence collected thus far would be sufficient to support responder definitions and clinically meaningful difference?
- Does the Agency agree that the proposed approaches are sufficient to support clinical meaningfulness of selected COAs?
- Company intends to propose COA-related label claims based on a significant difference in <XXX>. Does FDA agree that the study design, choice of endpoints, and statistical analysis plan are adequate to determine whether treatment with <Name of product> results in clinically meaningful benefit and statistically significant change in <XX, YY, ZZ>?
- Does FDA agree with validation and documentation of the psychometric properties of <instrument> for evaluating <COA measure> in support of eventual labeling claims?

(5) B-R Assessment and Approval Decision

Information/Data to share with FDA

Additional analyses

☐ Timeline for all qualitative work up to present
☐ Results for primary, secondary, and all exploratory instrument and COA endpoints evaluated in Phase 3 trials
☐ Demonstrate both clinical meaningfulness and statistical significance
☐ If modifying endpoints, submit red-line version of amended protocol and COA specific SAP for review by FDA Biostatistician
☐ Analysis based on both raw score and transformed score data

COA dossier submission preparation

☐ Timeline for all quantitative and qualitative work up to present to identify COI, develop COA and interpret treatment effect
☐ Results for primary, secondary, and all exploratory COA endpoints evaluated in Phase 3 trials
☐ Demonstrate both clinical meaningfulness and statistical significance
☐ If modifying endpoints, submit reasons for modifications and red-line version of amended protocol and COA-specific SAP for review by FDA Biostatistician
☐ Analysis based on both raw score and transformed score data, as appropriate

Questions / Topics for Discussion

- Discuss how the COA endpoint(s), which is clinically meaningful and statistically significant, can factor into the benefit-risk assessment, including:
    - COA endpoints used as primary and/or key secondary efficacy endpoints
    - COA endpoints not included in the statistical hierarchy (i.e., exploratory/descriptive)
- Discuss whether and how results obtained with COA endpoint(s) can be included in labeling and promotional materials
- Discuss other options for communicating COA data obtained from the clinical program, including from primary/key secondary and exploratory COA endpoints, such as Project Patient Voice for oncology products.[9]

[9] Food and Drug Administration Oncology Center of Excellence. Project Patient Voice. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice. Accessed October 24, 2022.

Appendix A: Supporting Tables (From FDA PFDD Guidance 3: Selecting, Developing and Modifying Fit-for-Purpose COAs)

Table 1: Summary of Rationale and Support for COA to Measure Concept of Interest in Target Population

	Component	Support
A	**The concepts of interest, [FILL IN], should be assessed by a [PRO/ObsRO/ClinRO/PerfO], because . . .**	
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**	

Table 1 is recreated from FDA's PFDD Draft Guidance 3: Appendix E, Table 1

Table 2: Evidence to Support 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***
. . . within the same rater for the same patients (when the patients have not clinically changed)	Intra-rater reliability			**X**	**X***
. . . across different but highly related or similar tasks	Evaluation of score differences between related tasks or sets of tasks				**X**

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

Table 2 is recreated from FDA's PFDD Draft Guidance 3: Table 2

Appendix B: BIO Recommended FDA - Sponsor Engagement Timeline

This figure highlights timepoints during drug development when sponsors should consider engaging FDA to discuss their COA development strategy and implementation. The drug development phases has been combined with key steps in COA development as highlighted in FDA's Roadmap to Patient-Focused Outcome Measurement in Clinical Trials to show clear timepoints to consider engaging FDA during COA development. Please note that the timepoints may vary based on therapeutic area, existing preliminary research, de novo vs. modified COA, etc.