September 23, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: Docket No. FDA-2022-D-1385: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments**

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO and its members appreciate the opportunity to work with the Agency to develop and align on approaches that are robust, practical, and expedite patient focused drug development. To further enhance the Guidance, we believe that a few areas would benefit from more explanation, examples, and references. We have identified through our comments areas where these additions would be beneficial.

## *I. Enhanced Validity Framework and Concepts/Terminology*

BIO appreciates FDA's effort to develop the series of guidance documents to assist reviewers, drug developers, patient organizations and other stakeholders with the collection, analysis, and use of patient experience data for drug development and decision-making of regulators. The draft guidance recognizes advances in measurement science since the publication of the 2009 PRO guidance and describes a modern validity framework supported by evidence-based rationales. BIO commends this shift to a fit-for-purpose evidentiary framework and believes this will support thoughtful and pragmatic COA development. BIO also supports the draft guidance's recognition

that some health aspects are complex, more than one type of COA might be used to assess different aspects of a concept of interest, and COAs might measure concepts of interest that are indirect reflections of a meaningful health concept.

BIO recognizes that the concepts covered in this guidance are complex and technical; and FDA has provided helpful, thorough COA considerations. To further enhance the guidance, BIO recommends the inclusion of references and case examples (real/hypothetical). For example, it would be helpful to include more detailed guidance regarding what FDA considers to be adequate evidence supporting COA development and validation. For example, on page 26, the discussion of IRT models to "design, evaluate, and score" the COA is unclear and appears to only apply to the reflective COA model. We suggest adding references, more practical examples, and case studies to guide sponsors how best to implement these methods in developing and validating a COA.

We also note that some of the concepts discussed in this draft guidance overlap with the FDA (2009) "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" Guidance for Industry, whereas others do not. For example, some concepts (e.g., criterion validity) appear in the FDA (2009) PRO guidance, but not in the current draft guidance. However, some other concepts (e.g., fit for purpose, content validity) appear in both documents. BIO respectfully requests the Agency to provide clear definitions and descriptions of new concepts to ensure maximal understanding and clarity of FDA's thinking in the final guidance. We further recommend that the Agency seeks harmonization with other important stakeholders in this space, such as ICH, with regards to the use of terminology and definitions to avoid confusion. BIO appreciates the September 9, 2022, FDA Public Webinar which served as a very useful informational session related to this Draft Guidance and the prospective PFDD Guidance 4. We would appreciate seeing the same content discussed at the webinar detailed in the Final Guidance for consistency and clarity.

BIO additionally notes that with a shift in thinking, the draft guidance introduces new terminology and concepts that have not been previously discussed in prior PFDD guidances or discussion documents. We request that the Agency consider providing an updated glossary and/or detailing new or shifting terminology between the final guidance and previous PFDD guidances.

## II. *FDA-Sponsor Interactions on COA Development and Implementation*

FDA interactions with sponsors are critical for sponsors to successfully implement the recommendations in this draft guidance and ensure that critical concepts are discussed early and throughout development. BIO appreciates the flexibility afforded by the draft

guidance; however, it may be difficult for sponsors to anticipate what approaches will be required in specific scenarios. Accordingly, we emphasize the importance of clearly defined opportunities for FDA-sponsor interactions early and throughout drug development. Given the new concepts and methods introduced in this draft guidance, communication between sponsors and FDA will be necessary to ensure that the guidance recommendations are implemented correctly. Therefore, BIO proposes that the Agency work with the industry to ensure that FDA-Sponsor communications are streamlined and consistently implemented across the Agency. Specifically, it would be helpful to provide more clarity on the timing and operational aspects of how sponsors can engage with the Agency to discuss COA development to ensure that sponsors and FDA have robust and productive communications. BIO would be pleased to work with the Agency to develop recommendations on how interactions regarding COA development can be incorporated into drug development. Such recommendations could be considered as part of revisions to the Best Practices for Communication Between IND Sponsors and FDA During Drug Development guidance that will be updated during PDUFA VII.

## III. *COAs in Registrational Trials*

BIO appreciates the Agency's inclusion of guidance regarding situations where no COA exists for the Concept of Interest which a sponsor is attempting to measure.
We acknowledge that the FDA does not recommend evaluating measurement properties in a registration trial. However, evaluating these in standalone observational study or earlier trials might provide preliminary data on score interpretability only and would not represent the final context of use. Therefore, one can only evaluate the final context of use in Phase III. The guidance does not make it clear how the sponsor can achieve this earlier in development.

Further, in rarer diseases or in accelerated programs or even new COAs might be administered the first time in phase 3, registration trials (not for the first indication). A standalone validation/observational study in parallel with the registration trial might not be possible in several cases. BIO requests the Agency to share whether they agree that there are some exceptions from the best practice rules described in this section or give any guidance specific to these circumstances. Again, the question refers to a drug that is on the market/FDA approved and the new/modified COA is used for the second indication.

We suggest that FDA acknowledge that in-trial validation may be pragmatic and acceptable in some cases, despite the known risks involved, if justification of the approach is provided. We further note that it is not possible to demonstrate sensitivity to treatment effects in an observational study, nor is it always possible to understand group differences in outcomes given variations in treatments and lack of randomization. Therefore, we would appreciate clarification of whether it is satisfactory for this property to be evaluated for the first time in a registrational trial.

## IV. *Communicating COA Data*

We appreciate the Agency's recognition that patient experience data may inform not only efficacy outcomes but also safety and tolerability outcomes. While we agree that descriptive endpoints may not be sufficient to form the basis of a label claim, we nonetheless believe that methodologically robust patient experience data beyond that used as a primary or key secondary endpoint provides rich contextual information that may inform patient and provider decision-making. We encourage FDA to clarify how this information could be included in the Patient Experience section of the USPI or to work with the industry to develop alternative means to convey this information to patients.

## V. *Advancing Digital Health Technology Tools and Clinical Outcomes Assessments*

We appreciate the guidance's recognition that DHTs may be used to administer PROs and PerfO measurements. We are also encouraged by the Agency's other activities that are advancing the use of DHTs, including the 2021 Draft Guidance Digital Health Technologies for Remote Data Acquisitions in Clinical Investigations. However, we note that DHTs introduce the possibility to measure aspects of the patient experience that previously could not be measured adequately. We believe that passive monitoring of patient activities in daily life can enable quantification of patient function, and that this is distinct from electronically administered "standardized task" PerfOs. Currently, the FDA draft DHT guidance states: "*The principles that should guide development of novel endpoints based on data captured by DHTs are the same as the principles for developing novel endpoints captured by other means. Sponsors should obtain input from stakeholders (such as patients, disease experts, caregivers, clinicians, engineers, and regulators) to ensure that the novel endpoint is both clinically relevant and the data is adequately captured by the DHT. Discussions with the relevant review division are also important in these situations.*" BIO further recommends that FDA consider how the standards it adopts may be harmonized globally to support adoption of these methods.

We note that DHTs introduce the possibility to collect and combine different types of measurements that may include both biomarkers (e.g., physiological parameters) and clinical outcome assessments (e.g., functional measures). While we acknowledge that additional guidance may depend on the therapeutic area and development program, we encourage FDA to describe in PFDD Guidance 4 whether and how these different measurement types can be combined to support regulatory decision-making. We also ask that FDA clarify the appropriate groups to engage with at the Agency (i.e., Biomarker or COA staff) for feedback on such endpoints.

BIO also acknowledges that guidance regarding COA development via DHTs will ultimately require harmonization. Harmonization considerations in this space may

include privacy, data confidentiality, and evidentiary considerations for demonstrating clinical relevance of DHT-derived measures.

## *VI. Leveraging Existing COA Instruments*

FDA provides considerations on when an existing COA can be used without providing additional evidence of validity for the context of use, versus when additional evidence is required to justify use of the existing COA. While these considerations are thorough, it is unclear how they are weighed. For example, FDA indicates literature reviews may be evidence that enables use of a COA as is but does not provide enough detail about the characteristics of such a literature reference and what other data may need to be combined with that literature reference to justify use as is. It seems unlikely that FDA will accept a COA for use merely based on a peer-reviewed literature reference. In addition, such references are unlikely to provide the same amount of supporting data to the public domain that is available to the original COA developer (e.g., interview notes, patient quotes, interview transcripts, and individual item revisions based on cognitive debriefing).Therefore, it would be helpful if FDA provided specific case studies or hypotheticals to illustrate various scenarios of successful re-use (with or without additional validation) and the underlying evidence that is needed (and note what's not needed) for the COA to be re-used in that particular context of use.

## *VII. Conclusion*

BIO appreciates this opportunity to submit comments regarding the Draft Guidance Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed and we look forward to future opportunities to collaborate with the Agency on this critical topic.

Sincerely,

Leslie Harden, Pharm.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

**SPECIFIC COMMENTS:**

| LINE/ SECTION | ISSUE | PROPOSED CHANGES<br>Added text is noted with underlined font |
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| I. INTRODUCTION | | |
| 13-14 | When finalized, Guidance 3 will represent the current thinking of CDER, CBER, and CDRH on ~~this topic.~~ | BIO suggests the following language to describe the purpose of Guidance 3.<br>When finalized, Guidance 3 will represent the current thinking of CDER, CBER, and CDRH on **clinical outcomes assessments (COAs) and approaches to select, modify, develop, and establish measurement properties of COAs to support robust capture of meaningful outcomes to patients in clinical trials.** |
| 61-62 | This guidance is intended to help sponsors use high quality measures of patients' health in medical product development programs. Ensuring high quality measurement is important… | BIO suggests the following edits to define "high quality" measurement.<br>"This guidance is intended to help sponsors use ~~high quality~~ robust measures (**i.e., measures that are valid, reliable, sensitive to change and interpretable)** of patients' health in medical product development programs. Ensuring **the appropriate level of rigor in** ~~high quality~~ measurement is important…" |
| 64 | Scope of the guidance | In line 64 refers "...being clear about what was measured; appropriately evaluating the effectiveness, tolerability, and safety of treatments". The scope of the guidance is not restricted to treatments, also consider vaccines and medical |

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| | | devices. Could it be referred as "medical product", as it is done in other sections of the guideline.<br><br>Regarding the role of PROs in safety evaluation and adverse events, we suggest including a declarative statement based on previous communications from the FDA with respect to the PRO-CTCAE that patient-reported events do not represent safety reports and are not to be reconciled with adverse events. (Cite e.g., Presentation given by Paul Kleutz (US FDA) on 01-Aug-2017, titled 'PRO-CTCAE in Oncology Clinical Trials: a US Regulatory Perspective) |
| 91-93 | 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 | These best practice publications have been released over a number of years by different authors. In the case of conflicting recommendations between publications and over time, how will sponsors reconcile the best practices to follow endorsed by FDA? |
| 119-122 | 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 | We recommend FDA provide an example of a COA endpoint (akin to the examples provided in the paragraphs above for COA "scores"). |
| 121 - 124 | "*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* | We urge FDA to describe in PFDD Guidance 4 whether and how these different measurement types can be combined as well as the appropriate groups to engage (i.e., Biomarker or COA staff). |

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| | *combined (see Guidance 4, when available, for a discussion of COA-based endpoints).*"<br><br>We note that Digital Health Technology tools (DHTs) introduce the possibility to collect and combine different types of measurements which may include both biomarkers (e.g., physiological parameters) and clinical outcome assessments (e.g., functional measures). | |
| II. Overview of COAs in Clinical Trials | | |
| 129 | "*A. Types of COAs*" | We recommend adding a reference to the BEST glossary[1] for the definitions of COAs and each COA type. |
| 135-136 | Considering the recent FDA-ASCO workshop on dose optimization, please consider adding "dose optimization" to-the following statement:<br><br>"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." | BIO recommends the following edit: "COA scores can be used to support efficacy, effectiveness, **dose optimization**, and safety in the context of a clinical trial to determine the clinical benefit(s) and risks(s) of a medical product." |
| 141 | "*The following are the four types of COAs*"<br><br>We note that some passive monitoring digital measures may fit the definition of a COA, by providing insight into how patients function, but these do not fit into any existing COA category. | We encourage FDA to provide additional guidance that will advance the use of DHT-passive monitoring |

[1] FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338448/. Accessed August 1, 2022.

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| 149-151 | The same example is used throughout the document. This should also include people with cognitive deficits. | BIO recommends the following edit to consider additional situations for utilizing ObsROs: "Observer reported outcomes are useful when patients such as young children **or people with cognitive deficits** cannot reliably report for themselves, or to assess observable aspects related to patients' health (e.g., signs, events or behaviors)" |
| 162-165 | "FDA acknowledges that there are instances when it is impossible to collect valid and reliable self-report data from the patient."<br>Does this imply that sponsors should only use ObsROs when no one in the patient population can answer questions by themselves, or rather when there is a substantial number of patients who cannot answer questions for themselves? | BIO recommends the following edits: FDA acknowledges that there are instances **when** ~~it is impossible to~~ **collecting valid and reliable self-report data from a substantial proportion of the population is not feasible**. 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 patients' experience |
| 193 - 196 | "*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*."<br>We note that patients may consider slowing of disease progression and delaying loss of function to be an important treatment outcome. In addition, we note that new treatment modalities, such as cell and gene therapies, hold the potential to reverse disease course and restore lost function. | We suggest that FDA edit the text as follows to recognize different potential patient-relevant treatment goals:<br>"... the intent of treatment may be to improve a symptom(s) or a specific function (e.g., ambulation); **delay or** 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; **or restore a specific function**." |
| 203-207 | "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 | BIO requests that the Agency provides more insight regarding whether industry can leverage available/pre-existing concepts of interest and evidence to support these concepts. If this is so, there may be no need for additional concept elicitation |

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| | interest." | research assuming all other requirements are met (i.e., context of use, including the target patient population). |
| 215 | 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. | We recommend the Agency provide clarity on the expected benefits and risks of the medical product (e.g., whether, based on its mechanism of action, the product is expected to improve all core concepts or just a subset). This includes mention of COA strategy given the multitude of concepts that could be measured and how the COAs/COA based endpoints fit together to provide needed information for stakeholder decision-making.<br><br>"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. **Sponsors should also identify the expected benefits and risks of the medical product. For example, some medical products may target a subset of disease-related signs and symptoms while others may be broader in scope. COA objectives may also include tolerability or safety objectives as reported by patients."** |
| 232-233 | Original text:<br><br>"This input will help sponsors in selecting or developing a COA that measures what is important to patients." | BIO recommends the following modification to the text below: |

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| | Concept elicitation should provide an overview of the patient experience and impact of disease. | "This input will help sponsors **help gain an understanding of the disease experience and treatment burden** and in selecting or developing a COA that measures what is important to patients." |
| 235- 249 | It is unclear whether the Agency is discussing the disease conceptual model or COA conceptual model. Figure 1 title suggests conceptual model of an impact on ADLs, not conceptual model of a disease | BIO requests clarification regarding whether disease conceptual model is different than ADLs conceptual model and if only one or both should be included in the evidence package. |
| 246-247 | "*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*."<br>We appreciate that FDA has acknowledged elsewhere in this draft guidance that some concepts of interest are complex and may require a combination of COAs in order to be adequately characterized. However, we note that this text could be interpreted as suggesting that a COA should always capture the entirety of a COI. | We recommend that FDA consider adding a sentence to the end of this paragraph such as **"Multiple COAs may be needed to capture all concepts of interest"** as is noted in lines 644-645. |
| 249 | Figure 1. Hypothetical Conceptual Model for Activities of Daily Living | The conceptual model does not seem to include the core concepts, i.e., symptoms, that would result in the limitations to activities/health concepts presented in the model. BIO recommends that the Agency adds a statement that a model could include the symptoms of the condition and link these to the proximal impacts associated with these symptoms in the domain of activities of daily living. |
| 261-264 | Original text: | BIO recommends the following revision: |

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| | "**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)"<br><br>For multi-national trials, some items in the COA may not be applicable across different cultures. Context of use under target population should consider the COA applicability to cultures as well. | "**Target Population:** Including a definition of the disease or condition; participant selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, **cultures**, comorbidities); and expected patient experiences or events during the trial (e.g., that some patients will require assistive devices)" |
| 265 | "Study Context: The clinical trial design in which the COA is to be used, …" | The use of "study context" as a context of use consideration is confusing (use of similar terms). BIO suggests adding "clinical trial design" as the consideration, as follows:<br><br>**"Clinical Trial Design: The clinical trial design in which the COA is to be used, …"** |
| 271 | "…how the COA will be collected (e.g., DHT, paper form)" | The industry standard for eCOA is "mode." BIO suggests the following revision:<br><br>**"…how the data will be collected (e.g., mode of administration such as DHT, eCOA, or paper form)"** |
| 276 | "the level of validation associated with a medical product development tool is sufficient to support its context of use" | BIO requests the Agency to consider that there are multiple possible types of validation, and we ask that the Agency clarify the relevant type(s) of validation in this phrase: "level of validation" |
| 297-298 | 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 | BIO requests clarification as to whether this is meant to imply that regardless of the endpoint hierarchy of the COA, the sponsor would be required to submit a PRO dossier to support a COA as fit-for-purpose. Are there cases in which |

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| | | the rationale included in the study protocol or submission document would be adequate justification? In cases in which a COA evidence dossier is not required, which study or submission documents would the FDA expect the sponsor should provide to support this rationale? |
| 297-299 | It is understood that for use of a COA (existing, modified or newly developed), the sponsor should present a well-supported rationale with evidence on why the COA should be considered fit-for-purpose. Additional clarification on what requirements would be necessary for COAs to be included in the labeling. | BIO requests that FDA considers adding requirements that are necessary for COAs to be included in labeling such as, COAs which are assessing primary/key secondary endpoints in regulatory relevant clinical Phase 3 trials |
| 308-309 | "The evidence for a particular part of the rationale is weighed relative to the degree of uncertainty about that part." | We suggest the Agency describe how the degree of uncertainty is assessed, and who should assess it. In addition, we suggest outlining the elements that impact uncertainty in this context. |
| III. A Roadmap to Patient-focused Outcome Measurement in Clinical Trials | | |
| 326 | Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials | BIO suggests that the first arrow may need to specify that use of an existing COA along with its associated evidence supports the fact that it is fit for the context of use |
| 326 and 374 | Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials<br>What level and type of evidence is required to support the use of an existing COA? While the guidance states the following:<br>"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 | BIO requests clarity on whether providing the enumerated examples will meet FDA expectations, or if FDA will expect more qualitative research (e.g., if use PROMIS, is additional qualitative evidence/measures to support content validity required, or can we proceed direct to use in clinical trial without additional more qualitative evidence). |

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| | 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"<br><br>We note that cognitive debriefing and additional patient input are not included in the list, and that published literature does not typically include detailed information from the qualitative research, i.e., patient quotes or interview transcripts | If FDA views this is as a need for evaluation on a case-by-case basis we suggest providing what considerations trigger the need for additional evidence. |
| 329 | "A. Understanding the Disease or Condition and Conceptualizing Clinical Benefits and Risks" | It would be helpful to separate the two topics into two separate headers to mirror the way they are laid out in Figure 2. Consider also including letters in the figure corresponding to the sections of text below to help guide the reader. BIO suggests the following language:<br><br>"**A. Understanding the Disease or Condition**<br><br>**B. Conceptualizing Benefits and Risks"** |
| 348-356 | "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 | Some conceptual models tend toward being comprehensive, including all identified symptoms/impacts of a particular condition. In order to conceptualize clinical benefit and risks, it may be ideal to only describe the core symptoms of the disease within a particular context of use and to keep the conceptual model simple and fit for that particular use.<br><br>BIO requests Please clarify if conceptual models can be developed to describe the core concepts of interest within a particular context of use and not necessarily an all-encompassing disease experience.<br><br>It's unclear whether this is intended to focus on the concept of interest, or the overall health experience associated with a |

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| | framework (see section III.C)." | disease or condition. A conceptual model describing patients' experience with a disease or condition may include multiple concepts of interest.<br><br>Also, even a seemingly simple concept generally has multiple aspects which could be assessed (e.g., intensity, frequency, duration). Part of identifying the concept of interest is identifying what aspect of the concept of interest would be most meaningful and relevant. |
| 358 | Select/Develop the Outcome Measure | In addition to III.B.3 – Special Considerations for Selecting or Developing COA's for Pediatric Populations we suggest that - another section be added for other special populations, e.g., rare disease populations. We also suggest that the guidance explicitly callout unique considerations for rare diseases given the small patient populations, disease heterogeneity, lack of natural history data and information, changes in physical or cognitive function due to disease/condition progression and/or treatment effects. |
| 367-368 | When would using multiple COA types be of value? | BIO recommends that FDA consider adding the following example for when it may be appropriate to use multiple COA's at once: **Patients with cognitive deficits may be capable of self-report but their patient experience should be supplemented by ObsROs that can be administered to caregivers. This may include patients in the early stages of Alzheimer's disease or stroke patients with mild cognitive deficits.** |
| 373 | "FDA recommends conducting a search to identify a COA that measures…"<br><br>Recommend specifying what kind of search FDA recommends. | BIO Proposes the following changes:<br><br>**"FDA recommends conducting a search of publicly available information, such as the scientific literature and** |

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| | See suggested text. | **<u>FDA Summary Basis of Approval, to identify a COA that measures…"</u>** |
| 385-485 | Approaches to Evaluating Existing and Available COAs | Throughout, BIO requests that the Agency please clarify appropriate time points for FDA review of the existing evidence and recommendation on sufficiency of that evidence prior to registrational submission<br><br>Please also consider adding the following additional language to each section, for example, after line 405-406:<br><br>"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. **One way of ensuring the evidence is sufficient would be to meet with FDA at X point in development, at which time, FDA will provide feedback and recommendations to the Sponsor if there are adjustments that need to be made to increase the likelihood that such evidence will be deemed sufficient from a methodological perspective for registrational purposes** **<<***this same template could be added after a number of sub-sections on pgs 385-485, with FDA changing the timepoint such that its relevant for that subsection***>>** |
| 419-428 | Original text:<br><br>"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:<br><br>• Instructions/training materials<br><br>• Item or task content (e.g., omitting, adding, or modifying wording of items and/or response options; translating from one | For clarity, BIO recommends the proposed edit:<br><br>"A sponsor may also consider **<u>other modifications, such as</u>** modifications **<u>to improve an existing COA for the same concept of interest and context of use</u>** ~~or modifications intended to improve the COA's ability to reflect the concept of interest~~. Modifications could include, but are not limited to, changes to: |

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| | language to another; modifying the activity performed for a PerfO)<br>• Order of the items or tasks<br>• Recall period<br>• Format of the measure (e.g., paper or electronic device)<br>• Method of scoring, including changes to the scoring algorithm"<br>FDA should acknowledge other types of modifications that may be made to an existing COA, such as modifications to a COA for the same concept of interest and context of use. | • Instructions/training materials<br>• 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)<br>• Order of the items or tasks<br>• Recall period<br>• Format of the measure (e.g., paper or electronic device)<br>• Method of scoring, including changes to the scoring algorithm" |
| 430 | The sponsor should carefully consider the impact of the proposed modifications to an existing COA. | Instrument developers may decline to allow changes to the wording of their instruments, which is another consideration during instrument modification. We suggest the following language, "The sponsor should carefully consider the impact of the proposed modifications to an existing COA **and should seek permission of the instrument copyright holder where appropriate."** |
| 436-441 | "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." | It would be helpful if FDA provided examples for the type of evidence would be acceptable to support modifications of a COA. |
| 451-468 | Original text: | BIO recommends that a bullet be added to this section. |

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| | "There are general principles regarding the development process for any type of new COA: […]"<br><br>New COA development should include input from patients and/or caregivers and this guidance should explicitly provide this recommendation. | "There are general principles regarding the development process for any type of new COA:<br><br>[…] **• Consider co-creation with patients and/or caregivers when developing new COAs."** |
| 457 – 463 | 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.<br><br>What is considered "convincing evidence"<br><br>We suggest clarifying and providing examples of what constitutes convincing evidence when "No COA Exists for the Concept of Interest" and a sponsor is: "Develop[ing] a New COA and Empirically Evaluate[ing]" by expressly listing the relevant items from Table A. Example Table to Summarize and Support for a Measure in a Target Population. | BIO recommends the following edit for clarity: "Develop and provide **scientific-based** evidence."<br><br>Please consider adding the additional text after line 459:<br><br>Examples of "convincing evidence" for developing a new COA where no COA exists for the concept of interest could include items in Appendix E, Table A. Example Table to Summarize and Support for a Measure in a Target Population.:<br><br>BIO also suggests the following language to include other study personnel, "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 **and other study personnel**, patients, observers, or clinicians) so that assessments are conducted in a consistent way." |
| IV. DEVELOPING THE EVIDENCE TO SUPPORT THE CONCLUSION THAT A COA IS APPROPRIATE IN A PARTICULAR CONTEXT OF USE | | |

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| 490 | 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.<br><br>What are the available paths to request a meeting to discuss COA development?<br><br>To facilitate that collaboration, it would be helpful for FDA to provide a roadmap of the optimal touchpoints in terms of both when in the development cycle, and the optimal type of engagement/meeting that FDA would prefer. In addition, it is important to have a consistent and timely mechanism for sponsor-FDA follow-up to clarify concepts included in written correspondence. | We suggest the following revisions to clarify what is meant by "simple". "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 that can be understood across the spectrum of ages** for **use in** patients of all ages in a study."<br><br>BIO requests that FDA please expand this section by adding a roadmap of the optimal FDA-sponsor interactions with examples of types and timing in terms of 1) when in the development cycle, 2) the optimal type of engagement/meeting, and 3) the disciplines that FDA would prefer to include. In addition, we suggest FDA outline a timely mechanism for sponsor-FDA follow-up interactions to clarify concepts included in written correspondence. |
| 497 | Using multiple COAs to measure a concept in a trial impacts statistical analysis plans and trial power (see Guidance 4, when available). | This should be further explained. It would be helpful to refer to Agency discussion document for Guidance 4 instead of referring to a Guidance 4, which is not yet available. One situation often arises is whether one could/should pool resulting scores of ObsRO instruments with those of PRO instruments. |
| 504-506 | Self-administration and self-report may not be suitable with very young children or patients with cognitive deficits and therefore might call for alternative approaches such as interviewer administration by a trained interviewer and/or different COA types. | BIO requests that FDA include guidance on when to use interviewer administration vs other COA types |
| 511 | Other examples should also be provided. | BIO Requests that the following text be added following line 511: The level of cognitive deficits in the patient population should also be evaluated to determine whether self- |

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| | | administration is feasible in the vast majority of patients. This may depend on the length and complexity of the questionnaires as well as the level and type of cognitive deficits in the population. |
| 525-527 | 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; however, a rationale is not required to be submitted when using an eCOA DHT because it is not an outcome, but rather a tool, and it has been routinely accepted that eCOA collection provides advantages over paper | When referring to digital health tools (DHT), BIO suggests the Agency distinguish eCOA DHTs and wearable DHTs. As written, it is unclear in what context a sponsor needs to provide a rationale for using an eCOA device. We suggest the Agency clarify that a sponsor does not need to provide a rationale for using an eCOA DHT, because it is not an outcome, but rather a tool, and it has been routinely accepted that eCOA collection provides advantages over paper. |
| 536 - 539 | "*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).*"<br><br>We appreciate the need to assess usability for accessibility features of COAs. However, we note that the guidance referenced applies to medical devices and that other approaches beyond the human factors studies described in this guidance may be appropriate to determine if a COA is fit to be used by its intended use population. Other methods may include, but are not limited to, cognitive debriefing studies, usability, or satisfaction surveys. | We recommend that the guidance be amended to enable sponsors to take advantage of the many methodological approaches available. |
| 586-590 | "*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* | We ask FDA to clarify that a clearly established MOA is not required for COA development, and suggest the following edit: |

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| | *feasibility of observing intervention effects within the context of a clinical trial (e.g., trial duration).*"<br><br>We appreciate the Agency's guidance that the intended drug effect will guide the selection of concepts of interest to measure in a clinical trial. However, we note that mechanism of action (MOA) may not be known, particularly early in development when the COA strategy is still being developed. | "*...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 (e.g., putative mechanism of action, targeted function); and the feasibility of observing intervention effects…*" |
| 599 (Figure 3) | Please clarify what details FDA is expecting to receive under the following two headings in "Figure 3. Illustration of a Generic Conceptual Framework Summarizing Which Patient Experiences Will be Targeted and How They Will BE Measured": 1) Patients in the Target Population; 2) Patients in Trial Sample. Currently, the illustration only provides a depiction of different numbers of colored shapes of patients, and it's not clear what FDA expects sponsors to provide in this part of the framework. | BIO requests that FDA provide examples and/or clarification regarding the characteristics of the target population and of the patients in the trial sample that should inform Figure 3. |
| 599 | Figure 3. Illustration of a Generic Conceptual Framework Summarizing Which Patient Experiences Will Be Targeted and How They Will Be Measured | BIO appreciates the inclusion of Figure 3. While the figure combining the conceptual model and framework is useful in theory, in practice there may be too much data to present in a single model. We request that the Agency provide an example of a populated model to confirm feasibility, because often these have been presented separately as conceptual models, instrument conceptual frameworks, and endpoint models. |
| IV. Developing the Evidence to Support the Conclusion That a COA is Appropriate in a Particular Context of Use | | |
| 634-638 | Table 1 | BIO requests that FDA please clarify where each component included in Table 1 should be recorded in the COA dossier. |

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| 650 | The COA Measure Selected Captures All the Important Aspects of the Concept of Interest | BIO requests that FDA clarify the evidence required to justify concepts of interest as relevant and comprehensive for ClinRos and PerfOs. For example, are interviews with clinicians sufficient or are interviews with the target patient population recommended to justify concepts as patient-relevant even if ClinRo is ultimately selected/developed? |
| 653 - 661 | "*All important aspects of the concept of interest should be covered by the chosen COA*"<br>We note that this language contradicts other text in the draft guidance that acknowledges that in some cases multiple COA types may be needed to fully characterize a concept of interest. | We encourage the FDA to consider adding language similar to that in lines 644 - 655 here which states: "*Note that more than one type of COA might be used to assess different aspects of a concept of interest.*" |
| 668-675 | "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."<br>This section discusses cognitive interviews, but the process for PRO/ObsRO is different from ClinROs/PerfOs. Alternative language is suggested in the adjacent column. | BIO Proposes the following changes:<br>Line 668: "For PROs and ObsRO measures, the most straightforward type of support…"<br>Line 672: "For PerfO and ClinRO measures, cognitive interviews with patients regarding task instructions combined with…" |
| 699-702 | Regarding measurement invariance | BIO recommends adding the following language after line 702 to define measurement invariance: **Measurement** |

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| | | **<u>invariance is a statistical property of measurement that indicates that the same construct is being measured across some specified groups. It is intended to ensure that comparisons across various groups of participants are both meaningful and valid.</u>** |
| 706-707 | Recommendation to conduct translation, cultural adaptation assessment and linguistic validation (TLV) early in COA selection and development process contrasts with request that TLV activities are conducted using the final instrument in preparation of the regulatory relevant trials. This has a huge impact on company's clinical trial preparatory work and should be done with the final instrument. | BIO recommends that the Agency includes the clarification that these activities are conducted with the use of the final instrument, and not at other timepoints in development. |
| 737 | Regarding cognitive interviews, we acknowledge that cognitive interviews cannot provide evidence that the recall period chosen minimise any recall bias (and provides accuracy) but we believe that cognitive interviews can provide evidence to support the selection of a given recall period. | We suggest adding following after the '*…instrument)*' In line 737: '*or support selection of a given recall period.'*<br>"Note that cognitive interviews can provide justification that a given recall period is inappropriate (e.g., by documenting that respondents generated their response thinking about a shorter period of time than specified by the instrument <u>or support selection of a given recall period</u>)." |
| 752 - 753 | "*Sponsors may wish to explore approaches to reduce burden, such as having patients complete assessments at home the day before a clinic visit*"<br><br>We note that the at-home administration example given to reduce burden raises additional considerations, such as the acceptable timeframe for administration. | We suggest that FDA consider a more straightforward suggestion such as careful consideration of the administration schedule and/or reducing frequency of administration. |

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| 766-767 | Similarly, using different collection modes in the same trial (e.g., different modes for different sites) would raise concerns regarding comparability of assessments in the study. | It is important to understand why the switches in modes of administration are occurring as a first step to ensure scores from different modes are still interpretable without significant measurement error. We suggest the following language, Similarly, using different collection modes in the same trial (e.g., different modes for different sites) would raise concerns regarding comparability of assessments in the study. **Documentation of reasons for switch in mode of COA administrations will be important to contextualize the changes in addition to evaluating the extent of changes and need for establishing mode equivalency."** |
| 773-775 | The Agency provides references for ePRO best practices, though would benefit from the addition of a reference for eClinRO best practice recommendations. See suggested additional text in next column. | BIO proposes the following changes:<br>"Critical Path Institute ePRO Consortium 2014a and 2014b; Byrom et al. 2019; Eremenco et al. 2014; Romero, H, et al. 2022, Recommendations for Electronic Migration and Implementation of Clinician-Reported Outcome Assessments in Clinical Trials, *Value in Health,* 25*(7)*:1090-1098). |
| 776-778 | FDA recommends conduct of usability testing of different data collection devices with a small number of respondents. It should be clarified if it is recommended that usability should be tested in patients (regulatory trial population). | In addition, BIO requests that FDA please clarify if the usability testing is in respondents or patients (regulatory trial population) and for which type of COA usability testing is recommended. In addition, please clarify when a new equivalence study is not needed. There is published literature on the level of modification in determining level of evidence needed. |
| 805-818 | The Agency provides an example of how expectation bias might influence how a respondent or an administrator interprets the meaning of items using an example: "*consider two patients suffering from rheumatoid arthritis—one 49 years old and the* | BIO requests that the Agency includes in the guidance its current thinking regarding techniques for mitigating expectation bias in single-arm or open label trials which may |

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| | *other 82 years old. Relative to the 49-year-old, the older patient might expect that pain and discomfort are normal parts of aging*." And then provides a way to mitigate using "*…double-masked trials. Concealing the patients' assignment to study arms will also minimize the influence of patient expectations"*. While this mitigation is helpful for circumstances where RCTs are feasible, it would help if the Agency could provide guidance on how to mitigate expectation bias in disease areas like oncology where sponsors may be conducting single-arm or open label trials. | be the only feasible study design in some oncology and rare disease development programs. |
| 815 - 818 | "*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."* | We urge FDA to recognize in this draft guidance that COAs can be considered valid and meaningful even in the absence of placebo-controlled, blinded trials. We note FDA has issued guidance[2] stating that "the use of a placebo in double-blind, randomized controlled clinical trials may present practical and ethical concerns" in development programs for malignant hematologic and oncologic disease. Nevertheless, FDA encourages sponsors to collect PROs and other COAs in such settings. |
| 842-843 | 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 between 0 and 3. | BIO recommends adding what 0's and 3's could denote in terms of response options for additional clarity.<br><br>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~~ **(response options),** producing an observed between 0 and 3 **(e.g., 0= not severe and 3= very severe).** |

[2] FDA CDER and CBER. "*Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products Guidance for Industry*." August 2019.

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| 882 | "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)…" | We suggest splitting psychometric methods to MODERN and CLASSICAL test theory and discussing their pros and cons. Modern test theory was not endorsed or discussed so far in previous guidance; this is new. Some context/introduction would be helpful to get some insight into why and how the Agency changed its position/thinking |
| 939 and 946 | Subsection 5: Scoring Approaches Based on Computerized Adaptive Testing | BIO appreciates the Agency's new way of thinking on CAT is appreciated. We suggest splitting the discussion of the Agency's new thinking to STATIC and DYNAMIC health assessment and discussing their pros and cons.<br><br>Further, we are wondering if the Agency's concerns from the past have been addressed in the currently available item banks. We refer to two major issues: 1) content validity of the items in the item bank, i.e., How were these items derived or developed? 2) does the Agency find it acceptable that not all patients respond to the same and/or the same number of items? The item bank (CAT) is not only efficient (and is becoming a reality with the evolution of digital modes of administration) and less burdensome than the static health assessment but (more) precise. References should be added here to acknowledge the pioneering work of scientists in this field already some 20 years ago. For example, the PROMIS initiative (Cella et al., Med Care. 2007 May; 45(5 Suppl 1)) and even earlier work done by Dr John Ware (Ware et al., *Quality of Life Research 2003, 12 (8): 935-52)*. |
| 952-953 | For point 3 of CAT evidence requirements, please clarify whether the calibration must be within the target trial population, or if it can be calibrated in a wider population. For example, PROMIS | BIO recommends the following edit: |

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| | item bank items were commonly calibrated in a general population sample. We would recommend that for this purpose, a wider population is acceptable. | **"(3) the items are well-calibrated in the context of a well-fitting IRT model (where calibration can be performed in a wider population)"** |
| 1079-1081 | The statement on evidence for responsiveness to change only mentions a correlation coefficient. However, the use of a correlation coefficient alone can mask underlying issues with responsiveness, such as a large change within stable patients, and does not allow for the separate exploration of responsiveness to improvement/worsening. We recommend responsiveness to change is primarily assessed as described by Revicki et al (2008):<br>*"Once groups of patients are identified as improving, worsening, or remaining stable based on several relevant external anchors, several data analyses and indicators can be used to examine responsiveness. First, analysis of variance or covariance procedures can be performed comparing differences in mean baseline to endpoint changes in the PRO scores across the meaningful change groups (i.e., stable versus small improvement, stable versus moderate improvement, etc.). Second, responsiveness to change is frequently evaluated using different indicators, such as the effect size (ES), standard response mean (SRM), and responsiveness statistic (RS)."*<br>Dennis Revicki, Ron D. Hays, David Cella, Jeff Sloan. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes, Journal of Clinical Epidemiology, Volume 61, Issue 2, 2008, Pages 102-109. | We request that FDA adds a reference and note that responsiveness to change is primarily assessed as described by Revicki et al (2008): **"Once groups of patients are identified as improving, worsening, or remaining stable based on several relevant external anchors, several data analyses and indicators can be used to examine responsiveness. First, analysis of variance or covariance procedures can be performed comparing differences in mean baseline to endpoint changes in the PRO scores across the meaningful change groups (i.e., stable versus small improvement, stable versus moderate improvement, etc.). Second, responsiveness to change is frequently evaluated using different indicators, such as the effect size (ES), standard response mean (SRM), and responsiveness statistic (RS)."** |
| 1092 | Table 2. Possible Assumptions About Consistency of Scores | BIO notes that there is no difference between test-re-test and intra-rater reliability for ClinROs (same score expected within |

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| | | stable patients for same rater). An observer such as a caregiver should provide the same rating for a patient when there has been no clinical change, otherwise this undermines the instrument's ability to detect change. Similarly, different observers should be able to reliably provide the same rating for the same patient. Therefore, this may need to be clarified in a footnote or provide an explanation for the difference, if there is one. |
| 1106 | *"For measures developed using IRT modeling, an alternative estimate of reliability can be generated based on the information function"*<br>We recommend adding text that reliability estimates can be obtained from CFA models too. Also, we recommend replacing the word 'alternative' with 'additional, so that IRT/CFA-based composite reliability is not interpreted as a sufficient replacement for test-retest reliability. | BIO recommends the following edit:<br>"For measures developed using IRT modeling, an **additional** estimate of reliability can be generated based on the information function. **Similarly, reliability estimates can be obtained from confirmatory factor analysis models."** |
| V. Abbreviations | | |
| VI. Useful References for Selecting, Modifying, and Developing Clinical Outcome Assessments | | |
| 1470<br>Figure A | The content of the figure is unclear:<br>What is the relationship between "feeling" and "symptom"?<br>As reported in the text, if Function A is a single item daily diary, why does the measurement model depict 4 items? | BIO requests that FDA please include an explanation of how the conceptual model that has a single daily diary measure translates into a measurement model that has four items in the score. |

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| 1481 | An ObsRO measure does not rely on medical judgment or interpretation… | BIO requests clarification that an ObsRO is categorized as such even if a clinician completes it if it doesn't require medical judgment |
| 1521 | In Figure B, why is the arrow from Items to Observed Behavior Rating? Doing so would suggest a composite indicator model, not a reflective model. | If the items are meant to o be reflective of Observer Behavior Rating, then BIO recommends that the three arrows for the three items should point in the opposite direction, from Observer Behavior Rating to each of the three items. |
| 1553 | "Use a masked assessor for primary efficacy or effectiveness data collection" is not clear | BIO requests the Agency please clarify "masked" in this context. |
| 1577-1667 | The potential role of COAs based on accelerometry measurement should be considered as a sub-category of performance outcome measures (Appendix D, line 1577) or as a separate category subject to a different set of selection and implementation considerations (line 1615-1667). Accelerometry based measures of daily activity are mentioned in the FDA draft guidance document "Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry" as potential endpoints, they are also being explored as part of the Critical Path Institute PRO consortium Heart Failure Working Group with FDA ongoing involvement and project funding. | BIO requests that the Agency add cross reference the draft guidance document Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry, as an example of accelerometry as a subset of PerfOs. |
| 1683 | Key aspects of quantitative validation are missing -- such as construct validity (convergent, discriminant, known-groups); criterion validity; and ability to detect change | BIO proposes adding the follow fundamental elements to the checklist:<br>construct validity (convergent, discriminant, known groups); criterion validity; and ability to detect change |

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