

September 27, 2022

Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Docket No. [FDA-2022-D-1385](#)

**Draft Guidance: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments**

Dear Sir or Madam,

This letter is in response to the FDA draft guidance: **Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments**. The International Society for Quality of Life Research (ISOQOL) Special Interest Group for Regulatory and Health Technology Assessment Engagement (R&HE SIG) appreciates the efforts of the FDA to encourage and improve patient focused drug development (PFDD). This draft guidance (PFDD Draft Guidance 3) represents another step forward in FDA's development of the 4-guidance PFDD series.

ISOQOL is a global community of researchers, clinicians, health care professionals, industry professionals, consultants, and patient research partners advancing health related quality of life research (HRQL). Our vision is to improve quality of life for people everywhere by creating a future in which their perspective is integral in health research, care and policy. Collectively, we have extensive experience in patient engaged quality of life research and initiatives that are intended to establish best practices in research, educational efforts and model programs. The ISOQOL Regulatory and Health Technology Assessment Engagement Special Interest Group (R&HE SIG) is comprised of members who seek to advance ISOQOL's vision through the specific objective of actively engaging with regulatory agencies and health technology assessment bodies to address critical applied measurement issues raised by these entities or that emerge from their public communications (e.g., commenting on draft guidance documents).

ISOQOL's R&HE SIG appreciates this opportunity to engage with the FDA by providing these comments for consideration to the docket. The comments shared in this document are a collection of comments contributed by R&HE SIG members. The comments below do not necessarily reflect the views of all ISOQOL R&HE SIG members, nor do they necessarily reflect the views of the members' respective organizations, employers, or affiliations.

## **General comments:**

### Significant changes from 2018 PFDD-3 discussion document - request for another public meeting

- This draft guidance includes significant changes from the previously released PFDD-3 discussion document that was the basis for public discussion during the FDA public workshop held in 2018. The PFDD-3 discussion document was well-received by the clinical outcome assessment (COA) scientific community during that public workshop. The PFDD-3 discussion document included practical, actionable advice, with the key request from stakeholders asking the FDA to include even more pragmatism and practical advice in the then-forthcoming PFDD Draft Guidance 3. The departure from the PFDD-3 discussion document in this draft guidance unfortunately meant that much of the practical advice from the PFDD-3 discussion document was removed. This PFDD Draft Guidance 3 reads as much more theoretical and academic, without providing specific advice that stakeholders have requested. It is strongly suggested that another public workshop be held after updates are made to this draft (as another discussion document) but prior to finalizing this guidance. This would provide stakeholders an opportunity to discuss and share concerns and recommendations with the FDA before this, such an important guidance, is finalized.

### Discrepancies in draft guidance text and common recommendations from CDER reviewers

- Understandably, it is difficult to draft a guidance document that is applicable across all Centers at the FDA as well as for multiple stakeholders, including both COA experts and non-experts. However, in this effort, it seems this guidance has become overly academic without offering practical advice and is adding to confusion about current Center thinking. For example, there are some topics appearing as options in the guidance that current FDA CDER comments do not generally support. For example, there is a section dedicated to computerized adaptive testing (CAT). Members of this SIG have reported receiving recent FDA CDER comments that do not endorse the use of CAT for FDA decision-making (e.g., CAT has generally not been considered appropriate for endpoints planned for product labeling). There may be some instances where CAT has/will be acceptable (within CDER or in other Centers), but the discussion of CAT in this draft guidance as an equally appropriate method to static forms seems to be out of alignment with most FDA CDER reviewers' current thinking and recent comments to sponsors. Please consider redrafting in a way to reflect what is current advice being provided by Centers or at least by highlighting challenges with some methods that may make them less acceptable to different Centers. It would be useful to indicate that Centers may have different tolerances, and where possible, outline those differences. As an alternative, it may be useful to develop a COA-specific guidance for CDER that is able to convey CDER-specific, practical advice for COAs (similar the PRO-specific guidance for CDRH and CBER).

### Removal of “Content Validity” is concerning

- A central issue in PFDD Draft Guidance 3 is the abandoning of terminology (such as content validity) that has become standard in the industry and a move to even more theoretical terms that makes it challenging for experts in the field and uninterpretable for novices.
- Both the 2009 PRO Guidance and the 2018 PFDD-3 discussion document nicely cover the importance of developing evidence for “content validity,” which relies on input from patients and/or other reporters – namely concept elicitation interviews and cognitive interviews. In this draft guidance there is a large emphasis on psychometric methods, however, it omits any discussion on the need for evidence of “content validity”. This is in direct conflict with current CDER comments (and good principles of measure development) that indicate that the evaluation of psychometric properties cannot be conducted until there is satisfactory evidence of content validity, nor can other evidence of measurement properties take the place of or overcome problems with content validity. The omission of a discussion of content validity and the steps typically needed to document (e.g., patient interviews in the case of a PRO measure) in this draft guidance, has already led to confusion by some sponsors. At least one sponsor client in a SIG member’s consulting practice has proposed that with this new draft guidance, patient interviews/input is no longer needed to develop a novel PRO measure to evaluate symptoms of a disease for which there are no treatments nor available symptom measures, as long as the psychometric evidence of validity is strong, given that “content validity” has been removed from the guidance. While the term content validity is not found within US regulations, it is a very practical and clear way for the FDA to describe how they interpret and evaluate the need for outcome assessments to be “well defined” (21 CFR 314.126(b)(6)) related to clinical outcome assessments, which rely on patient (or other reporter) input. Please consider for the final guidance a section on “content validity”, highlighting the importance of documenting content validity based on input from patients and/or other reporters, as an important element of evidence needed. It is very concerning that the omission of this term has already led some down the path of believing patient input is no longer the foundation of PRO (or other patient-centered) measures, and this could threaten some of the progress made towards patient-focused drug development.

### Unitary concept of validity - removing labels for types of validity evidence increases confusion

- The idea of a unitary concept of validity has emerged from educational testing, which often drives the methods employed in COA development for evaluating treatment benefit. However, in instrument development for evaluating treatment benefit, the unitary concept on its own becomes confusing and loses the practical ability to discuss types of evidence needed with non-expert stakeholders that includes both qualitative and quantitative evidence. Dr. Garrard’s presentation during the FDA webinar (September 9, 2022) very clearly and usefully walked through Table 1 of the draft guidance and linked the points in the table with the types of evidence that may support the decision-making and the

rationales (e.g., linking Table 1 component B to “content validity”, linking component F to “construct (e.g., convergent, known groups) validity”). It appears that the FDA is still appropriately expecting the same types of evidence – which are important components of COA evidence - as was described nicely in the 2009 PRO Guidance and 2018 PFDD 3 discussion document; however, FDA has now removed those terms from this draft guidance in favor of a unitary concept of validity. While the concept of validity may be theoretically unitary, there are different, distinct components of validity evidence that contribute to documenting validity overall and correspond to building rationales for decision-making in Table 1. Removing the recommendations for these types of evidence (content, construct (convergent, known-groups)) is likely to lead to confusion across the industry. Including those types of validity evidence in the guidance would help in providing actionable advice, aiding sponsors to understand what types of evidence are likely important to develop. In addition, when sponsors are evaluating legacy measures as fit for purpose based on existing published literature, these various types of validity evidence are typically described in publications by name. It will be confusing for stakeholders to try to map evidence described in the existing literature onto the principles in Table 1 of PFDD Draft Guidance 3 unless the draft guidance clearly describes the specific types of evidence that may be important to consider for each row in the Table 1. Please include in the final guidance the types of evidence, with the well-known and established labels (e.g., content, concurrent, convergent, known-groups), that may support the components in Table 1. If there is concern or question by FDA about whether to include or exclude these labels for types of validity in the guidance, please consider discussing this during a public workshop where the advantages and disadvantages of each approach might be considered before finalizing the guidance. If FDA considers this suggestion to include components of evidence of validity that are important, below are example suggestions to revise rows in Table 1 to include these important types of validity evidence:

	Component	Types of evidence that may support:
B	The COA measure selected captures all the important aspects of the concept of interest.	Evidence of content validity: Literature review Interviews with clinicians Concept elicitation qualitative research (e.g., interviews, focus groups) with patients and/or other reporters representative of the population of interest
C	Respondents understand the instructions and items/tasks of the measure as intended by the measure developer.	Evidence of content validity: Cognitive interviews with respondents representative of the population of interest
F	Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest.	Evidence of construct (concurrent, known-groups) validity

2009 PRO Guidance being replaced with four guidances and long list of references is challenging for stakeholders

- There was an expectation in the COA field that this PFDD Guidance 3 would replace the PRO Guidance (2009). However, what has become clear is that the series of four PFDD guidances will actually replace the single PRO Guidance. It would be optimal to redraft this current PFDD Draft Guidance 3 to incorporate all of the key elements of instrument selection or development in this single guidance rather than referring out to multiple other guidances and a long reference list provided in PFDD Draft Guidance 3. Guidance 3 could be revised to walk stakeholders through the steps of developing or selecting a measure and documenting evidence in a very pragmatic way, so that guidance 3 can stand on its own, finding more details of methods in guidance 1, 2, and 4, as needed. It adds to confusion when stakeholders must rely on four guidances plus a long list of references in guidance 3 to try to piece together the steps of documenting evidence for COAs. There is an opportunity to make this guidance 3 a practical, “how to” that would improve patient-relevant COA selection and use. It is appreciated that FDA was striving to show flexibility in this draft guidance, however, with flexibility can come uncertainty and inefficiency. It seems that CDER COA staff are already finding it challenging to meet COA review timelines with heavy workload. There are significant concerns that the “flexibility” (laundry list of potential research options stretched across four guidances) will decrease clarity that was provided by the 2009 PRO Guidance and 2018 PFDD-3 discussion document, and therefore will increase the demands on FDA COA reviewers resulting in more interactions needed with FDA and further review delays.
  - In the unfortunate situation that it will not be possible to make guidance 3 more of a practical start-to-finish “how to” develop or select a COA, please then at least clarify in guidance 3 (and FDA talking points) that multiple guidances in the PFDD guidance series are actually needed to determine how to develop or select a fit for purpose COA – one cannot rely on guidance 3 alone. Lines 199-203 make reference to this to some extent, though may not go far enough to make clear to many that the elements in guidance 2 are critically important to the development or selection of a COA. This may be best included in the introduction section, expanding on lines 30-31 of the guidance, and then throughout the guidance 3 as applicable (e.g., lines 199-203).

Evolving terminology – glossary needed

- There are a number of field-specific and/or new terms (e.g., DIF, measurement model, conceptual framework) throughout the guidance. Providing a glossary would be useful to make this guidance more accessible to non-expert stakeholders.

Outline for evidence submission needed

- In practice, sponsors need to submit the evidence with their marketing applications. All practical information on the content of these submissions that was formerly in the 2009 PRO Guidance and

Appendix 1 of the PFDD-3 discussion document has been removed. This detail is useful in ensuring information is submitted consistently and in a logical order. COA developers and sponsors rely on this guidance to ensure clarity in submissions and to reduce re-work or resubmission and request that the final guidance include this practical tool (i.e., a content outline for dossiers/evidence submission).

**Specific comments by line number:**

- Line 96-102: Thank you for including the point beginning in line 96. The need for evidence-based rationales is critical and something that FDA reviewers have typically sought. Having this described explicitly in guidance form is very helpful.
- Line 104-124: The text in this section is very helpful. Helping sponsors to think through the differences between COAs, scores, and endpoints is useful as these are often conflated leading to lack of clarity, rationale for decision-making and failures of patient-centered endpoints making it to labeling. Please keep this in the final guidance.
- Lines 127-179: Useful information to retain for final guidance and the expansion to COA types beyond PROs for providing information on how patients feel and function is in line with the scientific best practices and important for medical product development.
- Lines 249-250, Figure 1: this figure is a departure from the typical way the field of instrument developers for regulatory purposes has thought about a “conceptual model”. The figure seems to represent what the field has previously referred to as a “conceptual framework” – showing how the concepts in a measure group together to produce domains and an overarching score. Conceptual models have typically been more in line with disease models – showing all the concepts of interest that might be relevant to patients with the disease/condition, and then highlighting which have been selected for measure in a clinical trial – typically grouped by symptoms and impacts (sometimes showing proximal and distal impacts separately). There seems to be no advantage to this new use/definition of “conceptual model” (or “conceptual framework”), and to avoid confusion in a field that already uses these terms in a certain way, please consider for the final guidance going back to the typical definitions of “conceptual model” and “conceptual framework” (e.g., from the PRO Guidance, 2009 and the PFDD-3 discussion document, 2018). If the new definitions remain in place, please include a glossary to clearly define each.
- Lines 326-328, Figure 2: This is a very useful figure. Suggest maintaining this figure in the final guidance.
- Lines 419-444: We request FDA include a statement in this section reminding users to assess any licensing or copyright issues related to altering a measure. Though it may be out of scope for the FDA to address this issue directly, it is in the interest of the entire field that instrument modifications be clearly documented and approved by license holders. Standardization of instruments and clear versioning will help all stakeholders evaluate the meaningfulness of COA data.
- Line 449-452: The FDA states that it is beyond the scope of this guidance to provide specific recommendations for developing all types of COAs and refers readers to a long list of helpful references. Stakeholders are looking to this guidance for specific recommendations – where FDA

has them – to aid in developing or selecting COAs. CDER often provides very practical advice in individual comments to sponsors, even using template language seen across responses to sponsors. It would be very useful to provide some of the common advice in guidance form for all to benefit from. The list of helpful references is academically interesting but does not provide the practical advice all stakeholders are seeking. See general comment above about the possibility of developing a more practical, COA-specific guidance for CDER.

- Lines 472-475: The guidance nicely describes that measurement properties are best evaluated in early phase trials and warns of the risks of these analyses being conducted for the first time in a pivotal study. This guidance suggests a standalone observational study when early phase trials were not used for these analyses. It is almost impossible in a non-interventional, observational study to evaluate meaningful within person change (because often there is no appreciable change) to provide guidelines for interpreting meaningful treatment benefit. It would be helpful for FDA to describe this limitation, highlighting the further importance of undertaking the research in early phase trials, as well as describing practical steps that can be undertaken in this situation of determining what is meaningful change within a pivotal trial.
- Lines 502-506: Request that the Agency provide more guidance on the appropriate age ranges one might consider using a self-completed PRO measure versus an ObsRO measure in pediatric clinical trials, and/or more practical advice on the types of research that is appropriate to undertake to determine which COA is most appropriate in which age groups.
- Lines 521- 533 and Appendix D: DHTs are an increasingly important method for assessing outcomes in clinical trials. The current section on DHTs would benefit from additional clarity on what to consider when selecting or developing a DHT for use in a clinical development program.
- Line 557: It is not clear how the proposed conceptual framework represents the results of each step of the Roadmap to arrive at a fit-for-purpose COA. We request that the Figure 6 from the PFDD-3 discussion document be added back to the guidance to provide specific information on how to implement the roadmap with the specific associated evidence requirements.
- Lines 599-601: It is not clear from the figure how FDA recommends sponsors depict the patients in the target population and the trial sample. Is this meant to be a pictorial or include the eligibility criteria? Also, the conceptual model typically is derived from qualitative and quantitative data (as described in PFDD-2) – should the left hand side of patients reflect eligibility criteria from that information or the target population for eventual labeling? Providing more practical advice related to these questions would be very helpful.
- Lines 599-601: It is not clear how the concepts in the conceptual model depicted align with the measurement model depicted. For example, there are 3 important behaviors shown associated with symptom B that appear relevant for assessment with an ObsRO, however, there is only one corresponding item in the measurement model that appears to be meant to assess symptom B. Is this meant to imply that it is not necessary to assess all important, relevant concepts from the conceptual model? This combined conceptual model and measurement model may be most helpful if it provides a direct mapping of concepts of importance to the items that measure them (i.e., there

are 3 important behaviors related to symptom B in the conceptual model, there should be 3 items assessing those 3 behaviors in the measurement model).

- Lines 634-636, Table 1: this table is helpful in that it drives home the key point that rationales for decision-making along these steps is critical to FDA decision-making. What is not made clear here is what types of evidence may be needed to support these components and how these eight components fit in with the typical evidence dossiers that have been previously used by sponsors in submissions to the FDA. The reduction of the prior information supporting a COA as fit-for-purpose to Table 1 (Line 634-638) is especially problematic. It is not clear exactly what data are recommended or required to support each component and it is not clear if the expectation is for COA dossiers to now follow this order in Table 1. For the final guidance, it will be critical to describe where this table fits into a COA evidence dossier. One proposal the FDA might consider is to place this table in the beginning of the dossier to summarize the rationales for decision-making. Then, the details of the evidence supporting these rationales/decision-making can be provided in subsequent sections in a typical dossier format (e.g., following the outline that was provided in appendix 1 of the PFDD-3 discussion document). Currently, the draft guidance could be interpreted as suggesting that only a brief set of rationales for these eight points can be provided without highlighting that much more evidence will be needed to be submitted, nor describing in what format FDA would like to receive that evidence. A table placed in the beginning of a dossier based on Table 1 and Appendix E in the draft guidance may be useful. Here is an example row of such a table:

	Component	Brief rationale	Detailed rationale and supporting evidence can be found:
B	The COA measure selected captures all the important aspects of the concept of interest.	Evidence of content validity, based on a literature review, interviews with clinicians, and concept elicitation interviews, with patients representative of the clinical trial population supports the Hypothetical Symptom Measure (HSM) as including all the relevant and important symptoms of Hypothetical Disease.	See Section IV. Content Validity Evidence, pages X-Y.

This was undoubtedly a difficult guidance to draft, and all FDA efforts to publish this draft – during a pandemic when FDA resources were likely stretched thin – are very much appreciated. However, there are significant concerns that this guidance in its current form is confusing, too academic without offering practical, actionable advice, removes clarifying terms regarding types of validity evidence that make discussions between





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instrument developers, sponsors, and FDA more challenging, may inadvertently imply that the patient voice is not as relevant to COA selection or development, and may make it more challenging for FDA reviewers to review and provide responses to submissions that will become unstandardized and thus require more rounds of FDA review and feedback. Please consider the strong recommendation to develop another discussion document and hold another public workshop to discuss the direction of this guidance and to consider significant editing prior to finalization. Thank you very much for considering these comments.

Respectfully submitted,

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