

July 5, 2023

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

**Re: Docket No. FDA-2023-D-0026 Patient-Focused Drug Development:  
Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory  
Decision-Making**

Dear Sir or Madam:

On behalf of the Innovation and Value Initiative (IVI), thank you for the opportunity to provide comments on the Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders (Draft Guidance 4). We are supportive of the Food and Drug Administration's (FDA) commitment to patient-focused drug development, and we encourage the FDA to build on this commitment to ensure that patient centered priorities are a driving consideration in the development of new healthcare technologies.

IVI is a 501(c)3, non-profit research organization committed to advancing the science, practice, and use of patient-centered health technology assessment to support decisions that make healthcare more meaningful and equitable. Founded in 2017, the organization includes members from the research, patient, payer/purchaser, clinician, and innovator stakeholder communities. IVI's work emphasizes collaboration and exploration of new solutions in pursuit of a U.S. learning healthcare system supported by patient-centered health technology assessment (HTA) and focuses on high-quality, efficient, innovative, and equitable care for all people and communities. We believe this is only possible with a fundamental shift in resource allocation, coverage, and access-related decision making that aims to maximize value for all stakeholders—particularly patients and other covered individuals.

As an organization focused on HTA and decision making in the healthcare market, IVI explores methods for modeling costs and benefits of therapies and advancing the ability to estimate the value provided to patients by therapies post-approval. However, both the value delivered to patients and our ability to estimate it are a function of the degree to which upstream therapy development, clinical research, and approval processes emphasize/incorporate patient experience and preferences. Our belief is that value must be seen through the lens of the patient, and it is increasingly clear that estimating patient-centered value and paying for it in the marketplace must prioritize therapies that achieve endpoints important to patients and consequently generates the evidence needed to evaluate them. The patient-focused drug development (PFDD) program is a key step in shifting the overall research approach in clinical research.



IVI applauds FDA's ongoing work to develop detailed guidance for patient-focused drug development. We strongly support use of these guidance by researchers, innovators, regulators, and further downstream, payers and other decision makers. IVI has previously contributed to work by Everylife Foundation for Rare Diseases, National Health Council, and others in work related to the FDA PFDD initiative.

We are grateful for the opportunity to offer comments on Guidance 4. The selection and construction of endpoints is a critical step in meaningful measurement of relative efficacy, effectiveness, safety, and in our ultimate ability to capture what matters in evaluating relative benefits and risks of available therapies. Many of our comments apply to the patient-focused drug development process as a whole and to clinical research writ large, and we hope these comments can be helpful in other contexts as well.

### **PFDD Guidance Should be Based on Principles of Patient-Centricity and Health Equity**

IVI's work is guided by our Principles for Value Assessment.<sup>1</sup> These principles apply not only to the narrow context of HTA but are the foundation of a patient-centered and equitable health system based on value to all stakeholders, starting with the development and study of new technologies. Of the principles that guide IVI's work, two of the most foundational ones are patient-centricity and health equity. We believe that all PFDD guidance and regulatory practice at FDA should reflect these principles in both theory and practice. In particular:

#### *Patient-centricity*

By definition, patients are central to PFDD. It is essential that patients not merely serve as subjects, but they be included as equal contributors in design and conduct of research. We encourage FDA to explore approaches to encouraging patient-participatory research for drug development, and we urge researchers applying PFDD guidance to do the same.<sup>2</sup>

#### *Health Equity*

Equity considerations should be part of all guidance development and application in research and regulatory practice. Likewise, the equity implications of research design and endpoint selection should be a primary consideration for researchers and regulators. In practice, this presents challenges for innovators, researchers, and FDA alike. From a practical standpoint, measurement of differential treatment effects across specific groups of patients must be balanced against the time and resources required to do so. Applying health equity considerations also requires normative judgements that may prove controversial. This is no excuse for disregarding health equity, however, and FDA generally and the PFDD guidance specifically<sup>3</sup> should explicitly recognize the

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<sup>1</sup> Full description of our Principles for Value Assessment in the U.S. available at: <https://thevalueinitiative.org/principles-for-value-assessment-in-the-us/>

<sup>2</sup> Malik E et. al, (2023). A Research Framework to Understand the Full Range of Economic Impacts on Patients and Caregivers. Alexandria, VA. Innovation and Value Initiative and AcademyHealth.

<sup>3</sup> IVI, Health Equity Initiative Overview: How Patient Engagement and Innovation of Methods Can Move Us Closer to Achieving Health Equity, 2023. <https://thevalueinitiative.org/wp-content/uploads/2022/05/Health-Equity-Initiative-Overview.pdf>



importance of engaging in related discussions and incorporating equity concerns into research planning, trial designs, and reporting of results.<sup>4</sup>

This extends beyond selection of endpoints to the conduct of trials and the collection of evidence to show significance in study endpoints. Though it may require additional time and resources, a recent IVI study demonstrated the feasibility of oversampling to attain sufficient sample size to compare across often-underrepresented groups.<sup>5</sup> These approaches apply to both trials in general and to patient preference info specifically, especially to understand differences between subgroups.

### **PFDD Methods Must Balance Individual Experience Against Generalizability**

The current Draft Guidance 4, as well as previous PFDD Guidances, reflects the fundamental tension between the individualized experiences of patients—both individually and as groups—and the need for consistent and generalizable measures for use in development and appraisal of therapies.

#### *Standardization of PFDD Endpoints*

Informed clinical, coverage, and payment decision making depends on having an evidence base that allows comparison across therapies, both within a given indication and where possible across disease areas.

Increased generalizability of study results begins with selection of clinical outcome assessments (COAs), patient reported outcomes (PRO), and preference measures; consistency across endpoints is not possible without consistency across these measures. As feedback on previous Guidances has indicated, multiple efforts are underway to define consistent measures of patient-important outcomes. For example, IVI collaborated with National Health Council, the EveryLife Foundation for Rare Diseases, and others to develop a Patient-Centered Core Impact Set (PC-CIS) that can be used to elicit a comprehensive set of impacts of a disease and its treatments on patients.<sup>6</sup> IVI and researchers from the University of Maryland Patient-Driven Values in Healthcare Evaluation (PAVE) are engaged in a proof-of-concept study to identify key drivers of preferences for treatments in major depressive disorder, which can also be applied in different disease areas.

With consistency in the definition and application of COAs and other measures, it is possible to develop standardized patient-focused endpoints and encourage their uses across different trials. We encourage FDA to emphasize the need for consideration of generalizability in study design and, ideally, to apply this need to regulatory processes and review of submitted evidence. To support standardization, FDA should maintain a “library” of both COAs and study endpoints for use by others in the research community.

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<sup>4</sup> Richard Xie et al.(2023). Strategies to Include Underrepresented Patient Populations in Patient-Centered Research. [https://thevalueinitiative.org/wp-content/uploads/2021/12/ISPOR-EU-Poster\\_Strategies-to-Recruit-Underrepresented-Patient-Populations\\_Upload.pdf](https://thevalueinitiative.org/wp-content/uploads/2021/12/ISPOR-EU-Poster_Strategies-to-Recruit-Underrepresented-Patient-Populations_Upload.pdf)

<sup>5</sup> Amill-Rosario, A., Huang, P. L., Xie, R., Chapman, R., & Slejko, J. F. (2023). P47 A Discrete Choice Experiment to Assess Patient-Informed Preferences for Major Depressive Disorder Treatment By Depression Severity. *Value in Health*, 26(6), S10.

<sup>6</sup> Peretto, E.M., Oehrlein, E.M., Love, T.R. et al. Patient-Centered Core Impact Sets: What They are and Why We Need Them. *Patient* 15, 619–627 (2022). <https://doi.org/10.1007/s40271-022-00583-x>



Such a resource should include detailed descriptions of measures and endpoints, rationales for their selection, and information on the disease areas, indications, and populations they are relevant to. Where standardization is difficult or COA measurement is inconsistent, FDA should encourage data sharing through this clearinghouse to allow researchers to address these differences in later efforts at meta-analysis and other studies.

The Draft Guidance does identify several approaches for potentially standardized endpoints. We applaud the inclusion of Goal Attainment Scaling (GAS) as a potential approach to combining patient-important outcomes in an aggregate measure. A recently published study conducted by IVI and RAND researchers highlights the potential for use of GAS as an endpoint to capture what matters the most to patients in managing a specific disease condition.<sup>7</sup> In particular, the study demonstrates the potential to use GAS as an effective way to “crowdsource” patient goals and priorities within a given disease area or population, rather than depending upon patient-provider dyads for their identification. A dynamic goal inventory can also be constructed over time with continual input from different patient subgroups.

#### *Incorporation of Qualitative Evidence*

While standardization of endpoints to allow comparison across studies is essential, it is also important that the unique insights provided by qualitative data on patients’ experiences and perspectives be incorporated into study design. Where possible, the Draft Guidance should highlight potential use of qualitative data in selection and definition of endpoints and encourage use of mixed methods approaches in clinical studies. In addition, we encourage FDA to provide specific guidelines for submission of mixed qualitative-quantitative data for consideration.

#### **Continue to Advance PFDD**

IVI wholly supports the ongoing efforts at FDA to establish clear and well-supported processes for PFDD, and we applaud the work conducted by the FDA to date. To increase the impact of this work and the potential for it to benefit patients, FDA and policymakers at large should consider establishing a more meaningful role for PFDD guidance in regulatory processes. As general guidance without regulatory implications, the current guidance is insufficient to move the field or substantially impact value delivered to patients by the healthcare marketplace.

We strongly recommend that policymakers and regulators:

- Consider establishing concrete and specific requirements for use of PFDD approaches in evidence development and approval.
- Explore inter-agency and public-private partnerships with organizations like CMS and PCORI (and others).

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<sup>7</sup> Predmore, Z., Chen, E. K., Concannon, T. W., Schrandt, S., Bartlett, S. J., Bingham, C. O., ... & Frank, L. (2023). Treatment goals for rheumatoid arthritis: patient engagement and goal collection. *Journal of Comparative Effectiveness Research*, 12(5), e220097.



We appreciate the opportunity to comment on the Draft Guidance 4 and to contribute to the PFDD process. We hope that this process and recommendations like ours will help increase the impact and use of the PFDD program. IVI looks forward to continuing to advance this important work through our research. We welcome opportunities to collaborate with FDA and other interested partners.

Please do not hesitate to contact me or Mark Linthicum, Director of Policy, at [mark.linthicum@thevalueinitiative.org](mailto:mark.linthicum@thevalueinitiative.org) for further discussion.

Sincerely,

A handwritten signature in black ink, appearing to read "Jason", with a long horizontal flourish extending to the right.

Jason Spangler, MD, MPH, FACPM  
Chief Executive Officer  
Innovation and Value Initiative