



July 5, 2023

Robert M. Califf M.D., MACC  
Commissioner  
United States Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Patient-Focused Drug Development (PFDD): Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; Availability

Dear Commissioner Califf:

The National Health Council (NHC) thanks the Food and Drug Administration (FDA) for the opportunity to provide input to the proposed fourth guidance on patient-focused drug development. The NHC was a strong supporter of the inclusion of these guidances in the Prescription Drug User Fee Act (PDUFA) VI agreement. We are pleased that we have reached this historic point when all four PFDD guidances are released and commend the FDA, patient advocacy organizations, and medical product sponsors for the significant effort to get here.. The process has been long and complex, but it will be incredibly impactful. The FDA's work to increase patient engagement in medical product development has made tremendous strides and having all four guidances finalized will help create consistency in how patients can contribute to drug development efforts and clarity for sponsors in how the FDA views meaningful patient experience data. We look forward to continuing to work with the FDA on supporting successful implementation of these guidances and working together to review and improve the PFDD's efforts.

Created by and for patient organizations over 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, equitable, and sustainable health care. Made up of more than 155 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses and organizations representing biopharmaceuticals, devices, diagnostics, generics, and payers.

Our specific comments and recommendations for next steps are included below.

## Specific Recommendations for Guidance 4

### *Importance of Patient Engagement Regardless of Measure Used*

The NHC particularly appreciates that the FDA makes it clear throughout the guidance that all clinical outcome assessment-based (COA-based) endpoints should correspond to changes relevant to patients. Importantly, the guidance clarifies that this is a critical element of any type of COA, not just patient-reported outcomes (PROs). We have noted in the past that there is often an incorrect assumption that PROs inherently measure what is meaningful to patients because they are reported by patients. Similarly, we have noted that researchers have not always felt the need to ensure that non-PRO measures, such as clinician-reported outcomes (ClinRO), Observer-reported outcomes (ObsRO), or performance outcomes (PerfO) are meaningful to patients because they are not reported by them. The NHC has emphasized this dynamic in comments on previous guidances and is incredibly grateful to the FDA for distilling these notions and clarifying the importance of the patient perspective in COAs. We encourage the FDA to make this point consistently throughout the guidances when they are finalized.

As a note, the NHC has previously created methodological materials to attempt to get at the “core sets” of outcomes and impacts that are most important to patients and caregivers. This work is disease and measure agnostic. A [patient-centered core impact set \(PC-CIS\)](#) can improve efficiency and reduce burden in collecting patient experience data from patients and families. Patient experience data is the primary source of data, and the pipeline into a PC-CIS. Thus, a PC-CIS serves as the first way for researchers to identify relevant impacts important to a patient and caregiver community (regardless of later downstream use). A disease- or population-specific PC-CIS, provides a clear starting place, reducing the need for redundant primary data collection. New data collection can inform a PC-CIS and help build new knowledge, but an existing PC-CIS provides the foundation for alignment across all types of work (e.g., COA development or study endpoint selection).<sup>1</sup>

### *Patient Burden and Timing/Site of Measurement*

The NHC appreciates that the FDA devotes a significant portion of this guidance on considerations regarding timing of assessments for COA-based endpoints. We agree participant burden must be considered and reduced. It is important to get the patient perspective on collection, so as to minimize the patient burden and its effect on data. We agree with the FDA that “to demonstrate respect for the patients and/or caregivers who participate and maximize the quality and completeness of information collected in a clinical trial, sponsors should consider ways to minimize the burden of participation and increase the convenience and value of participation to patients and/or caregivers.” We also feel strongly that such a burden should be avoided as much as possible. Patient engagement, for example, through mock-trial participation, may be useful in identifying the right balance between data collection needs and minimizing participant burden.

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<sup>1</sup> National Health Council. Patient-Centered Core Impact Sets Blueprint. 2022.

At: <https://nationalhealthcouncil.org/a-blueprint-for-developing-patient-centered-core-impact-sets-pc-cis/>

The patient perspective is also useful when determining timing and location of assessments and how they relate to patient burden and accuracy of measurement. As stated by the FDA in the guidance, “The COA schedule should consider the natural course of the disease or condition (i.e., acute, chronic, or episodic), the research questions to be addressed, the trial duration, patient burden, the disease stage of the target patient population, the expected time frame when the investigational product is likely to affect the COA-based endpoint, and timing of collection of COAs if temporary study interruptions or discontinuation of study interventions are anticipated to occur.” COA data collection, particularly in regard to timing and location, should correspond with patients’ day-to-day life flow to the greatest extent possible. For example, if the target population is likely to be experiencing pain and that measure is important to the study, attempting to collect data at a location that requires significant travel — or other aspects that may increase pain and patient burden — could impact the outcomes. We recommend trial sponsors engage members of the patient community when determining timing and location of assessments and when assessing administration burden and schedule.

### *Multi-Component Endpoints*

The NHC appreciates that the FDA included information on the use of multi-component endpoints in studies. For many diseases and patients, it is important to consider how treatments can impact different symptoms, and multi-component endpoints are one way this could be done. We have also seen some of the challenges of using multi-component measures, such as how the meaningful improvement in one symptom can be diluted when less pronounced changes in other symptoms are factored into the endpoint. Our members report some concerns with the use of multi-component measures because they can provide unclear signals as opposed to single-component measures. Although we recognize that some of this may be addressed on a case-by-case basis in discussions between the FDA and the sponsor, we encourage the FDA to include more content on best practices for selecting endpoints (multi-component or otherwise) for heterogeneous diseases in the final Guidance 4.

Specifically, the NHC appreciates that the FDA included information on working to develop personalized endpoints in the guidance. We also understand the complexity of this process. We encourage the FDA to work with sponsors to gauge and support the implementation of more personalized endpoint development. It will be important that the FDA work with sponsors to develop endpoints that not only meet patients’ goals but also support effective research. The FDA should create methods to collect and share best practices on multi-component endpoint development and share that information broadly with sponsors.

### *Communication with the FDA*

We appreciate that the FDA has emphasized the need for sponsors and patients to interact with the Agency early and often when utilizing these guidances. This clear

communication will help achieve a smooth transition and effective application of the four guidances. However, the NHC recommends that the final guidance clarify when and how this communication can occur. In particular, we recommend clarity on how the new Type D and INTERACT meetings can be used to discuss patient engagement strategies. In addition, the guidance specifically mentions communicating early with experts (page 2; line 52). We recommend that patient organizations be specifically referenced in this section either as "clinical and disease experts" or as an additional category.

## **Guidance Dissemination and Implementation**

The NHC is excited to have the full array of guidances finalized and to begin working with the FDA to disseminate and increase the use of the guidances. Given the long process to finalizing these guidances, the NHC recommends a final review to assure alignment with other guidances that have been developed in the interim. For instance, guidance on diversity in clinical trials and decentralized trials may benefit from alignment with the PFDD guidances before finalization.

In addition, the NHC believes these guidances will benefit from additional examples, as implementation will simultaneously lead to best practices and raise additional questions. The NHC encourages the FDA to develop a process for collecting and adding new examples to the guidance package as the opportunity arises.

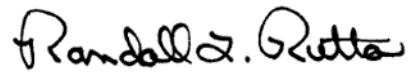
Another key aspect to supporting the successful implementation of these guidances will be aiding sponsors with transition from the current guidance — *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (2009). The NHC has heard from our membership that there is a need for clarity from the FDA in the final guidance on whether and how the 2009 guidance can be used, especially for products already under development. We recommend the final guidance clearly state what trials will be able to continue using the 2009 guidance and at what point the new guidance becomes appropriate.

Finally, the NHC recommends a final review and update of the PFDD glossary and other supplemental materials in earlier guidances as needed. This process of review and refreshment should be a continuous process to assure that the FDA is receiving feedback on the use of the guidances, while updating information to align with advances in science and regulation. The field of patient engagement has evolved since the last update of the glossary, and this guidance introduces several new terms and concepts that are not defined in the glossary. We encourage the FDA to work with the patient community and sponsors to update it. Specifically, we would appreciate the definition of "clinical outcome assessment" to incorporate this guidance's framing that they should aim to measure changes relevant to patients.

## Conclusion

The NHC thanks CMS for the opportunity to provide input on this important guidance. Please do not hesitate to contact Eric Gascho, Senior Vice President of Policy and Government Affairs, if you or your staff would like to discuss these comments in greater detail. He is reachable via e-mail at [egascho@nhcouncil.org](mailto:egascho@nhcouncil.org).

Sincerely,

A handwritten signature in black ink that reads "Randall L. Rutta". The signature is written in a cursive, flowing style.

Randall L. Rutta

Chief Executive Officer