



# National Health Council

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The Honorable Norman E. "Ned" Sharpless, M.D.  
Acting Commissioner, Food and Drug Administration  
Dockets Management Staff (HFA-305)  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Dear Acting Commissioner Sharpless:

The National Health Council (NHC) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA's) draft guidance on Enhancing the Diversity of Clinical Trial Populations. While industry has moved toward increased diversity in clinical trial enrollment, more work needs to be done. We support FDA's guidance to industry on this important issue. The NHC urges FDA to ensure that its final guidance leads to enrollment plans that are deliberate, guided by patient involvement, and fit for purpose, while avoiding creation of a set of new requirements that could disrupt clinical trial efficiency or delay patient access to promising new treatments.

Founded in 1920, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. The NHC provides a united voice for the more than 160 million people in the United States with chronic diseases and disabilities and their family caregivers. Made up of more than 125 diverse national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include professional and membership associations; nonprofit organizations with an interest in health; and representatives from the pharmaceutical, generic drug, health insurance, device, and biotechnology industries.

The NHC strongly supports any efforts to ensure that individuals with chronic diseases and disabilities have the opportunity to participate in clinical trials to facilitate the availability of new and innovative treatment options. We agree with FDA's statement that "failure to include complex participants in a development program may lead to a failure to discover important safety information about use of the investigational drug in patients who will take the drug after approval." Similarly, for many individuals, the ability to take part in the drug-development process is an empowering step that aligns with their health care goals and could allow earlier access to treatments to significantly improve health outcomes.

The NHC has actively engaged with the FDA and other stakeholders over the past several years to help ensure the patient voice is meaningfully represented, including in – but not limited to – the development of clinical-trial protocols. The NHC has worked to build consensus across a range of issues to advance the dialogue on patient engagement, from identifying key priority areas and topics for guidance development to providing feedback and suggestions on a common glossary of terms.

Our comments reflect our continuing commitment to ensuring a range of patient voices is meaningfully represented. We focus on the need for early, meaningful, proactive patient engagement to ensure a balance between the benefits of increased participant diversity and the risk of unduly complicating clinical-trial design or delaying access to treatment improvements. The NHC's overarching comments are:

- Clinical trial sponsors should engage patient organizations in the design of trials;
- Representativeness in patient engagement is key;
- Clinical-trial sponsor efforts to enroll a diverse set of participants should be condition specific;
- The NHC strongly supports guidance provisions focused on reducing the burden of clinical-trial participation;
- We appreciate the FDA's additional considerations for clinical-trial design for rare-disease products; and
- This guidance offers clear direction without imposing overly-burdensome requirements on sponsors that could result in unintended consequences.

### **Clinical trial sponsors should engage patient organizations in the design of trials.**

The NHC has commented on the FDA's patient-focused drug development (PFDD) discussion documents related to Guidance 2: "Methods to Identify What is Important to Patients" and Guidance 3: "Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments (COAs)." As we noted in those comments, patient engagement in drug development occurs at two levels:

- Patients engaged as partners informing the drug-development process and
- Patients participating as study subjects, such as those that provide data on the patient experience and in clinical trials that have been designed in a more patient-centered way.

We have expressed the concern that historically the primary role of patients has been limited to their role as a study subject. We appreciate the FDA's recent efforts to enhance patient engagement in the entire process. We urge the FDA to recognize that any efforts related to promoting diverse clinical trial enrollment should begin early in clinical-trial design with patients engaged as partners, informing the drug-development process.

We continue to believe that, through meaningful engagement with the patient community, the FDA and clinical-trial sponsors can conceive of clinical-trial designs that incorporate patient input, reduce the burden of participation, facilitate inclusion of a diverse set of participants, and consider patient preferences when selecting study endpoints.

**Representativeness in patient engagement is key.**

The NHC believes strongly that the scope and breadth of patient involvement in trial design and participation is fundamental to any efforts to increasing clinical trial diversity. In practical terms, this means that those engaged - patients, caregivers, advocates, and advocacy organizations - should be *representative* of the target patient population. Patient engagement strategies that fail to focus on securing perspectives of populations representative of a specific disease state, will likely fall short of delivering diversity in protocols and study enrollment.

In 2017, the NHC convened a half-day Roundtable with key stakeholders, including representatives from patient groups, life science companies, value-assessment framework developers, payers, research organizations, and the FDA. This Roundtable focused first on building a consensus understanding on what “representativeness” means when applied within the context of drug development, regulatory decision-making, and value assessments. Stakeholders agreed that representativeness means that a sufficient number and types of people are included in the engagement activity to ensure that those engaged can speak on behalf of the target population. It refers to “who” and “how many” individuals to include in an interaction (e.g., discussions intended to inform strategies on securing a diverse set of clinical-trial participants) in order to, as closely as possible, engage with individuals that represent the broader, target patient population.

Participating stakeholders then built upon this understanding to develop a set of recommendations on good practices to address the challenges of ensuring patient representativeness in patient engagement. The resulting white paper<sup>1</sup> describes six key principles with guiding recommendations and good practices, briefly outlined below:

- *Define – Clearly define the objective(s) for each engagement effort.*
- *Understand – Understand as much as possible about the full population and subpopulations and the challenges to reaching them.*
- *Specify – Develop a description of the minimum target(s) for representativeness for the engagement activity.*
- *Plan – Develop a plan to achieve the minimum target(s) defined.*
- *Evaluate – Develop an evaluation plan to assess progress on achieving target(s) or make adjustments if they need to be adjusted based on new information.*
- *Document – Record how patient representativeness was defined, targeted, achieved, and assessed.*

Taking a proactive approach to patient engagement, with an eye toward ensuring that activities include a patient population representative of the disease state, would enable clinical-trial sponsors to understand and address participation barriers. For example, if cognitive impairment is a known symptom or common comorbidity in a target disease, clinical-trial protocols should include mechanisms that address the need for caregiver participation and minimize caregiver burden. These mechanisms should be sufficiently flexible to accommodate divergent needs associated with geographic factors and differences in age, race, cognitive function, socioeconomic status, and language proficiency.

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<sup>1</sup>Tackling Representativeness: A Roadmap and Rubric. National Health Council. 2017.  
<https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf>

**Clinical-trial sponsor efforts to enroll a diverse set of participants should be condition specific.**

We appreciate both FDA's interest in encouraging clinical trials with broader representativeness, and its focus on patient-engagement strategies to accomplish that goal. In particular, we commend the Agency for recognizing the importance of ensuring that individuals with comorbid conditions and/or at varying levels of disease severity are not summarily excluded from clinical trial participation due to their complexity. The NHC agrees that, for many conditions, including participants at various stages of disease trajectory and those with comorbid conditions may be valuable.

While we understand the challenges research sponsors face in balancing study efficiency with a participant population representative of the disease state, we agree with the FDA that there is a fundamental difference between exclusion criteria based on factors presenting safety risks (e.g., decreased liver function, concomitant medications) versus those designed to reduce "noise" or ensure an enriched population. However, excluding those patients considered not ideal study subjects dilutes the information available to patients and providers who will eventually use the treatment in the real world. We are encouraged by FDA's recent work to facilitate more and better post-approval collection of real-world evidence (RWE) and believe it is useful in filling knowledge gaps as treatments are incorporated into evolving standards of care. However, we believe the health care ecosystem would benefit from a more thoughtful approach to excluding populations with comorbid conditions or varying levels of severity.

Engaging with the patient community is an essential first step toward determining when it is, and when it is not, appropriate to expand clinical trial enrollment beyond a narrow subpopulation.

**The NHC strongly supports guidance provisions focused on reducing the burden of clinical-trial participation.**

The NHC appreciates that the FDA recognizes that "potential participants may face additional challenges to enrolling in clinical trials." The draft guidance discussed several burdens that can significantly hamper clinical-trial diversity, including:

- requiring participants to make frequent visits to specific sites may overly burden the elderly, children, disabled and cognitively impaired individuals who require transportation or caregiver assistance, or participants who live far from research facilities, such as those in rural or remote locations;
- burdensome financial costs (e.g., travel, missing work), including study visits that interfere with work and family responsibilities;
- added clinical trial study visits for patients receiving regularly scheduled care from their community provider; and
- mistrust of clinical research among certain populations.

The NHC applauds FDA for addressing impediments that deter diverse clinical-trial populations. We agree that sponsors can address these issues with patient engagement during the early study-design phase. A meaningful dialogue with the patient community can inform sponsors on the best ways to facilitate enrollment and in ways that will not impede study validity (e.g., reduced frequency of study visits and use of technology to collect data on safety and efficacy). Perceptions of burden may vary significantly across disease states (e.g., added burden for this

with mobility challenges) and patient engagement is crucial to determining strategies that are most effective and valuable to patients across those states.

We appreciate FDA’s discussion of the types of accommodations reimbursements that should be encouraged to ensure participation is feasible for all patients. We believe sponsors should be allowed to offer a range of accommodations without fear of fraud and abuse repercussions. The January 2018 guidance for institutional review boards and clinical investigators on this topic<sup>2</sup> offers clarity, and this guidance reaffirms FDA’s thinking. However, we encourage a broader discussion, particularly around the role of caregivers. For example, increased enrollment of children and individuals with cognitive impairments will likely require participation of parents or caregivers who may have to take significant time away from work and other responsibilities and require travel expenses.

Once again, the NHC urges FDA to encourage sponsors to work directly with the patient community to address participant needs and to involve patients, patient advocates, and caregivers in the design of clinical-trial protocols (including logistical modifications, and compensation and reimbursement mechanisms). Patients can provide valuable insight into challenges and burdens associated with clinical trial participation. As FDA noted in its draft guidance, “[c]ommunity-based participatory research promotes the design of clinical research with the assistance of community members and leaders to more effectively meet the needs of potential participants.”

The NHC strongly supports the FDA’s general guidance toward reducing participant burden, including:

- Providing clinical-trial sites in geographic locations with a higher concentration of racial and ethnic minority patients;
- Incorporate diversity considerations when selecting health care providers to assist with clinical-trial recruitment;
- Incorporate strategies for public outreach and education; and
- Facilitate collaboration among industry, patient advocacy groups, medical associations, and other stakeholders to educate participants about clinical-trial participation.

**We appreciate the FDA’s additional considerations for clinical-trial design for rare-disease products.**

For rare-disease treatments, flexibility in designing clinical trials is especially important. Clinical-trial recruitment can be a significant challenge for product sponsors in all disease areas, but these challenges can become more significant with a smaller patient population from which to recruit. The NHC continues to believe that increased flexibility in clinical trial design is necessary to ensure that people with rare diseases can participate. We support the suggestions offered in the draft guidance, including suggesting that sponsors:

- Re-enroll earlier-phase participants in phase 3 trials and
- Consider an open-label extension study after early-phase studies to ensure that all study participants, including those who received placebo, will ultimately have access to the investigational treatment.

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<sup>2</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects>

Additionally, we wholeheartedly agree with the recommendation to engage patient advocacy groups early in the drug-development process to elicit suggestions on clinical-trial design, including protocols participants will be willing to enroll in and support. As previously stated, we believe this is a best practice for sponsors and for all diseases, but it can be an especially important tool in rare diseases.

**This guidance offers clear direction without imposing overly-burdensome requirements on sponsors that could result in unintended consequences.**

We believe this guidance does a good job of offering clear direction on increasing clinical trial diversity without being overly prescriptive, inhibiting innovations in trial design, or delaying access by reducing efficiency. Additionally, we are concerned that if the final guidance becomes more prescriptive, there could be an unintended consequence of government and commercial payers excluding coverage of newly-approved treatments for patient populations not studied.

### *Conclusion*

We thank the FDA for the opportunity to provide comments on the draft guidance. We believe that it is a very strong draft that will significantly further our shared goal of integrating the patient perspective into the research, development, and regulation of medicines while also ensuring that the diverse sets of patients suffering from a disease have meaningful opportunities to participate in important research. We support the FDA's work to advance diverse clinical-trial enrollment through meaningful patient engagement and look forward to continuing to engage with the Agency as it moves toward structural mechanisms to incorporate the patient voice in medical product development.

Please do not hesitate to contact Eric Gascho, Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable by phone at 202-973-0545 or via e-mail at [egascho@nhcouncil.org](mailto:egascho@nhcouncil.org).

Sincerely,



Marc Boutin, JD  
Chief Executive Officer  
National Health Council