NATIONAL HEALTH COUNCIL

May 2, 2023

The Honorable Robert M. Califf M.D.
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852.

Re: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; Draft Guidance for Industry

Dear Commissioner Califf:

The National Health Council (NHC) thanks the Food and Drug Administration (FDA) for the opportunity to comment on draft guidance for industry on externally controlled trials. The clarity that this guidance will provide helps advocates and sponsors collaborate more effectively to expand the types and methods of data used for controls in trials when appropriate.

Created by and for patient organizations more than 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, 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 representing biopharmaceutical, device, diagnostic, generic drug, and payer organizations.

Overarching Comment: Clarifying the Scope of the Guidance

We encourage the FDA to be mindful as you implement this guidance that trials do not always use exclusively randomized control arms or external controls. We urge the FDA to recognize this in the guidance by clarifying its utility for sponsors that look to conduct trials with mixed methods.

The Importance of Real-World Evidence

The NHC was a leading advocate for including language in the 21st Century Cures Act that expanded the use of external controls, particularly real-world data (RWD), for trials. We believe that if appropriately implemented, external controls can help increase the efficiency and effectiveness of trials and reduce the burden of participation in clinical trials. We also recognize the importance of taking a stepwise and nuanced approach to ensure the FDA receives sufficient data to determine whether products are safe and effective. We appreciate that this guidance lays out the benefits and limitations of external controls and includes appropriate safeguards to assure safety and efficacy. We

have already seen significant advances in patient-provided and generated information and interest from patient advocacy groups in building real-world evidence (RWE). This guidance will further increase the use of this important data. In addition, the NHC knows that the use of RWE is particularly important in the rare disease community, and we encourage you to work with rare disease advocates to refine and implement this guidance in a way that works for this unique population.

Patient Engagement on RWE

The ability of patient groups and others to generate and judge useful, quality RWD is central to the success of this guidance. It is crucial that FDA continue to engage with patient organizations to solicit their views on the use of RWE in decision-making. On July 31, 2017, the NHC brought together a multi-stakeholder roundtable, with patient advocacy organizations comprising the majority of participants. The objectives were to elicit patients' views on RWE, including:

1. Definitions and uses;
2. Characteristics needed for RWE to be understood and trusted; and
3. Skillsets and tools needed by patients.

The findings from this roundtable reflect the things that the FDA needs to consider as they increase the use of RWE. They include:

1. Patient Views on RWE Definition and Uses:
    a. Most patients have little understanding of RWE or that controversies exist with respect to selection of types of evidence used in decision making.
    b. The ultimate focus of RWE should be to answer the questions: "Does this work for me? Is this safe for me?"
    c. Acceptable uses of RWE must be linked to the context of its use.
2. Questions that Aid in Patient Understanding and Trust of RWE:
    a. Who or what group conducted the study(ies)? Was the study(ies) co-developed with patients?
    b. What is the purpose/objective of the study(ies)? Does it have pre-specified study aims versus post-hoc (i.e., data mining to "see what we find")?
    c. What are the key findings and how are they meaningful to patients ("Why is it relevant to me?")?
3. Skill Sets and Tools Needed by the Patient-Advocacy Community to Make the Best Use of and Communicate About RWE to Constituents:
    a. Standardized, concise RWE definition, universal to all stakeholders that is understandable and useable by patients;
    b. Guidance to assist organizations with creating a scientific advisory council or identifying a medical director resource to help with community understanding of RWE studies and findings; and
    c. Patient organization education materials/program on RWE uses, sources, and key issues (e.g., 15-minutes with Q&A; offer at patient advocacy organization conferences).

The FDA, in this guidance, has a role in equipping patient advocates to be partners in developing and communicating RWE. The NHC recommends that the FDA provide specific information on how patient groups can communicate with the FDA and identify appropriate contacts for questions or concerns. In addition, ongoing communication with patient groups to identify needed education or tools would be useful.

Use of Registries

Patient registries are another important tool in helping advance RWE. In 2020, the NHC sponsored a webinar on Sources of Real-World Data an Introduction to Patient Registries. This summary of the webinar gives a good overview of why registries sponsored by patient groups are important in the U.S. health system, and how the role of patients, families, and caregivers is essential in registries to expand the movement toward patient centeredness. Also in 2020, the Council of Medical Specialty Societies (CMSS) and the NHC produced Enhancing Patient Partnerships: How Patient Organizations and Medical Societies Can Enhance Patient Engagement in Clinical Registries and Research. This resource provides important information on patient engagement in registries run by specialty societies. The NHC encourages the FDA to use this information to continue to support new and evolving registries and assure they are more patient centered.

We encourage the FDA to continue to work with the NHC and patient advocacy organizations to support the development of quality RWE.

Health Equity

In addition, the NHC thanks the FDA for including health equity considerations in the guidance. The FDA rightfully notes that demographic and related factors (e.g., age, sex, race, socioeconomic status, geographic region) may differ in external controls. The NHC appreciates the recognition of this potential issue and that the FDA is encouraging review of the characteristics of an external control population and how it may affect the trial. We encourage FDA to continue to provide guidance to both patient groups and sponsors on assuring clinical trials represent the broad demographics of the patient population. This includes finalizing the FDA guidance on increasing diversity in clinical trials.

Applying Best Practices

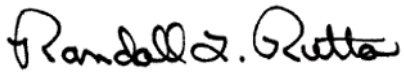
The release of this guidance is well timed. While we understand and appreciate the guidance creates a structure for the FDA to judge the use of external controls on a one-off basis, we encourage the FDA to leverage lessons learned from successful use of RWE. For example, the NHC is encouraged by the pilots conducted through the Advancing RWE Program authorized under the Prescription Drug User Fee Act (PDUFA VII) to generate valuable best practices. Similarly, given the significant amount of available RWD on COVID-19 vaccines and therapeutics authorized for emergency use, it is likely their full approval can be achieved through the use of RWE. This process,

while perhaps unique, can also generate best practices to be applied by other sponsors. To support these initiatives, the FDA will need to explore the patient advocacy community's needs, concerns, and potential contributions and uses of RWE to ensure the patient voice is considered.

Conclusion

The NHC thanks CMS for the opportunity to provide input on this important issue. 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.

Sincerely,



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