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February 5, 2019

The Honorable Scott Gottlieb, MD
Commissioner, Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Framework for a Real-World Evidence Program; Availability (Docket No. FDA-2018-N-4000)

Dear Commissioner Gottlieb:

The National Health Council (NHC) is pleased to provide comments on the Food and Drug Administration's (FDA) solicitation for feedback on FDA's framework for a Real-World Evidence (RWE) Program,¹ and appreciates the opportunity to provide input on this important topic. We fully support FDA's multifaceted approach to implementing its RWE program.

Founded in 1920, the NHC is the only organization that brings together all segments of the health community to provide 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 supports the FDA's efforts to develop a framework that aims to support the evaluation of RWE for potential use in regulatory decision making. The NHC has actively engaged with the FDA and other stakeholders over the past several years to help ensure that the patient voice is meaningfully incorporated. On July 31, 2017, the NHC convened a multi-stakeholder roundtable aimed at gathering patient-community views on RWE. From this workshop, key themes and approaches to increase the patient uptake, co-development, and application of RWE emerged, which are captured in our recently published manuscript,

¹ FDA. Framework for a Real-World Evidence Program. [December 7, 2018](https://www.federalregister.gov/documents/2018/12/07/2018-26546/framework-for-a-real-world-evidence-program-availability).
<https://www.federalregister.gov/documents/2018/12/07/2018-26546/framework-for-a-real-world-evidence-program-availability>

*Patient-Community Perspectives on Real-World Evidence: Enhancing Engagement, Understanding, and Trust.*² Findings include:

- Common definitions for real-world data (RWD) and RWE are vital;
- Acceptable uses of RWE are context specific;
- Partnerships between patient groups and the scientific community support high-quality RWE; and
- Authentic sources of patient-provided data, including patient-generated data (e.g., patient-organization registries), should be considered.

Our responses to the Framework are organized by these findings.

Common definitions for RWD and RWE are vital.

We appreciate that the draft framework includes a standardized, concise definition for both RWD and RWE. Clear and consistent definitions of both RWD and RWE and their applications will be crucial to ensure regulatory certainty and stakeholder understanding. We also appreciate the inclusion of potential examples of RWD and RWE. However, inclusion of “routinely collected” in the definition of RWD may inadvertently limit RWD to administrative claims or electronic health records (EHR). For example, patient registries or patient-generated surveys are sources of real-world data but may not be collected on a regular basis.

Additionally, inclusion of a definition for “patient registry” is helpful. However, it does not differentiate among the various types of patient registries - e.g., patient-powered patient registries and patient-generated research networks, versus a patient registry collected by a pharmaceutical company or other stakeholders. We urge FDA to utilize existing definitions of these types of registries, such as the definitions described in the paper *Defining Patient Registries and Research Networks*.³

To promote alignment with other FDA activities that include stakeholder engagement, we recommend adoption of additional related definitions from FDA's Patient-Focused Drug Development initiative (e.g., patient experience data) as it relates to engaging patients in RWE.

Partnerships between patient groups and the scientific community support high-quality RWE.

The NHC applauds FDA's engagement of external stakeholders, especially patient advocates, in the development of FDA's RWE Framework. In addition to the RWE Framework, it would be helpful to understand how patients and other stakeholders can contribute to RWE development and evaluation.

² Oehrlein, E.M., Graff, J.S., Harris, J. et al. Patient (2019). <https://doi.org/10.1007/s40271-019-00356-z>

³ Workman TA. Engaging Patients in Information Sharing and Data Collection: The Role of Patient-Powered Registries and Research Networks [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Sep. *Defining Patient Registries and Research Networks*. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK164514/>

Development of RWE

To ensure that RWE is patient centered and accurately reflects “real-world” patient experiences, patients should be engaged in RWE development. We echo the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-International Society for Pharmacoepidemiology (ISPE) Special Task Force on Real-World Evidence in Health Care Decision Making recommendation that stakeholder engagement is a good procedural practice when designing, conducting, and disseminating real-world evidence (RWE).^{4,5}

For example, patient input can be useful in hybrid or pragmatic trials and also ensure alignment with FDA’s Patient-Focused Drug Development initiative.⁶ Another example where patient engagement would be helpful and greater clarity is needed is in defining clinically meaningful differences within the context of RWE.

Evaluation of RWE

In addition to the development of RWE, the NHC strongly believes the FDA should develop a process to systematically incorporate patient perspectives in the collection of RWD and evaluation of RWE. This can ensure regulatory decisions appropriately consider patient concerns and address issues most pertinent to patients.

Authentic sources of patient-provided data, including patient-generated data (e.g., patient-organization registries), should be considered.

The NHC appreciates the FDA’s inclusion of patient-generated data as a source of RWD that may be used to generate RWE for regulatory review. We agree with the FDA’s acknowledgement that patient experience data – whether from patient registries, mobile technologies, wearables, etc. - can be useful in overcoming limitations that exist when analyzing EHRs and administrative claims data. For example, Schneeweiss and colleagues describe a novel technique to adjust for residual confounding using external data.⁷

Regarding EHRs, it should also be acknowledged that even if a patient’s experience is recorded as a clinical event by a health care provider in an EHR, it still represents a clinician-selected and interpreted patient experience. Data such as symptoms, patient-reported outcomes (PROs), changes in a patient’s response to medication, or non-serious adverse events may not be recorded by a clinician.

⁴ Berger ML, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. https://ispor.org/docs/default-source/strategic-initiatives/rwe-data-treatment-comparative-effectiveness-guideline.pdf?sfvrsn=b4b98f3b_2

⁵ Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology From Bed to Bench*. 2012;5(2):79-83. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017459>.

⁶ Mullins CD, Vandigo J, Zheng Z, Wicks P. Patient-centeredness in the design of clinical trials. *Value Health*. 2014;17(4):471-5.

⁷ Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: The example of COX2 inhibitors and myocardial infarction. *Epidemiology*. 2005;16(1):17-24. doi: 00001648-200501000-00004 [pii].

Acceptable uses of RWE are context specific.

The NHC agrees that the acceptability of RWE in regulatory decision-making is linked to the context of use. For example, patients engaged in our work generally agreed that RWE should not be used for assessment of new, unapproved therapies. However, patients saw opportunity for RWE to inform new uses of approved therapies in, for example, new patient subgroups (e.g., children), for treatment of comorbid conditions, and to achieve patient-defined endpoints not part of completed clinical studies. These examples are aligned with the FDA's RWE Framework.

While general guidelines for evaluating RWE and conducting studies to generate RWD do exist, the appropriateness of specific study choices must be evaluated on a case-by-case basis in the context of both the regulatory question at hand as well as the other available evidence. We caution FDA from developing guidance that results in a binary assessment of an isolated RWE proposal (i.e., it does or does not fit the regulatory standard) without considering that context. Such contextual considerations will necessitate a case-by-case evaluation that ensures that each RWE proposal is considered as part of a larger body of evidence.

Conclusion

The NHC fully supports the FDA's efforts to enhance the use of RWE in the regulatory decision-making process and believe that the Framework lays a strong foundation for future work in this endeavor. We look forward to guidances the FDA is planning to publish on this topic. As part of the guidance development process, we emphasize that the patient voice must be given the appropriate role throughout the development of the FDA's RWE program and look forward to working with the agency.

Please do not hesitate to contact Eric Gascho, our 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.

Sincerely,



Marc Boutin, JD
Chief Executive Officer
National Health Council