



# AMERICAN SOCIETY OF HEMATOLOGY

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June 17, 2024

## 2024

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Robert M. Califf, MD  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Re: *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Products Guidance for Industry (FDA-2023-D-5470)*

Dear Dr. Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance on the *Real-World Evidence (RWE): Considerations Regarding Non-Interventional Studies for Drug and Products Guidance for Industry (FDA-2023-D-5470)*.

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease (SCD). In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

In 2018, ASH founded the ASH Research Collaborative (ASH RC) to accelerate advancements in hematology by making it more efficient to conduct research, from increasing access to high-quality clinical data to making it easier for individuals with hematologic conditions to participate in research studies. Current ASH RC initiatives focus on multiple myeloma and SCD clinical research. One of its major initiatives is the [ASH RC Data Hub](#), which will be the largest shared information resource with real-world data (RWD) to serve the hematology community. Access to these data can accelerate research and development, support regulatory decision-making, and help identify opportunities for quality improvement in clinical care. The [SCD Research Network](#), the second major component of the ASH RC, is fostering collaborative partnerships to accelerate progress in clinical research and improve outcomes for individuals living with SCD by expediting the development of therapeutics and generating high-quality evidence to support clinical decision-making.

The ASH RC and the Reagan-Udall Foundation for FDA recently launched the [RWE Consortium for SCD](#) to improve the lives of individuals living with SCD through RWE generation and cutting-edge research. The Consortium will develop consensus recommendations on clinical outcomes that will be beneficial for the treatment of people with SCD and apply those standards for use in the ASH RC Data Hub. In recent years, the ASH RC partnered with the [Innovative Genomics Institute \(IGI\)](#) on the "Accelerating Innovations for SCD with RWE" initiative to recommend data to collect and methods to coordinate clinically relevant and reliable longitudinal RWD for genomic therapies for genetic blood disorders, particularly SCD. We were pleased to engage

representatives from FDA and other stakeholders throughout the effort. This initiative led to the following two reports that outline a future for regulatory science and for genomic therapies.

- [Coordinated Registry Network Work Group's Report](#)
- [Genomic Therapies Work Group's Report](#)

ASH encourages the FDA to leverage these efforts and utilize these recommendations as a resource as the Agency continues to engage in this space.

ASH commends the FDA for releasing this draft guidance and appreciates that the Agency is providing critical direction for sponsors of non-interventional observational research using RWD. This guidance is consistent with other FDA RWE guidance and principles and continues the Agency's efforts to establish RWD as an important source of evidence to support regulatory decision making—a step forward for all of medicine. ASH specifically appreciates the consistency of this draft with the Oncology Center of Excellence's Oncology Quality, Characterization and Assessment of Real-World Data (QCARD) Initiative to facilitate high-quality early RWD study proposals in oncology. There is a great deal of interest in RWD-based non-interventional research in hematology to understand natural history of disease, impact of specific disease manifestations (like hemolysis) on end organ toxicity, rates of unexpected adverse events like secondary malignancies following specific types of therapies, development of external control arms, and others. These studies are critical to understanding the risk-benefit analysis of novel therapies in SCD, multiple myeloma, and other therapeutic areas, including the background rates of adverse events attributable to the natural history of the underlying disease. Additionally, RWE noninterventional studies can address health equity and access to new treatments, including the impact of social determinants of health for these diseases—critical elements to understand for many hematologic conditions.

ASH is supportive of the overall guidance, and particularly appreciates (1) the specific considerations provided around study design and analysis; and (2) the Agency's interest in collaborative dialogue to ensure that these issues are handled appropriately. ASH encourages the Agency to consider the following recommendations to help strengthen the final version of this guidance and ensure its successful implementation:

- Provide additional specificity regarding how the Agency determines whether a data source is fit for purpose to support RWD research.
- Include guidance on the development of data sources that can be considered reliable for observational analyses and provide insight on how these sources will be evaluated (i.e., should data sources be fully reevaluated on a case-by-case basis for each new project under consideration?).
- Include a flowchart or checklist summarizing essential attributes of well-designed non-interventional studies to help provide clarification for those who use this guidance.
- Encourage sponsors to include input from patients and their caregivers and other stakeholders (e.g., healthcare providers, researchers) during the design, implementation, and dissemination phases of non-interventional studies.
- Consider including examples of data validation techniques and best practices to ensure acceptable data quality from RWD sources.
- Establish additional training programs, such as the valuable [December 2022 FDA Clinical Investigator Training Course on RWE](#), and develop educational materials for sponsors and researchers.

ASH appreciates the opportunity to provide these comments. Please consider ASH a resource; we would be pleased to provide additional information, support and/or schedule a meeting to discuss these issues further. If you have any questions or would like to arrange a meeting with the Society, please use ASH Director of Government Relations and Public Health, Stephanie Kaplan ([skaplan@hematology.org](mailto:skaplan@hematology.org) or 202-776-0544), as your point of contact.

Sincerely,

A handwritten signature in black ink that reads "Narla Mohandas". The signature is written in a cursive style with a horizontal line underlining the name.

Mohandas Narla, DSc  
President