



# AMERICAN SOCIETY OF HEMATOLOGY

2021 L Street, NW, Suite 900, Washington, DC 20036-4929 **ph** 202.776.0544 **fax** 202.776.0545 **e-mail** ASH@hematology.org

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## 2022

### President

Jane Winter, MD  
Northwestern University  
Robert H. Lurie Comprehensive Cancer Center  
676 N. Saint Clair Street, Suite 850  
Chicago, IL 60611  
Phone 312-695-4538

### President-Elect

Robert Brodsky, MD  
Johns Hopkins University  
Ross Building, Room 1025  
720 Rutland Avenue  
Baltimore, MD 21205  
Phone 410-502-2546

### Vice President

Mohandas Narla, DSc  
New York Blood Center  
310 E 67 th Street  
New York, NY 10065  
Phone 212-570-3056

### Secretary

Cynthia Dunbar, MD  
NHLBI/NIH  
Translational Stem Cell Biology Branch  
Building 10-CRC, Room 5E-3332  
10 Center Drive  
Bethesda, MD 20892  
Phone 301-402-1363

### Treasurer

Mark Crowther, MD  
McMaster University  
50 Charlton Avenue East  
Room L-301  
Hamilton, ON L8N-4A6  
Canada  
Phone 1-905-521-6024

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Martha Liggett, Esq.

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

Re: Draft Guidance for Industry – *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (Docket No. FDA-2021-D-1146)

Dear Dr. Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) on the Agency's draft guidance on *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products*.

### ***About ASH, the ASH Research Collaborative, and Relevant Programs***

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 non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. 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 foster collaborative partnerships that accelerate progress in hematology to improve the lives of people affected by blood diseases. The foundation of the ASH RC is its Data Hub and Sickle Cell Disease Clinical Trials Network. The ASH RC Data Hub captures high-quality, real-world data for research to enhance clinical care and patient outcomes. The first two Data Hub programs, built for multiple myeloma and sickle cell disease, include patient data contributed through electronic health record (EHR) integration, direct data entry through electronic data capture, and external data sources. Analytic datasets are assembled from Data Hub data and are available for display in real-time dashboards. The Data Hub also collects data on the novel coronavirus (COVID-19) and its impact on individuals living with hematologic conditions (COVID-19 Registry). The long-term goal of the ASH RC is to address the entire spectrum of malignant and non-malignant hematologic diseases.

In addition, the ASH RC and the Innovative Genomics Institute (IGI), in collaboration with the U.S. Food and Drug Administration (FDA), have engaged stakeholders to support the development of the ASH RC's Data Hub and to explore methods for Accelerating Innovations for Sickle Cell Disease with Real-World Evidence. The initiative's stakeholder

participants will recommend data to collect and methods to coordinate clinically relevant and reliable real-world data (RWD) for genomic therapies (genome editing and other gene therapies) and genetic blood disorders, particularly sickle cell disease. The findings from the project will apply to all hematologic diseases within the ASH RC Data Hub. More information is available at: <https://www.ashresearchcollaborative.org/s/data-hub/real-world-evidence-initiative>.

### ***Comments on the Draft Guidance***

ASH is pleased to provide comments on the Draft Guidance. Overall, the Society is supportive of this document and the Agency's goal of providing sponsors and other stakeholders with considerations when either designing a registry or proposing to use an existing registry to support regulatory decision-making.

Beyond the ASH RC project mentioned above, there are several registries in which patients with hematologic conditions participate, including those sponsored by the Center for International Blood and Marrow Transplant Research (CIBMTR), the Multiple Myeloma Research Foundation, state-specific cancer registries, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, and the industry-sponsored Connect MM and Insight registries. Data from Connect MM have been used to provide a benchmark for the outcome of patients at a certain stage of their disease and after specific therapy to compare the efficacy of new drugs. The Insight study was used in Europe to provide regulators with data to support the use of Ixazomib. Additionally, the FDA used the CIBMTR database to inform their approval of prophylaxis for acute graft-versus-host disease. Data from these registries have shown that patients in the real world are different from study patients.

The Society agrees with a number of the specific considerations included in the Draft Guidance, though we have additional comments:

- We agree that the relevance and reliability of key indicators are vital considerations to evaluate if a registry is "fit for purpose." We encourage the Agency also to provide feedback to the study sponsor to help inform future registry efforts and ultimately improve reliability. There should also be a standard approach to assessing relevance and reliability so other Center staff reviewing FDA study protocols are consistent.
- We believe that registries enhance the use of real-world data when they include patient data from clinical trial participants and patients who received standard therapy. Registries providing longitudinal data and patient-reported outcomes are also especially valuable.
- We also believe that consideration should be given to assess registries' fit-for-use that capture consecutive patients versus random sampling, their ability to provide contemporaneous control groups, when possible, and to address healthcare disparities. Other criteria for assessing registries' fit-for-use should include an adequate number of patients from groups traditionally underrepresented in biomedical data so that regulatory approvals are based on data from a diverse group of patients impacted by the disease, such as older adults, racial and ethnic minorities, and those residing in rural areas.
- We agree with the Agency's focus on the importance of consistency in registries used for regulatory approval. Registries should report data elements consistently and build quality checks to ensure that data entered are complete, consistent, and accurate. Registries should also have consistent and regular procedures for the entry of follow-up data.

We encourage FDA and Sponsors to not only consider completeness of data assessed in terms of traditional 'missing' information, but rather completeness of information for a particular patient. For example – for the outcome of hospitalization – are all hospitalizations for that individual captured in the registry? It is possible that patients seek care at institutions that are not reflected in the registry – this can impact how representative the outcome is that is being used for assessment.

- We encourage the Agency to discuss endpoints more fully in the Final Guidance. Most regulatory approvals in hematology are based on endpoints that are surrogates of overall survival, such as progression free survival, response rate, and in some cases, biomarker-based endpoints. For a registry to be fit-for-use in approving a drug in a given hematologic condition space, it needs to collect reliable data on all endpoints relevant to regulatory approval for that disease.
- For new registries, we encourage more attention to outcomes not traditionally found in an EHR, such as data gathered for claims and patient-reported outcomes.

ASH appreciates the opportunity to provide these comments. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Deputy 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,



Jane N. Winter, MD  
President