



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

May 1, 2023

2023

President

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

President-Elect

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

Vice President

Belinda Avalos, MD
Atrium Health
215 N. Pine Street, Unit 4703
Charlotte, NC 28202
Phone 980-442-2000

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

Joseph Mikhael, MD, FRCPC, MEd
Translational Genomics Research Institute,
City of Hope Cancer Center
445 N. Fifth Street
Phoenix, AZ 85004
Phone 602-343-8445

Councillors

Christopher Flowers, MD, MS
Alison Loren, MD, MS
Bob Löwenberg, MD, PhD
Charlotte Niemeyer, MD
Sarah O'Brien, MD, MSc
Betty Pace, MD
Jamil Shammo, MD
Wendy Stock, MD, MA

Executive Director

Martha Liggett, Esq.

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

Re: *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (Docket Number: FDA-2022-D-2983)*

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the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (Docket Number: FDA-2022-D-2983)*.

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 (SCD), 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 accelerate the development of evidence-based options for individuals with hematologic conditions by making it more efficient to conduct research. This research varies from increasing access to high-quality clinical data to increasing access for individuals with hematologic conditions to clinical trials. Current ASH RC initiatives focus on SCD and multiple myeloma clinical research. The foundation of the ASH RC is its [Data Hub](#), a technology platform that facilitates the exchange of real-world information by aggregating research-grade data on hematologic diseases. The SCD [Clinical Trials Network](#) optimizes the conduct of clinical trials research in SCD and leverages the Data Hub to collect key information and identify gaps to advance SCD research and treatment.

ASH commends the FDA for releasing this important draft guidance that has the potential to support the advancement of many therapies, including important drugs and biologics for hematologic conditions that are poised as appropriate candidates for external control arms. Many hematologic diseases are rare, which can result in slow trial accrual. Often, a randomized trial accrual is so slow that the landscape evolves faster than a trial can accrue.

External control arms can overcome randomized trial design challenges when applied to rare hematologic diseases with extremely small populations. One recent example of how this can be successful is the use of an external control cohort to support the approval of idecabtagene vicleucel in relapsed myeloma.

Overall, the Society is supportive of the recommendations provided in this document. ASH is pleased to share the following comments about areas where additional clarification will benefit sponsors that we encourage the Agency to consider as the guidance is finalized, implemented, and evaluated over time.

GENERAL FEEDBACK

- **Feedback for sponsors and data providers**

The guidance focuses on potential issues and challenges sponsors and data providers may face related to various aspects in design consideration, data and analysis consideration. Although the draft includes general recommendations when considering each of these aspects, ASH encourages the FDA to include more details about how to address these issues. ASH encourages the FDA to consider strengthening the guidance by providing more details in the following areas:

- Provide specific examples of how the FDA would like information to be prepared and presented for planning meetings with sponsors and data providers around external controls.
- Share examples of what potential outcomes could emerge from these meetings.
- Include more details and specific methods when appropriate to overcome the external control arm design challenges outlined in this guidance.
- Clarify whether certain surrogate endpoints are preferable in externally controlled trials.

- **Use of real-world data (RWD)/real-world evidence (RWE)**

ASH notes that the guidance clarifies that RWD/RWE as an external control will require careful assessment of how and when that use will be implemented. The Society appreciates that the Agency is providing this assessment for sponsors, and ASH encourages the Agency to work with sponsors to ensure that implementation of RWE in trial design meets the expected standards of the Agency. ASH also encourages the FDA to provide recommendations to sponsors on using quality of life and patient reported outcomes data. We agree with the guidance document assessment that some endpoints will be much more suitable for comparison than others. For example, overall survival and health care usage are likely to be suitable for external control arm endpoints. However, in some cases the endpoints can get somewhat esoteric (i.e., in myeloproliferative neoplasms where transfusion-independence, thrombosis-free intervals, and other such endpoints are used) or less available in RWD (gene expression, mutations, fusions). For these reasons, we believe the guidance could benefit from clarification of specific matching strategies that need to be used in comparing cohorts as well as clarification if some surrogate endpoints are preferable to others in externally controlled trials. The Society believes that hematologic conditions such as Waldenström's Macroglobulinemia, primary amyloidosis, molecularly-defined subgroups of patients t(11;14) and potentially BRAF mutated myeloma would be strong candidates for clinical trials that use RWD/RWE in an external control arm.

LINE SPECIFIC COMMENTS

Section III B Table. Summary of Considerations for Assessing Comparability of Data (Line 375)

- *(Line 376) Prognosis:* ASH seeks clarity on whether a sponsor using RWE might first identify a very large potential control group, with the intention of ultimately addressing prognostic factors based on demographic and clinical characteristics through a propensity score matched approach once the composition of the experimental group is known. We see this as a potential way of addressing differences in prognostic features that cannot be known in advance.
- *(Line 376) Missing Data:* From ASH's perspective, the time to consider the implications of missing data is in the initial trial design. If a trial plans to use external controls, it will not help to include data that is not likely to be in the external data set, however much it might be needed for a better understanding of the experimental arm.
- *(Line 216) In Section III A, Design Considerations,* ASH notes that the table does not include language about designation of an index data (time zero) although it is addressed in the guidance. The Society believes this should merit inclusion in this section as well, since identifying an appropriate index data may not be simple in the RWE setting. Additionally, while confounders are touched upon briefly in *Section III A, 2. Characteristics of Study Populations,* we feel that separating out potential confounders that are “disease-related” (i.e., disease severity), and “disease-unrelated” (i.e., age, comorbid conditions) would be important inclusions in the table, as well as social determinants of health that correlate both with ability to be in a trial and with long-term outcomes.

Section III C 1 General Considerations

- *(Line 400):* ASH encourages the FDA to provide examples of successful analysis methods in external control arm trials.

Section III C 4 Additional Analyses

- *(Line 486):* ASH asks for clarification on whether the FDA would consider using a method without proportionality assumption as the primary analysis if the proportional hazards do not hold for the treatment arm vs the external control arm.

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 or 202-776-0544) as your point of contact.

Sincerely,



Robert A. Brodsky, MD
President