



# AMERICAN SOCIETY OF HEMATOLOGY

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May 4, 2020

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

Re: FDA-2019-D-5572: Draft Guidance for Industry – *Inclusion of Older Adults in Cancer Clinical Trials*

Dear Dr. Hahn:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration on the Agency's *Draft Guidance for Industry - Inclusion of Older Adults in Cancer Clinical Trials*.

ASH represents more than 18,000 clinicians and scientists worldwide, who are committed to the study and treatment of 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.

Overall, the Society is supportive of this Draft Guidance and the Agency's goal of increasing participation of older adults in clinical trials. There are a number of hematologic malignancies prevalent among the elderly, including lymphoma, acute myeloid leukemia, myelodysplastic syndromes, and multiple myeloma. The Society agrees that these individuals must be included in clinical trials to benefit from clinical advances. Unfortunately, today older adults are underrepresented in clinical trials for acute myeloid leukemia (AML) even though the average age at diagnosis is 68 years, which limits our understanding of how these drugs work in elderly people. When older adults were enrolled in myeloma studies, dose-reduced lenalidomide bortezomib and dexamethasone (RVD-lite) was found to allow elderly and frail patients to benefit from this therapy.

By increasing enrollment of older patients in trials, trial outcomes will reflect the real-world patient population. At present, stringent inclusion criteria that exclude patients with any organ dysfunction and comorbid conditions may result in drug approval, but do not inform use nor predict outcome in the real world. Many published reports show that novel drugs achieve inferior results and have more toxicities when used in the real-world post approval than was observed in the registrational clinical trials. As noted in the Draft Guidance, there are now scales to assess patient physical status, ranging from frail to fit, and many elderly patients are frail and excluded from current clinical trials; again these frail patients need to be included in clinical trials, to reflect those who may benefit from such therapies in the real world, allowing for the true assessment of efficacy and toxicity for these patients.

In terms of the details included in the Draft Guidance, ASH agrees with the specific recommendation to evaluate drug interactions and concomitant medication use in early phase

## 2020

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trials to understand safety and inform eligibility and monitoring in later phase studies (lines 120-122). The Society further suggests adding another bullet to the Early Clinical Development recommendations to recommend routine capture of comorbidity information to inform interpretation of safety data in early clinical trials. Comorbid conditions are common among older adults and are readily collected in practice. Including these data in early phase clinical trials can facilitate identification and interpretation of safety signals or lack thereof in older adult populations and facilitate evidence-based design of studies aimed to enroll representative older adults.

Due to the importance of this recommendation, the language could be strengthened by replacing the qualifier “if appropriate” (line 116) with a more specific term such as “if the intervention tested could apply to older adults.” Moreover, lack of enrollment on early phase trials impedes evaluation of safety as well as evaluation of age-related differences in pharmacology during early phase drug development. This lack of knowledge can both serve as a barrier to subsequent enrollment of older adults in later trials and complicates the ability to adapt study design including dosing/scheduling of drug in later phase trials to optimize the risk-benefit ratio. Importantly, if older adults are not represented in early phase trials, sponsors should provide a scientifically based justification for lack of enrollment during drug development.

ASH also notes additional concerns about the inclusion of older adults in trials that the FDA could address in the final Guidance:

- Many early phase trials include upper age restrictions and the language in the Draft Guidance may not go far enough to mitigate this barrier. ASH recommends the Agency include stronger language to encourage or require sponsors to remove upper age limitations in clinical trials, when a drug is likely to be used by elderly individuals.
- Older adults have more difficulty making study-related appointments and undergoing study-related tests. ASH encourages the Agency to consider recommendations about making required components of trials more reflective of standard of care in older populations, for whom mandatory study visits and tests are a major obstacle to enrollment.
- The document provides guidance for large trials to be sensitive to special populations, but not smaller trials or single arm studies, which may be necessary for smaller subpopulations of patients (e.g., older AML patients with a specific molecular abnormality). The Society suggests emphasizing that these recommendations apply broadly to cancer clinical trials and that older adults should also be included in smaller and single arm studies.
- The Society believes that exclusion criteria (e.g. organ impairment, history of prior malignancies) that would disproportionately exclude older adults be well-justified scientifically, not just in the use of the criteria, but in the cutoff/level utilized (e.g. creatinine clearance <60ml/min vs <50/40 vs <30, etc.). On a related note, studies that traditionally utilize clinician-discretion/gestalt for age-related eligibility (e.g. “suitable for 7+3 induction” for AML; “eligible for high-dose therapy and autologous transplant” for myeloma) should use objective criteria based on existing literature where possible, and characterize the aging-associated domains for the included older adult to understand the health of the individuals deemed eligible for more intense treatment.
- In the “consider collecting additional information for older adults” section, ASH recommends language that better identifies geriatric metrics as the purpose of this guidance in lieu of “additional information.”

Again, ASH appreciates the opportunity to provide these comments. Please consider ASH as 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,



Stephanie Lee, MD, MPH  
President