Via Electronic Submission

May 5, 2020

Stephen M. Hahn, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

Subject: Inclusion of Older Adults in Cancer Clinical Trials (Docket No. FDA-2019-D-5572-0001)

Dear Dr. Hahn:

The Association for Clinical Oncology (the Association) appreciates the opportunity to provide input on U.S. Food and Drug Administration (FDA) draft guidance for the Inclusion of Older Adults in Cancer Clinical Trials. The Association is a national organization representing more than 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality patient care, our members are committed to ensuring that evidence-based practice for the prevention, diagnosis, and treatment of cancer are available to all Americans. The Association supports major quality initiatives that enhance performance measurement and improvement, clinical practice guidelines, big data analytics, and the value of cancer care.

The Association applauds the Agency for developing guidance with recommendations for including an adequate representation of older adults in cancer clinical trials to better enable evaluation of the benefit-risk profile of cancer drugs in this population. We commend Richard Pazdur, MD, director of the FDA Oncology Center of Excellence and his staff, specifically Harpreet Singh, MD, for their leadership and willingness to work with the Association and the American Society of Clinical Oncology (ASCO) on this important issue. We agree with the FDA that evidence is lacking when it comes to the treatment of older adults with
cancer due to their under-representation in clinical trials. Despite FDA’s efforts to increase the inclusion of older adults in clinical trials, still more evidence is needed to better inform treatment decisions.

This draft guidance provides strong recommendations and appropriately urges sponsors and researchers to include older adults in clinical trials when they can be safely and ethically enrolled. The Association appreciates that the draft guidance focuses on recommendations related to early phase studies, trial design, and post-market research.

**Early Clinical Development**

The Association agrees with the FDA that it is critically important to enroll older adults in early phase studies, when appropriate. As our population ages and more patients survive into the 8th decade of life and beyond with concomitant medical illness, it is important to enroll older adults who may otherwise be excluded because of concomitant drug use therapy for comorbid conditions, especially when evaluating drug-drug interactions early in drug development. Toxicity and safety in early phase data are important to assess in an adequate number of patients at particular risk for a safety signal to be achieved. Lower numbers of older adults enrolled in the early phases of trials may lead to an incomplete understanding of how best to refine the trial design and dosing for later phase studies and post-market use of therapeutics in the older adult population. Concomitant medication use should exclude patients from trial participation only when clinically relevant—known or predicted—drug-drug interactions or potential overlapping toxicities could impact the safety of trial participants or compromise efficacy.

In March 2018, a *Journal of Geriatric Oncology* review article “Are phase I trials safe for older patients?” noted that few clinical studies include older patients, in particular few phase I trials. In the review of safety and efficacy data in older adults in phase I trials, age did not seem to be
associated with more toxicity or less efficacy.¹ These data support allowance of patients with comorbidities not directly associated with drug toxicity to be enrolled to early phase trials. Additionally, confidence in dose derivation in early phase trials will be increased when older adults are included in escalation and expansion cohorts, potentially leading to fewer examples of approved drugs with high rates of dose reductions, drug holds, and discontinuations due to adverse events. Without older adult enrollment, there is a lack of understanding of potential differences in clinical pharmacology (e.g., pharmacokinetics, pharmacodynamics) and therefore exposure-activity and exposure-toxicity relationships due to age. Encouraging enrollment, particularly in those over 75 years, would not only improve understanding of drug activity in older patients but may also improve scientific knowledge of dose-exposure-age relationships across the entire enrolled population.

We acknowledge that there are some barriers to the enrollment of older adults in early phase studies, but many of these may be overcome by broadening eligibility criteria; providing more information about trials to oncologists and prospective enrollees; promoting decentralized trials to allow more sites to participate; and assisting qualified participants in navigating logistical barriers to enrollment. We recommend the FDA include in the final guidance a recommendation that sponsors should 1) expand work with oncologists in non-academic sites to provide opportunities where more older patients are likely to seek treatment and 2) work with social and behavioral scientists, patient advocates/navigators, geriatricians, and geriatric oncologists to consider the needs of older adults when designing clinical trials.² This could also aid in effective recruitment strategies for older adults. Additionally, as noted in the draft guidance, we support encouraging sponsors of cancer trials to discuss their plans for enrolling older adults with FDA staff, particularly when enrollment may be challenging. The FDA could highlight

² L.A. Levit et al. Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop. J Natl Cancer Institute. 110(11), October 2018
incentives for companies to enroll older adults in registration trials during these meetings, including the potential for broader label indications and the possibility that clinicians may use the agent in broader patient populations if sufficient evidence is collected. The FDA could also consider post-marketing commitments for companies that fail to follow these plans and/or achieve adequate numbers of older adults in their registration trials.

Clinical Trials

The Association agrees that sponsors should make every effort to enroll older adults in their pivotal randomized trials, and to utilize flexible approaches to trial design and analysis. We also believe sponsors should implement the eligibility criteria recommendations developed by ASCO and Friends of Cancer Research, with involvement of FDA and the National Cancer Institute. Trials routinely include eligibility criteria that have little relevance to the drugs being tested and that effectively exclude older adults. These stringent eligibility criteria result in younger and healthier trial participants, which can limit the generalizability of results and result in greater likelihood of trials failing to accrue or taking longer to accrue. Sponsors should implement these recommendations and provide a rationale for why the recommended criteria cannot be adopted.

We appreciate the FDA’s emphasis in the draft guidance on the importance of including adults specifically over the age of 75 and their highlighting of the lack of evidence in patients in this older age population. ASCO recommends that trial sponsors report detailed age distribution (by decade) of the population included in the study, not just the age ranges of population, and also conduct stratified analysis for age

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groups aged 65 years and older and 75 years and older to understand the drug’s benefits and risk in all older adults.⁴

The Association also agrees with the FDA’s encouragement of the collection of additional information to include not only age and performance status, but elements from geriatric assessment tools such as functional status and cognitive function, frailty measures, and assessment of comorbidities. We also agree that the incorporation of validated patient-reported outcomes instruments will increase information collected.

**Post-market Commitments and Research**

The FDA has issued several guidance documents encouraging sponsors to study the effects of drugs on older adults (particularly if they represent the majority of people who are likely to be prescribed the drug) and to modify trial design and eligibility criteria to increase enrollment of older patients. Clinical trials typically have been conducted with a select group of healthier, younger patients and are focused on bringing new treatments to market quickly. However, once drugs are approved, sponsors seldom conduct additional studies to test the effectiveness of treatments on older adults who were underrepresented in the registration trial.⁵ This means that drug approvals are based on data from younger, healthier participants, and that trials do not provide adequate information about drug efficacy, safety, and dosing in older adults.⁶ The Association agrees that data on older adults should be captured in premarket clinical trials, but sponsors should also plan to collect data on


a broader population, including older adults, in the post-market setting. The use of real-world data in studies, registries, or secondary data analysis can also be useful in providing additional evidence on the older adult population. We believe there is a need for more evidence to be included in the drug label describing use in older adults to aid in the safe and effective use of therapeutics and better inform treatment decisions.

Clinical trials represent the gold standard for developing evidence and are used to establish the standard of care. As such, enrolling a representative sample of older adults in trials remains critical to improving the evidence base in geriatric oncology. We thank the FDA for the opportunity to comment on this draft guidance and look forward to continuing our collaborative efforts as this guidance is finalized and the recommendations are implemented. Please contact Shimere Williams Sherwood at Shimere.Sherwood@asco.org with any questions and for further discussions.

Sincerely,

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Chair of the Board, ASCO Association for Clinical Oncology