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Via Electronic Submission

August 6, 2019

Norman Sharpless, MD
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Subject: Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs, Draft Guidance for Industry (Docket No. FDA-2019-D-1265-0001)

Dear Dr. Sharpless:

The American Society of Clinical Oncology (ASCO) appreciates the opportunity to provide input on the U.S. Food and Drug Administration's (FDA's) draft guidance recommending approaches for sponsors of clinical trials to broaden eligibility criteria, when scientifically and clinically appropriate, and increase enrollment of underrepresented populations in their clinical trials. ASCO represents nearly 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality patient care, ASCO members are committed to ensuring that evidence-based practice for the prevention, diagnosis, and treatment of cancer are available to all Americans. ASCO supports major quality initiatives that enhance performance measurement and improvement, clinical practice guidelines, big data analytics, and the value of cancer care.

Broadening Eligibility Criteria and Clinical Trial Designs

ASCO applauds the Agency for the release of this draft guidance focused on promoting enrollment practices that lead to improved clinical trial participation and inclusion of more diverse populations. We agree with the Agency that measures such as this can improve the trials' representation of the

population that is most likely to use the approved therapy. ASCO has supported extensive efforts in this area in recent years because we believe that broadening eligibility criteria will lead to the collection of trial data that are more relevant to the real-world population of patients that our members care for every day. ASCO supports and agrees with efforts to maximize generalizability of clinical trial results, while also protecting the safety of clinical trial participants.

As noted in this draft guidance, as well as in previous ASCO comments on FDA draft guidances on Cancer Clinical Trial Eligibility Criteria[1] and in the ASCO and Friends of Cancer Research *Journal of Clinical Oncology* Special Series, *Broadening Eligibility Criteria to Make Clinical Trials More Representative*[2], participants with multiple concomitant illnesses and therapies are often excluded because of concerns that such conditions could affect the determination of the investigational drug's safety or effectiveness. ASCO and Friends' eligibility criteria address this issue with the following recommendations:

- Patients with treated or clinically stable brain metastases should be routinely included in trials and only excluded if there is compelling rationale.

- In initial dose-finding trials, pediatric-specific cohorts should be included based on strong scientific rationale for benefit.

- Later phase trials in diseases that span adult and pediatric populations should include patients older than age 12 years.

- Patients with HIV, Hepatitis B virus, or Hepatitis C virus infection who are healthy and have low risk of AIDS or Hepatitis B or C-related outcomes should be included absent specific rationale for exclusion.

- Renal function criteria should enable liberal creatinine clearance, unless the pharmacology of the investigational agent requires renal excretion or suggests otherwise.

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[1] https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/pdf/ASCO-FOCR-Comments-FDA-Eligibility-Criteria_03May2019.pdf

[2] Kim, ES; Bruinooge, S; Roberts, S.; Ison, G.; Lin, N, et al. Journal of Clinical Oncology Special Series. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. November 2017. https://ascopubs.org/doi/full/10.1200/JCO.2017.73.7916

- Patients with prior or early stage concurrent malignancies should be included, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low.

- A standard of inclusion, unless otherwise specified, would give investigators the responsibility to provide rationale and use their own clinical judgment and discretion as to why patients should be excluded from trial participation. Known or suspected risks of the investigational therapy should be the primary factors that warrant exclusion of patients.

- These risks should be outlined in a concise, easy-to-read format and provided to investigators, pharmacists, and the clinical research team for review.

- Consistent with the draft guidance's approach of eliminating or modifying phase 2 criteria in phase 3 trials, eligibility criteria should be reconsidered at predefined time points or events and adjusted, if needed, during the clinical development plan to enable greater inclusion with an aim of having the study population in late-stage or registration trials reflect as closely as possible the indicated population

Additionally, ASCO supports and applauds the FDA efforts to ensure that sponsors provide a strong clinical and/or scientific justification for exclusion of trial participants in the trial protocol. ASCO shares FDA's concern that there is an underrepresentation of certain populations, including older adults with comorbid health conditions and racial and ethnic minorities, and believes trials should include meaningful endpoints that are important for older adults and other disparate populations.[3]

The draft guidance outlines various trial designs for sponsors to consider in enrolling a broader population. ASCO agrees and supports the Agency's suggestion for the use of inclusive trial practices and trial designs such as expansion cohorts and adaptive clinical trials. ASCO commented on FDA guidance in the past regarding these various trial designs and master protocols and believes these methodological approaches can make clinical trials easier for sites and patients, using one protocol with multiple cohorts rather than multiple protocols. However, as we previously commented, ASCO recommends the FDA provide more specific guidance in two areas: 1) transitioning from the dose escalation to

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[3] Laura A Levit, Harpreet Singh, Heidi D Klepin, Arti Hurria, Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop, *JNCI: Journal of the National Cancer Institute*, Volume 110, Issue 11, November 2018, Pages 1163–1170, https://doi.org/10.1093/jnci/djy169

cohort expansion phase, and 2) in scenarios where inclusion/exclusion criteria or the disease indication for an expansion cohort is sufficiently different from those in the dose escalation cohort. As these situations are critical to patient safety, the FDA might consider requiring the collection of additional safety data.

Other Considerations for Improving Enrollment

FDA notes in this draft guidance that beyond the limitations of narrow eligibility criteria, there are other challenges to enrolling patients in clinical trials. ASCO applauds FDA's efforts to minimize individual participant-level barriers that can negatively impact enrollment. ASCO's efforts have identified such barriers including: patient-specific issues with access and cost of care; a lack of trust in the health care system or clinical research; linguistic, cultural, or literacy-related barriers; contextual factors such as family and community engagement; and stringent exclusion criteria, or other study design-related barriers. Provider-associated barriers have been reported as well, whether at the health system/organizational level (e.g. funding/staffing for clinical trial sites) or related to individual providers failing to inform minority patients of clinical trial availability. ASCO stresses that underrepresentation results not only from failure to enroll in clinical trials, but also from differences in retention rates of minority populations while on study. Studies also consistently demonstrate that having a low income is an independent predictor of reduced clinical trial participation, even after adjusting for comorbidity, education, and age older than 65 (i.e., with universal access to Medicare). Data suggest that this is due to the sensitivity of patients with low income to the cost of cancer care.

Therefore, ASCO agrees with the suggestions in the draft guidance aimed at making trial participation less burdensome for participants, including financial assistance for expenses associated with the costs incurred by participation in clinical trials (e.g. travel, childcare, lodging).[4] Many of the draft recommendations have been previously identified by ASCO as necessary to improve trial participation, including by older adults, residents in rural areas, cognitively impaired individuals, and other underrepresented and underserved minorities. Specifically, we support reducing the frequency of study visits, including redundant testing, and leveraging electronic communication and mobile technologies whenever appropriate. We also thank the Agency for clarifying that the FDA does not consider reimbursement for

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[4] Winkfield, Karen M., et al. "Addressing financial barriers to patient participation in clinical trials: ASCO policy statement." *Journal of Clinical Oncology* 36.33 (2018): 3331-3339. https://ascopubs.org/doi/full/10.1200/JCO.18.01132

reasonable travel expenses to trial sites or lodging as undue influence, and we agree that payment for participation is best addressed by the Institutional Review Board (IRB).

ASCO appreciates the FDA's recommendation to "involve patients, patient advocates, and caregivers in the design of clinical trial protocols." In addition to frequency of study visits, these groups may also provide key feedback on whether the type, number, and frequency of study tests and procedures is reasonable. They may help trial sponsors determine whether elements of the trial should be optional.

ASCO agrees in principle with other draft recommendations to enhance inclusiveness in clinical trial participation, but it is unclear in practice how some recommendations will impact the established culture of clinical research programs. For example, recommendations to work directly with communities during protocol development or to incorporate strategies for public outreach, are vaguely defined and may fail to be effective without further clarification. In contrast, ASCO strongly supports recommendations to ensure clinical trial sites be geographically diverse and to explore agreements to foster inter-site exchange of medical records for purposes of participant retention. We also support FDA's recommendation to engage patient advocacy groups early in the drug development process to elicit suggestions for the design of trials, particularly those of rare diseases and conditions. We note that the degree of impact for proposed changes will depend upon clarity in the final guidance and FDA's willingness to enforce and/or incentivize adoption of these requirements on sponsors and research programs. For example, sponsors may be more willing to enroll broader populations in trials if the drug label includes information about safety and efficacy information specific to those populations.

ASCO agrees with the Agency's proposal to encourage trial participation by making available an open-label extension study for rare diseases and conditions after early-phase studies and by ensuring that all trial participants, including those who received placebo, ultimately have access to the investigational treatment. ASCO agrees with the recommendation to ensure all participants have access to the investigational treatment and recognizes there are scenarios, such as add-on trials or when existing therapies are minimally effective or have serious adverse effects, when the use of a placebo can be appropriate. Additionally, sponsors should provide a rationale for a placebo trial design and blinding in randomized controlled clinical trials. ASCO also agrees with the draft guidance to re-enroll patients from early-phase trials into later-phase trials when studying the effectiveness of treatments, particularly in rare diseases, in limited circumstances when medically appropriate and without safety issues.

In addition to the enrollment and retention practices outlined in the draft guidance to enhance inclusiveness, ASCO has developed strategies to improve diversity including oncology community awareness/engagement, improving clinical research practice, and addressing patient cultural/contextual factors. The FDA's draft guidance will complement activities of ASCO and other organizations related to insurance coverage for clinical trial participation (including refining coverage and prior authorization policies that may impede clinical trial enrollment), addressing clinical trial-related patient out of pocket costs (e.g. through removing impediments to targeted financial support), and improving the fragmented Medicaid policy related to clinical trial coverage.

In conclusion, we thank you for the opportunity to comment on this important and critical draft guidance to modernize clinical trials by improving patient enrollment and access to investigational therapies, trial accrual, and protect the safety of trial participants. Please contact Shimere Williams Sherwood at Shimere.Sherwood@asco.org with any questions and for further discussions.

Sincerely,

Howard A. Burris, III, MD, FACP, FASCO
President, American Society of Clinical Oncology