**Submitted Via Electronic Submission**

June 25, 2024

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

**Subject: Cancer Clinical Trial Eligibility Criteria; Series of Three Draft Guidance – Performance Status, Laboratory Values, and Washout Periods and Concomitant Medications (Docket Nos. FDA-2024-D-1377; FDA-2024-D-1402; and FDA-2024-D-1376)**

Dear Dr. Califf:

The Association for Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) thank the U.S. Food and Drug Administration (FDA), particularly the Oncology Center of Excellence (OCE), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER), for the recent release of three additional draft guidance for cancer clinical trial eligibility criteria. ASCO and *Friends* agree with the Agency that a clinical trial's eligibility criteria are essential to defining the characteristics of the trial's study population and provide more detailed characterization of the investigational drug's benefit-risk profile across the patient population. We appreciate FDA's continued leadership over the past several years encouraging researchers and sponsors to broaden eligibility criteria and provide sound scientific rationale for decisions that have the potential to limit patients' opportunities for trial participation. We are grateful for FDA's involvement in our ASCO-*Friends* joint initiative that encourages broader eligibility criteria for cancer clinical trials and has produced recommendations related to performance status (PS), laboratory values, and washout periods and concomitant medications.

ASCO and *Friends* applaud the FDA's recognition that "some eligibility criteria have become commonly accepted over time or used as a template across trials without a clear scientific or clinical rationale or justification. In other cases, eligibility criteria can be deliberately restrictive, even though it is not clinically merited." The recommendations in each of the draft guidance documents aim to maximize the generalizability of clinical trial results while also maintaining the safety of clinical trial participants. Broadening eligibility criteria will allow for the inclusion of more diverse patient populations on trials, which will lead to the collection of trial data that is relevant to the real-world population of patients that will use the FDA-approved therapies. We also applaud the FDA for ensuring that the sponsors of these trials provide a strong scientific and/or clinical rationale for exclusion of potential trial participants in the trial protocol. We are pleased to see that the draft guidance documents' content and strategies to modernize eligibility criteria for cancer clinical trials build upon the ASCO-*Friends* recommendations, which were developed by a consortium of patient advocates, investigators, drug/biotechnology manufacturers, and regulators.[1][2][3]

ASCO and *Friends* offer the following comments and suggestions for FDA consideration as the Agency finalizes the documents.

**Performance Status**

We are very pleased that the draft guidance closely follows the recommendations included in our ASCO-*Friends* manuscript. Inclusion of patients with low-functioning PS will help ensure that evidence from clinical trials has greater applicability to patients with cancer, given the demographics of patients with cancer. We support the FDA's suggestion that

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[1] Magnuson A, Bruinooge SS, Singh H, Wilner KD, Jalal S, Lichtman SM, Kluetz PG, Lyman GH, Klepin HD, Fleury ME, Hirsch B, Melemed A, Arnaldez FI, Basu Roy U, Schenkel C, Sherwood S, Garrett-Mayer E. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Performance Status Work Group. Clin Cancer Res. 2021 May 1;27(9):2424-2429. doi: 10.1158/1078-0432.CCR-20-3868. Epub 2021 Feb 9. PMID: 33563633; PMCID: PMC8102305.

[2] Spira AI, Stewart MD, Jones S, Chang E, Fielding A, Richie N, Wood LS, Thompson MA, Jones L, Nair A, Mahal BA, Gerber DE. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. Clin Cancer Res. 2021 May 1;27(9):2416-2423. doi: 10.1158/1078-0432.CCR-20-3853. Epub 2021 Feb 9. PMID: 33563636; PMCID: PMC8102342.

[3] Harvey RD, Mileham KF, Bhatnagar V, Brewer JR, Rahman A, Moravek C, Kennedy AS, Ness EA, Dees EC, Ivy SP, Ebbinghaus SW, Schenkel C, Uldrick TS. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group. Clin Cancer Res. 2021 May 1;27(9):2400-2407. doi: 10.1158/1078-0432.CCR-20-3855. Epub 2021 Feb 9. PMID: 33563635; PMCID: PMC8102304.

sponsors should incorporate exploratory cohorts early in the development process and use early-stopping rules in response to safety concerns. This early experience in a broader array of patients will enable later phase trials to resemble the intended-use population more closely. We also support the FDA's discussion of alternate ways to measure functional status, including the use of wearable devices. We agree that lower performance status may be due to disease burden and broadening the population enrolled in the trials will help demonstrate how treatment response may improve functioning. We suggest that the FDA could also incorporate into the guidance discussion of a broader array of trial design approaches – including parallel cohorts, embedded cohorts, and pragmatic designs.[4]

**Laboratory Values**

We thank the FDA for their thoughtful draft guidance on the use of laboratory values for eligibility determination in cancer clinical trials. This guidance adroitly addresses the need for flexibility in eligibility criteria to improve trial inclusivity and representativeness. We particularly agree with the guidance's consideration around the need for careful selection of the target population, especially in terms of including patients with organ impairments like renal or hepatic dysfunction. This approach is essential for developing treatments in a way that accurately reflects use in real-world patient populations. We also commend the guidance's focus on ensuring that laboratory value-based criteria are used only when necessary to protect patient safety. This approach not only safeguards patient safety but also enhances the scientific validity of trials by ensuring that the results are applicable to a wider patient population, which is critical for the generalizability of trial outcomes.

As the FDA seeks comments on the current draft, we would like to suggest enhancements to further align the guidance with clinical practices:

- The guidance on permitting a single repeat test within a certain period may be restrictive. We recommend expanding this to allow more than one reassessment for critical values like creatinine clearance. This would acknowledge the natural variability and real-world management of patients' conditions, preventing unnecessary exclusions due to transient laboratory values.
- We propose the inclusion of language that discourages the use of certain laboratory markers, such as albumin or lactate dehydrogenase (LDH), as surrogates for

[4] Le-Rademacher J, Mohile S, Unger J, Hudson MF, Foster J, Lichtman S, Perlmutter J, Dotan E, Extermann M, Dodd K, Tew W, Klepin H, Wildes T, Sedrak MS, Jatoi A, and Little RF. *Trial Design Considerations to Increase Older Adult Accrual to National Cancer Institute Clinical Trials.* JNCI Monographs, Volume 2022, Issue 60, December 2022, Pages 135–141, https://doi.org/10.1093/jncimonographs/lgac023.

performance status. These markers may not accurately reflect the patient's clinical status or be associated with the safety and efficacy of the therapy.

- We also suggest that the guidance include recommendations on flexible testing intervals associated with laboratory procedures, particularly in late phase trials (e.g., phase III). This adjustment would help reduce patient burden and enhance participation and retention in trials.

We support this draft guidance and believe that these enhancements will ensure high safety standards in cancer clinical trials and promote more patient-centered clinical trial design.

**Washout Periods and Concomitant Medications**

We are pleased that the guidance states that washout periods should be based on relevant clinical and laboratory parameters associated with the preceding therapy. We agree that time-based washout periods should not be used unless scientifically justified. We believe the guidance should also consider situations where concomitant medications may reduce the activity of the investigational drug. For example, corticosteroids can reduce the activity of immune-based therapies. We appreciate that the guidance discusses the potential for modification of the dosage or regimen of the concomitant medication or investigational therapy to account for drug-drug interactions. Finally, we agree with the FDA that sponsors should evaluate drug-drug interactions early in development and incorporate accumulated pharmacologic information as soon as possible to minimize washout periods and allow concomitant medications across clinical trial phases.

**Reporting on Implementation**

We commend the FDA for its leadership in broadening eligibility criteria through release of these draft guidance documents and finalization of the previous guidance documents. We hope that the release of these documents focuses attention on these important issues and prompts sponsors to modify their trial design to make trials more inclusive and representative of the broader patient population. In discussions with OCE staff, we understand that these documents set an expectation for inclusive eligibility criteria and enable reviewers to refer to these standards during review of pivotal trial designs. ASCO and *Friends* encourage FDA to report on implementation of this guidance to help the public understand how sponsors are using the guidance and where additional work may be needed. We know that tracking and reporting across applications can be challenging, and we are eager to work with FDA to help monitor and report on adoption.

We thank you for the opportunity to comment on the most recent FDA draft guidance for cancer clinical trials eligibility criteria and the opportunity to work with the Agency on this important issue and the very thorough and thoughtful guidance documents. We look forward to working with you in implementation of these criteria in cancer clinical trials. If you need additional information, please contact Shimere Sherwood, Director, Science and Research Policy, ASCO, shimere.sherwood@asco.org or Mark Stewart, Vice President, Science Policy, Friends of Cancer Research, mstewart@focr.org.

Sincerely,

Eric P. Winer, MD, FASCO
Association Chair of the Board
Association for Clinical Oncology

Ellen V. Sigal, PhD
Chairperson and Founder
Friends of Cancer Research