June 10, 2021

Guidance Document Submission

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Food and Drug Administration
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Silver Spring, MD 20993-0002

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Silver Spring, MD 20993-0002

Dear Drs. Janet Woodcock, Richard Pazdur, Patrizia Cavazzoni, and colleagues at the FDA,

The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) formally submit the following draft guidance documents for consideration by the Food and Drug Administration (FDA). The content and strategies to modernize eligibility criteria for oncology clinical trials build upon recommendations developed by a consortium of stakeholders composed of patient advocates, drug/biotech manufacturers, investigators, biostatisticians, and regulators.

In 2020, ASCO and *Friends* convened multi-stakeholder work groups to address the following common trial eligibility criteria: 1) Washout Periods, 2) Concomitant Medications, 3) Performance Status, 4) Laboratory Reference Ranges and Testing Intervals, and 5) Prior Therapies. ASCO and *Friends* published on February 9, 2021 a joint research statement and four supporting manuscripts containing consensus recommendations based on the review of evidence, consideration of the patient population, and consultation with the research community. In this submission, ASCO and *Friends* have adapated the recommendations outlined in the published manuscripts to serve as the foundation for three proposed FDA draft guidance topics. Prior ASCO-*Friends* consensus recommendations on broadening eligibility criteria (2017) are strengthened by Final Guidance for Industry documents that were released by FDA in July 2020.

Our recommendations aim to maximize the generalizability of clinical trial results while also maintaining the safety of clinical trial participants. We believe that the rationale for excluding patients from eligibility for a cancer clinical trial should be clearly articulated and should be based on the specific therapy under investigation and the study population to help improve trial accrual, ensure optimal patient access, and maximize information learned during the clinical trial.

FDA guidance indicates to sponsors the importance of designing more representative trials, as do discussions between FDA reviewers and sponsors. We value FDA's partnership on this project and welcome any questions or comments you may have regarding the proposed guidance documents enclosed in this submission. Thank you for your consideration of these proposed guidance documents and your continued dedication to ensuring cancer clinical trials are scientifically sound, broadly accessible and representative of the intended use population of the intervention under study.

Sincerely,

Julie R. Gralow, MD, FACP, FASCO
Senior Vice President and Chief Medical Officer
American Society of Clinical Oncology

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

Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications

Guidance for Industry

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Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) _____ 301-___-____, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010[others?].

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I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products regulated by CDER and CBER for the treatment of cancer. Specifically, this guidance includes recommendations regarding the appropriate use of washout period and concomitant medication exclusions. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, who are responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[2]

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice.

[1] This guidance has been prepared by the Division of [....] in the Center for Drug Evaluation and Research [*in cooperation with other centers?*] at the Food and Drug Administration.

[2] Kim ES, Uldrick TS, Schenkel C, et al: Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement. Clinical Cancer Research, 2021.

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II. BACKGROUND

A washout period is defined as a time between treatment periods that is intended to allow a prior therapy and/or its effects on the body to be eliminated from the body or reduced to acceptable levels and to thereby prevent mis-interpreting observations about study-related treatments that could be attributed to prior therapies. Currently, washout periods are often employed as non-specific surrogates for a clinical (e.g., adverse event) or laboratory (e.g., absolute neutrophil count) measurement that are included to ensure participant safety and prevent confounding of observations (safety or efficacy) on trial. Scientific or clinical justification for washout/waiting periods may exist for cancer trials following any type of previous treatment, including surgery, therapeutic radiation, cytotoxic chemotherapy, small molecule/tyrosine kinase inhibitors, monoclonal antibodies (with and without drug conjugates), and immunotherapies.[3]

Prohibited concomitant medications create eligibility and timing challenges, since patients receiving anticancer therapies often have comorbidities such as pain, diabetes, gastrointestinal or cardiovascular disorders, that require drug therapy. On average, patients with cancer take 5 chronic non-cancer medications, not including those that may be used to manage adverse events associated with anticancer therapy.[4] As patients age, the prevalence of comorbidities and associated polypharmacy increases.[5] While some medications may be necessarily prohibited early in investigational agent development, continued prohibition across trial phases reduces the applicability of a therapy to a broader patient population following approval.

Both washout period and concomitant medication exclusions are specified heterogeneously for registration trials across similar therapeutic classes and diseases, and lack of scientific justification is common.[3]

III. RECOMMENDATIONS

These recommendations should inform sponsors and investigators as they draft study eligibility criteria but are not intended as template language for trial protocols. Eligibility criteria should be tailored to the investigational treatment and patient population being studied. For that reason, the recommendations are inclusive, rather than specific and prescriptive. Recommended language

[3] Harvey RD, Mileham KF, Bhatnagar V, et al: Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group. Clinical Cancer Research, 2021

[4] Turner JP, Shakib S, Singhal N, et al: Prevalence and factors associated with polypharmacy in older people with cancer. Supportive Care in Cancer 22:1727-1734, 2014

[5] Balducci L, Goetz-Parten D, Steinman MA: Polypharmacy and the management of the older cancer patient. Annals of oncology : official journal of the European Society for Medical Oncology 24 Suppl 7:vii36-vii40, 2013

such as "clinically significant expected adverse event" should be replaced or supported by disease- and drug- specific, evidence-based examples.

Information gained from pre-clinical studies and early trials about investigational agent adverse event profiles and pharmacology should be incorporated as soon as possible in subsequent clinical trials to minimize unnecessary washout periods and liberalize concomitant medication allowances.

A. Washout Periods

1. Time-based washout periods (e.g., "at least 14 days must have elapsed since last treatment with [therapy] before the patient may be enrolled") should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified.

2. Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations (e.g., "[laboratory test value] must have returned to within normal limits prior to enrollment/initiation of study treatment").

3. Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

B. Concomitant Medications

1. Concomitant medication use should only exclude patients from trial participation when clinically relevant known or predicted drug-drug interactions or potential overlapping toxicities will impact the safety of trial participants or potentially compromise efficacy of the treatment being studied.

Cancer Clinical Trial Eligibility Criteria: Performance Status

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I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products regulated by CDER and CBER for the treatment of cancer. Specifically, this guidance includes recommendations regarding broader inclusion of patients with low-functioning performance status (PS). This guidance is intended to assist stakeholders, including sponsors and institutional review boards, who are responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[2,3]

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice.

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[2] Kim ES, Uldrick TS, Schenkel C, et al: Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement. Clinical Cancer Research, 2021.

[3] Magnuson A, Bruinooge SS, Singh H, et al: Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Performance Status Work Group. Clinical Cancer Research, 2021.

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II. BACKGROUND

Performance status (PS) is one of the most common eligibility criteria in oncology trials. Many trials are limited to high-functioning participants (i.e., "good" PS) and exclude low-functioning patients (i.e., "poor" PS)[4] based on one of two main scales: Eastern Cooperative Oncology Group (ECOG) and Karnofsky (KPS). PS is included as a common eligibility criteria and stratification factor because low-functioning PS (i.e., ECOG PS2-4 and KPS ≤70) is often correlated with lower overall survival (OS) and progression-free survival (PFS).[5,6,7] However, this practice prevents trial enrollment for many patients and limits generalizability of trial results. The underlying etiology for low-functioning PS is important. For patients whose low-functioning PS is due to disease burden, cancer-directed treatment may result in improved PS with tumor control and symptom alleviation, especially with highly effective treatments. However, current PS scales do not differentiate causes of low-functioning PS.

Additionally, there are limitations to PS assessments. PS determination is inherently subjective, which can affect inter-rater reliability[8] and invite potential bias particularly for patients at the borderline between values. For example, studies demonstrate that clinicians assign patients aged >65 years higher numeric ECOG PS[9] scores than younger patients, despite no difference in objectively measured physical activity.[10] Additionally, PS is less predictive of cancer-related

[4] Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. *J Clin Oncol.* 2017;35(33):3745-3752.

[5] Arboe B, Halgren Olsen M, Duun-Henriksen AK, et al. Prolonged hospitalization, primary refractory disease, performance status and age are prognostic factors for survival in patients with diffuse large B-cell lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplantation. *Leuk Lymphoma.* 2018;59(5):1153-1162.

[6] Song T, Wan Q, Yu W, et al. Pretreatment nutritional risk scores and performance status are prognostic factors in esophageal cancer patients treated with definitive chemoradiotherapy. *Oncotarget.* 2017;8(58):98974-98984.

[7] Wang JR, Habbous S, Espin-Garcia O, et al. Comorbidity and performance status as independent prognostic factors in patients with head and neck squamous cell carcinoma. *Head Neck.* 2016;38(5):736-742.

[8] Chow R, Bruera E, Temel JS, Krishnan M, Im J, Lock M. Inter-rater reliability in performance status assessment among healthcare professionals: an updated systematic review and meta-analysis. *Support Care Cancer.* 2020.

[9] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

[10] Broderick JM, Hussey J, Kennedy MJ, DM OD. Patients over 65 years are assigned lower ECOG PS scores than younger patients, although objectively measured physical activity is no different. *Journal of geriatric oncology.* 2014;5(1):49-56.

outcomes for older adults[11,12] and may be less relevant for more recently developed anticancer treatments that have different toxicities than chemotherapy.

III. RISK AND BENEFITS TO INCLUDING PATIENTS WITH LOW-FUNCTIONING PS

When considering inclusion of patients with low-functioning PS on clinical trials, sponsors should consider the following potential benefits and risks:

A. Potential Benefits

1. Increased Number of Patients Eligible and Shortened Enrollment Time

Studies have demonstrated that of patients deemed ineligible for a clinical trial, exclusion was related to poor PS in a significant proportion of patients, with variability across disease type, investigational therapy, and therapy line.[13,14]

2. Improved Assessment of Patients' Overall Health Status, Particularly in Older Adults

Most patients with cancer are aged ≥65 years, however, existing PS scales are inadequate in this population.[15] Multiple studies have demonstrated that alternate clinical tools, such as the geriatric assessment, are better than PS at evaluating older adults' overall health status[16] and better than KPS at predicting chemotherapy toxicity[17]. Restrictive PS eligibility criteria contribute to the pervasive age disparity between trial participants and the overall cancer population, raising concerns about whether PS is unjustly limiting older populations' ability to participate in trials.[18,19]

3. Improved External Validity of Trial Results

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[11] Broderick JM, Hussey J, Kennedy MJ, DM OD. Patients over 65 years are assigned lower ECOG PS scores than younger patients, although objectively measured physical activity is no different. *Journal of geriatric oncology.* 2014;5(1):49-56.

[12] Ghosn M, Ibrahim T, El Rassy E, Nassani N, Ghanem S, Assi T. Abridged geriatric assessment is a better predictor of overall survival than the Karnofsky Performance Scale and Physical Performance Test in elderly patients with cancer. *J Geriatr Oncol.* 2017;8(2):128-132.

[13] Network ACSCA. Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report. In:2018.

[14] Lara PN, Jr., Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol.* 2001;19(6):1728-1733.

[15] Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol.* 2011;29(25):3457-3465.

[16] Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2002;20(2):494-502

[17] Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol.* 2011;29(25):3457-3465.

[18] Ludmir EB, Mainwaring W, Lin TA, et al. Factors Associated With Age Disparities Among Cancer Clinical Trial Participants. *JAMA Oncol.* 2019.

[19] Canoui-Poitrine F, Lievre A, Dayde F, et al. Inclusion of Older Patients with Cancer in Clinical Trials: The SAGE Prospective Multicenter Cohort Survey. *Oncologist.* 2019;24(12):e1351-e1359.

Strict eligibility criteria may result in a group of trial participants who do not reflect the clinical and demographic diversity of patients with the indicated disease. As a result, the efficacy and safety outcomes experienced by participants with high-functioning PS may not adequately predict the outcomes for patients with low-functioning PS.[20,21] Enrolling a broader population of trial participants will help to provide experience that clinicians and patients will rely on in a post-approval setting.

B. Potential Risks

1. Increased Adverse Events

Rates of adverse events (AEs) may be greater in ECOG PS2 participants as compared to PS0 and PS1 participants, and this may influence patients' ability to complete the intended course of treatment, their outcomes and their ability to comply with study procedures necessary to assess their outcomes. Low functioning PS patients risk AEs with standard therapy options as well as investigational options, and thus participation on a trial may not necessarily pose a greater risk of AEs compared to standard therapy for a particular patient. Because targeted therapies often produce higher response rates, PS2 patients may experience a greater therapeutic index in a targeted therapy trial than standard of care (e.g., cytotoxic chemotherapy), even if their absolute rate of AEs is higher than in patients with PS0 and PS1. Where the comparative tolerability between an investigational agent and standard therapy is less clear, including PS2 patients (who may be more sensitive to toxicity) may unmask subtle differences. Including a subset of PS2 patients will add important safety data to facilitate decision-making for patients in the post-approval setting. Generating information about safety, tolerability, and efficacy in earlier phase trials with the agent may help to counteract clinicians' lack of familiarity with the investigational agent and concerns about the tolerability and safety.

2. Potential Impact on Trial Outcome Data

The risk of inferior trial outcomes by inclusion of low-functioning PS participants is a potential concern to sponsors, especially if compared to historical cohorts including high-functioning PS participants. In addition, FDA commentary has further indicated a willingness to restrict primary efficacy analysis to the participant subset who meet more conventional eligibility criteria when a sponsor enrolls a broader range of participants. FDA also notes that including a broader group of participants could offer benefits, such as additional information in drug labeling and/or reduced post-marketing commitments.[22]

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[20] Azad AA, Eigl BJ, Leibowitz-Amit R, et al. Outcomes with abiraterone acetate in metastatic castration-resistant prostate cancer patients who have poor performance status. *Eur Urol.* 2015;67(3):441-447.

[21] Blackhall F, Ross Camidge D, Shaw AT, et al. Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer. *ESMO Open.* 2017;2(3):e000219.

[22] Beaver JA, Ison G, Pazdur R. Reevaluating Eligibility Criteria - Balancing Patient Protection and Participation in Oncology Trials. N Engl J Med. 2017 Apr 20;376(16):1504-1505.

PS information can be considered as a stratification factor – similar to other prognostic markers identified in oncology – rather than a justification for excluding patients from trials. When safe, inclusion of participants with low-functioning PS provides valuable evidence to guide clinical care for more patients. Outcomes in low-functioning PS participants can also better inform statistical considerations for future trials.

IV. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients with low-functioning PS in cancer clinical trials. Patients with low-functioning PS should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining patient safety. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol.

A. Recommendations for inclusion based on PS

Patients with ECOG PS2 (or KPS 60-70) should be included unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations.

1. *PS eligibility criteria should be based on the patient population in which the intervention is expected to be applied in clinical practice.*

2. *PS eligibility criteria should be continually re-evaluated and modified throughout the drug development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later phase trials (e.g. phase II/III) should generally mirror the intended use population and ECOG PS2 (or KPS 60-70) patients should be included, unless safety concerns have manifested in earlier phase trials. The rationale for exclusion should be justified and stated explicitly.*

3. *Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients.*

4. *Performance status data should be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria.*

B. Recommendations for alternative trial designs

Consider alternative trial designs, such as pre-specified cohorts with lower-functioning PS that are exempt from the primary analysis, to encourage inclusion of these patients and collect safety data. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup

analysis should be determined during the study design phase and its implications for marketing and post-marketing requirements discussed with FDA when appropriate.

A. Recommendations for additional assessments of functional status

Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS2 patients and patients aged ≥ 65 years, such as Activities of Daily Living (ADLs) and Instrumental ADLs.

Cancer Clinical Trial Eligibility Criteria: Laboratory Reference Ranges and Testing Intervals

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Cancer Clinical Trial Eligibility Criteria: Laboratory Reference Ranges and Testing Intervals
Guidance for Industry[1]

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I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products regulated by CDER and CBER for the treatment of cancer. Specifically, this guidance includes recommendations to optimize the use of laboratory tests when considering trial eligibility. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, who are responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[2,3]

[1] This guidance has been prepared by the Division of [....] in the Center for Drug Evaluation and Research [*in cooperation with other centers??*] at the Food and Drug Administration.

[2] Kim ES, Uldrick TS, Schenkel C, et al: Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement. Clinical Cancer Research, 2021.

[3] Spira AI, Stewart MD, Jones S, et al: Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. Clinical Cancer Research, 2021

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population(s) likely to use the drug in clinical practice.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Laboratory tests are one of the most common categories of eligibility criteria in clinical trials. Minimum values for organ function tests are often required for therapies that are either metabolized by or pose toxicity risks to specific organ systems, although clinical trial eligibility criteria often include specific values that assess the function of organ systems not affected by the investigational therapy, as well.

Despite their importance to protect trial participants from treatment-related risks, there is potential for unintended consequences if laboratory test-based eligibility criteria are overly restrictive. Strict renal and hepatic function requirements were documented as one of the most common reasons for excluding potential patients from clinical trials.[4] In oncology, most patients are older adults, a population in which some degree of organ dysfunction is common but rarely has clinical consequences. Laboratory test abnormalities may also represent reversible manifestations of the underlying malignancy.

Laboratory test values may differ substantially between testing facilities and among populations. Among 38 standard laboratory tests analyzed among more than 3,000 healthy individuals in the National Health and Nutrition Examination Survey (NHANES), only five (glucose, phosphorus, potassium, total bilirubin, and uric acid) did not show significant racial/ethnic differences in distribution.[5] For many laboratory tests, there are significant differences according to gender (e.g., alanine aminotransferase (ALT), total bilirubin, cholesterol, bicarbonate, calcium, and total protein[6]) and age (e.g., alkaline phosphatase, creatinine clearance, postprandial glucose, and platelet count). When these differences are not accounted for, individuals may be unnecessarily excluded from trial participation and trial participants may not adequately reflect the population with the disease under study.

Analysis of industry-sponsored trials over time shows little variation in laboratory test-based eligibility criteria that suggests these criteria may be carried forward despite the accumulation of clinical experience – on trials or after approval that should be considered in formulating the

[4] Malik L, Lu D: Eligibility criteria for phase I clinical trials: tight vs loose? Cancer Chemotherapy and Pharmacology 83:999-1002, 2019

[5] Lim, E., Miyamura, J. & Chen, J. J. Racial/Ethnic-Specific Reference Intervals for Common Laboratory Tests: A Comparison among Asians, Blacks, Hispanics, and White. Hawaii. J. Med. Public Health 74, 302–310 (2015).

[6] Vastola, M. E. *et al.* Laboratory Eligibility Criteria as Potential Barriers to Participation by Black Men in Prostate Cancer Clinical Trials. *JAMA Oncol.* **4**, 413–414 (2018).

criteria.[7,8] Tracking clinical development across phases suggests a similar phenomenon of static laboratory test-based criteria that do not incorporate new or developing knowledge.[9]

III. RECOMMENDATIONS

Laboratory tests should be used as exclusionary criteria only when clearly necessary due to safety concerns. Among medical therapies, substantial differences in metabolism/excretion and toxicity profiles render broad recommendations challenging. Data and experience from similar in-class molecules should be used to inform selection of laboratory requirements for eligibility criteria with modification where relevant to the specific agent under study. Furthermore, as investigational therapies advance from early phase to late phase development, laboratory eligibility criteria should be adjusted based on clinical experience. The current "cut and paste" approach should be challenged and clinical trial protocols continuously re-evaluated as recommended in FDA guidance.[10]

A. Scientific justification for laboratory tests as exclusion criteria

Laboratory tests should only be used as exclusionary criteria when scientifically justified and when abnormal test results confer safety concerns.

1. **Laboratory test requirements should be customized to the therapy/therapies under investigation.** Ultimately, laboratory test requirements should be established with consideration of study therapy pharmacokinetics and pharmacodynamics and anticipated toxicities. For instance, if a therapy does not undergo hepatic metabolism and is not expected to cause hepatic toxicity, strict hepatic function eligibility criteria may not be necessary, or at a minimum, there should be very broad entry criteria. Wherever data is available from similar agents, previous experience should be used as a guide. In some instances (e.g., PD1/PDL1 checkpoint inhibitors) pharmacology and toxicity profiles are similar across agents, allowing use of comparable laboratory-related eligibility criteria. In other instances (e.g., ALK inhibitors), each individual drug may have different requirements depending on its individual PK/PD profile. Importantly, restrictions from earlier clinical trials should not be carried forward automatically but should be modified to reflect the experiences of patients in earlier trials and in post-market use.

2. **Laboratory test-related eligibility criteria should not be used as a surrogate for performance status or the presence of comorbidities.** Due to the older age of most cancer patients and the likelihood of identifying laboratory abnormalities of no clinical

[7] Jin S, Pazdur R, Sridhara R: Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. Journal of Clinical Oncology 35:3745-3752, 2017

[8] Spira AI, Stewart MD, Jones S, et al: Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. Clinical Cancer Research, 2021

[9] Ibid.

[10] U.S. Food and Drug Administration. Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry. (2019). Available at: https://www.fda.gov/media/123745/download.

significance, the use of laboratory tests to identify sufficiently healthy individuals is likely to result in unnecessary exclusion of potential trial participants. Instead, clinical trial protocols should specify functional status and comorbidity requirements in line with previous recommendations, as appropriate.[11]

3. **Consider adjusting laboratory-based eligibility criteria broadly rather than in specific clinical scenarios.** A frequent clinical trial practice is to relax laboratory-related eligibility criteria in populations more likely to have baseline laboratory abnormalities (e.g., allowing lower levels of renal function in patients with genitourinary malignancies, or allowing greater degrees of hepatic dysfunction in patients with primary or metastatic liver cancer). If these population subgroups can be treated effectively and safely, consideration should be given to applying similar laboratory-related eligibility criteria more broadly.

4. **Laboratory-based eligibility criteria should be limited to the clinical concern.** As an example, in clinical trials of therapies that may prolong the QTc interval, low levels of electrolytes such as potassium, calcium, and magnesium may increase the risk of cardiac arrhythmias. A common response to this concern is to require levels of these electrolytes to be within normal limits. This results in unnecessary exclusion of patients whose electrolyte levels may be slightly *above* the normal range, even though there is no increased risk of QTc prolongation. In these cases, precise protocol writing (e.g., requirements for laboratory tests to be above the lower limit of normal rather than within normal limits) with an understanding of the intent of the criteria and the normal variations among people as outlined above is of utmost importance. Furthermore, opportunities to allow for correction to the appropriate test value range should be allowed. While safety is of utmost concern, protocols should reflect the intended use population for the treatment being evaluated and not situations where the trial data cannot realistically be applied to post approval scenarios.

5. **Inter-laboratory variation should be accounted for when selecting laboratory-based eligibility criteria**. It is important to consider thresholds rather than specific normal values. Upper limits of normal (ULNs) can vary across labs, and criteria should reflect multiples of ULN, rather than absolute numbers (akin to National Cancer Institute [NCI] CTCAE [Common Terminology Criteria for Adverse Events] criteria). Across academic medical centers, there are substantial differences in serum creatinine determination, with laboratory site accounting for 50% and time of assay performance accounting for another 15% of this variation.[31] CrCl should be accounted for by accurate measurements, and options for direct measurements (24-hour urine CrCl) be allowed rather than using formulas that simply estimate the clearance (e.g., Cockcroft-Gault).

B. Accounting for potential normal variations in laboratory references values

[11] Lichtman, S. M. *et al.* Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. *J. Clin. Oncol.* **35**, 3753–3759 (2017).

Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and hormonal changes).

1. **The impact on trial eligibility, enrollment, and generalizability should be assessed when selecting laboratory-based eligibility criteria.** Laboratory abnormalities occur frequently without clinical significance. Reference intervals generally include 95% of test results obtained from a presumably healthy population. The chance that a healthy person has a test result falling outside this range is 5% for a single test, but rises to 64% for 20 tests (e.g., complete blood count and metabolic panel).[32] As noted previously, the likelihood of test results outside reference ranges is far greater among individuals with cancer and may not be of clinical significance with respect to the treatment being studied.

2. ***Demographic differences in laboratory test results, and their implication across populations, should be understood.*** Given differences among people based on race and ethnicity, those criteria that are included should be sufficiently broad to allow for these natural variations.[21,33] It should be noted that persons who have undergone surgery or take medications to align with their gender identity may have altered "normal" lab values despite being healthy.[34,35]

C. Routine reassessment of laboratory-based exclusion criteria

Routine reassessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier to later phase clinical trials.

1. ***Eligibility criteria should be expanded based on earlier clinical experience and in the absence of safety concerns.*** First-in-human trials should incorporate strict laboratory-related eligibility criteria as a precautionary measure, as the clinical pharmacology and toxicity profile of the novel therapy are not known. Once these characteristics have been established, laboratory-related eligibility criteria should be adjusted to reflect this experience. Currently, the initial criteria are often carried forward to later phase trials, resulting in unnecessarily strict requirements and exclusion of potential patients, and limiting applicability of results. Similarly, criteria and experience from drugs of a similar class may be used to formulate eligibility criteria.

2. ***Broadening eligibility criteria by employing less stringent requirements for laboratory eligibility requirements should be accounted for when assessing baseline and on-treatment abnormal laboratory values.*** In addition to grading of laboratory abnormalities using CTCAE, which accounts for the most severe laboratory value aberration, interpretation of results should take into account CTCAE adverse event attribution. If patients have baseline laboratory abnormalities prior to starting treatment, they may have more frequent and more severe laboratory abnormalities after initiating therapy. To account for this possibility, one approach is to focus on the degree of change in laboratory values, as conveyed by shift tables.[36] Shift tables display baseline laboratory

values and the shift at post-dose, which helps determine the potential impact of the investigational therapy on these results.

D. Increased intervals between protocol-specified tests

Increasing the intervals between protocol-specified tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of protocols from earlier to later phase clinical trials.

1. ***Restrictive test intervals could result in reduced interest in and commitment to clinical trials among patients, clinicians, and investigators.*** Oncology patients, in general, spend a substantial amount of time for treatment of their cancer. The average informed consent form for oncology trials is over 4,000 words and describes hundreds of procedures.[37] Unnecessary testing and procedures can lead to more patients choosing not to participate in trials or dropping out over the course of a study. Minimizing testing frequency to reflect what is truly needed to assess safety and efficacy may improve interest, enrollment, and adherence on clinical trials.