# Cancer Clinical Trial Eligibility Criteria: Laboratory Values

## Guidance for Industry, IRBs, and Clinical Investigators

***DRAFT GUIDANCE***

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**Oncology Center of Excellence (OCE)**
**Center for Drug Evaluation and Research (CDER)**
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*Contains Nonbinding Recommendations*

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# Cancer Clinical Trial Eligibility Criteria: Laboratory Values Guidance for Industry, IRBs, and Clinical Investigators[1]

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## I. INTRODUCTION

The purposes of eligibility criteria for cancer clinical trials are to select the intended patient population and reduce potential risks to trial participants. However, eligibility criteria are sometimes more restrictive than necessary, and expanding eligibility criteria to be more inclusive is one trial design consideration that may improve the diversity of clinical trial populations.[2] This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of investigational drugs[3] regulated by CDER and CBER for the treatment of cancer.[4] Specifically, this guidance includes recommendations for selecting appropriate laboratory values as trial eligibility criteria to avoid unjustified exclusions of diverse trial participants. This guidance intends to assist interested parties, including sponsors and/or institutional review boards (IRBs), 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.[5] Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation Research (CBER) at the Food and Drug Administration.

[2] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, references to *drugs* include both human drug products and biological products regulated by CDER and CBER, unless otherwise specified.

[4] See other cancer clinical trial eligibility criteria guidances for industry: *Brain Metastases* (July 2020); *Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020); *Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections* (July 2020); *Patient with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020); *Available Therapy in Non-Curative Settings* (July 2022).

[5] For the purposes of this guidance, the terms *trial* and *study* are used interchangeably.

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. The agency recognizes that some eligibility criteria may have become commonly accepted over time or used as a template across trials, but such criteria should be carefully considered and be appropriate for a specific trial context. 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.[6,7]

Appropriately broadening cancer trial eligibility criteria can improve the generalizability of trial results and provide a more detailed characterization of the investigational drug's benefit-risk profile across the patient population likely to use the drug in clinical practice.

This guidance describes general principles for selecting laboratory value-based eligibility criteria, e.g., minimum blood counts, with a focus on later phase trials. Overly restrictive laboratory-based exclusion criteria can adversely affect accrual and diversity for clinical trials, including cancer trials.

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 value-based eligibility criteria are one of the most common categories of eligibility criteria in clinical trials. Laboratory values within a range demonstrating that organs are functioning above a minimum acceptable level are often required for drugs that pose toxicity risks to specific organ systems or are metabolized and cleared by that organ system(s). However, clinical trial eligibility criteria often include specific laboratory values that may exclude patients, even when these considerations may not apply.

Despite the importance of eligibility criteria to protect trial participants from treatment-related risks when applied appropriately, there is potential for unintended consequences if laboratory value-based eligibility criteria are overly restrictive. Strict renal and hepatic function requirements have been documented as one of the most common reasons for excluding potential

[6] Kim ES, Uldrick TS, Schenkel C, et al, 2021, Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO–Friends of Cancer Research Joint Research Statement, Clin Cancer Res, 27(9):2394-2399.

[7] Spira AI, Stewart MD, Jones S, et al., 2021, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group, Clin Cancer Res, 27(9):2416-2423.

patients from clinical trials.[8] In oncology, many patients are older adults- a population in where some degree of organ dysfunction is common. However, such organ function status does not universally result in clinical consequences. Laboratory value abnormalities may also represent manifestations of the underlying malignancy. Additionally, laboratory values may vary among healthy individuals across different racial and ethnic population; therefore laboratory-value criteria that do not take these differences into account can hamper efforts to enroll a diverse and representative population.[9,10]

Analysis of industry-sponsored trials in oncology over time shows little variation in laboratory value-based eligibility criteria, suggesting that these criteria may have been carried forward from early-phase to late-phase trials despite the accumulation of clinical experience – during trials or after approval – that should be considered in formulating the criteria in late-phase trials.[11,12]

One potential concern that sponsors may have regarding broadening eligibility criteria is that laboratory-related adverse events during the course of a trial may occur more frequently and/or with higher severity if the enrolled population has baseline laboratory-related abnormalities. This possibility does not outweigh the importance of enrolling participants representative of the population that would receive the drug if approved. Importantly, this reality highlights the need for randomized trials. Randomized controlled trials are designed to distinguish the effects of a drug from other influences, which greatly facilitates the characterization of the drug's safety in addition to demonstration of its effectiveness. Excluding patients with abnormal baseline laboratory values in randomized trials without an evidence-based safety concern has little benefit to a drug development program as the between-arm differences in a randomized trial provide more interpretable data on the drug's adverse effects than other safety comparisons.

## III. RECOMMENDATIONS

Laboratory values should be used as exclusionary criteria only when clearly necessary to mitigate potential safety concerns. Among medical therapies, substantial differences in metabolism, excretion, and toxicity profiles render broad recommendations across all trials challenging. Restrictions based upon renal, hepatic, or bone marrow function should reflect specific, well-reasoned concerns regarding drug exposure that might result in toxicity, or organ susceptibility to toxicity, based upon available data (e.g., pre-clinical data, known safety profiles

[8] Malik L, Lu D, 2019, Eligibility Criteria for Phase I Clinical Trials: Tight vs Loose?, Cancer Chemother Pharmacol, 83(5):999-1002.

[9] Lim E, Miyamura J, Chen JJ, 2015, Racial/Ethnic-Specific Reference Intervals for Common Laboratory Tests: A Comparison among Asians, Blacks, Hispanics, and White, Hawaii J Med Public Health, 74(9):302-310.

[10] Vastola ME, Yang DD, Muralidhar V, et al., 2018, Laboratory Eligibility Criteria as Potential Barriers to Participation by Black Men in Prostate Cancer Clinical Trials, JAMA Oncol, 4(3):413-414.

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

[12] See footnote 7.

of other relevant products).[13] Furthermore, as investigational drugs advance from early phase to late phase development, laboratory eligibility criteria should be adjusted based on additional available clinical data (e.g., renal/hepatic impairment studies, drug-drug interaction studies, etc.). When developing eligibility criteria for later phase studies, appropriate efforts to broaden eligibility criteria should be implemented, removing or loosening any criteria no longer justified by specific concerns. Acknowledging that safety is of utmost concern, protocols should be written with an aim to enroll participants who reflect those expected to use the drug, if approved.

### A. Scientific Justification for Laboratory Tests as Exclusion Criteria

- **Laboratory value-based eligibility criteria should be customized to the drug(s) under investigation.** Laboratory value requirements should be established based on the investigational drug's mechanism of action, pharmacokinetics and pharmacodynamics (PK/PD), and anticipated toxicities. For instance, if an investigational drug does not undergo hepatic metabolism and is not expected to cause hepatic toxicity, hepatic entry criteria should be sufficiently broad to avoid unnecessary exclusions of patients (e.g., only excluding patients with elevations in ALT or bilirubin that are multiple-fold above upper limit of normal (ULN)). Wherever data are available from similar agents in a therapeutic class, previous experience should be used as a guide. In some instances (e.g., programmed cell death receptor-1/programmed cell death-ligand 1 checkpoint inhibitors), pharmacology and toxicity profiles are similar across agents, facilitating use of comparable laboratory-related eligibility criteria, as long as they are otherwise well-justified. In other instances (e.g., ALK inhibitors), each individual drug may have different requirements depending on its individual PK/PD profile. Importantly, laboratory value-related 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, as applicable.

- **Laboratory-based eligibility criteria should be only as restrictive as necessary to mitigate the clinical risk(s) of concern.** As an example, in clinical trials of drugs 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.

- **Inter-laboratory variation should be accounted for when selecting laboratory-based eligibility criteria.** Broadening laboratory-based ranges for eligibility, when appropriate, may be one way to factor in laboratory variation.

[13] See the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).

### B. Accounting for Potential Expected Variations in Laboratory Values

- **The impact on trial eligibility, enrollment, and generalizability should be assessed when selecting laboratory-based eligibility criteria.** Consider the target population of study. For a trial that seeks to evaluate the safety and efficacy of a drug in renal or urothelial cancer, allowing patients with lower levels of baseline renal function would facilitate generation of data that reflects the real-world population. For a trial that seeks to evaluate safety and efficacy in patients with highly advanced and aggressive cancer including those with hepatic metastases, allowing greater degrees of hepatic dysfunction while ensuring appropriate safety measures to protect patients, would facilitate drug development in a patient population with high unmet need. In cases such as these, early studies investigating alternative dosing regimens in patients with organ impairment may be beneficial.[14]

- **Demographic differences in laboratory test results, and their implication across populations, should be understood when eligibility criteria are written.** Given natural variations in laboratory values among people that may be associated with race and ethnicity, those criteria that are included should be sufficiently broad to allow for these natural variations.[15,16]

- Laboratory abnormalities occur frequently without clinical significance. Reference intervals generally include 95% of test results obtained from a presumably healthy population. 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. When appropriate for specific laboratory analytes, sponsors can consider including in the protocol the ability to conduct a single repeat test within a certain period where this is considered appropriate.

### C. Routine Reassessment of Laboratory-Based Exclusion Criteria

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

- **Eligibility criteria should be adjusted based on accumulating clinical experience.** First-in-human trials investigating first-in-class drugs or use of novel platforms should generally incorporate conventional laboratory-related eligibility criteria as a precautionary measure, as the clinical pharmacology and toxicity profile of the novel drug in humans are not known. For subsequent drugs in the same class, if there is known clinical pharmacology and toxicity data on drugs with similar mechanism of action, these

[14] Ibid.

[15] See footnote 10.

[16] Knight K, Wade S, Balducci L, 2004, Prevalence and Outcomes of Anemia in Cancer: A Systematic Review of the Literature, Am J Med, 116(7A), 11S-26S.

criteria can be revised early and often. Sponsors should carefully evaluate eligibility criteria, especially as the trials move to late phases, removing or reducing restrictions that had been incorporated in early phase trials when such restrictions are not scientifically justified and would result in unnecessarily narrowing the study population.