Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications

Guidance for Industry, IRBs, and Clinical Investigators

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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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 subjects. However, eligibility criteria are sometimes more restrictive than necessary, and expanding eligibility criteria to be more representative is one trial design consideration that may improve the applicability of clinical trial data to U.S. populations. This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of investigational drugs or biological products[2] regulated by CDER and CBER for the treatment of cancer, although many of the concepts may apply more broadly to other clinical areas.[3] Specifically, this guidance includes recommendations regarding the appropriate use of washout periods and concomitant medication exclusions. This guidance is intended to assist interested parties, including sponsors, clinical investigators, and institutional review boards (IRBs), who are responsible for the development and/or oversight of clinical trials.

A clinical trial's eligibility criteria (inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population.[4] 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] 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.

[3] 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); *Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020); *Available Therapy in Non-Curative Settings* (July 2022); *Lab Values* (July 2026); *Performance Status* (July 2026). 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.

[4] 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 subjects 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 subject 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.[5,6]

Appropriately broadening cancer trial eligibility criteria can improve the generalizability of trial results and provide a more detailed characterization of the therapy's benefit-risk profile across the patient population 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

Washout periods and concomitant medication exclusions are commonly included in cancer clinical trials. However, these exclusions often vary across trials for similar therapeutic classes and diseases and should be appropriate for the trial under consideration.

A washout period is a treatment-free period between the most recent anti-cancer treatment and treatment with the investigational drug. This treatment-free period is intended to allow a prior therapy and/or its effects on the body to be eliminated or reduced to acceptable levels preventing additional toxicity and/or interfering with the pharmacokinetics/pharmacodynamics (PK/PD) of the investigational drug when a new therapy is started. For clinical trials, this is also important to prevent misinterpreting safety or efficacy observations about study-related treatments that could be attributed to prior therapies. While washout periods are most often intended to allow clinical or laboratory adverse events to resolve that may be related to the prior treatment, there may be

[5] 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.

[6] 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.

other scientific or clinical justifications (e.g., surgical, radiation, systemic, or transplant therapy).[7]

Concomitant medications are any prescription or non-prescription medications (i.e., over-the-counter drugs) a subject may be taking in addition to the investigational drug product(s). Although this guidance is focused on concomitant medications, certain products such as dietary supplements that are not regulated as drugs or biological products may also interfere with drug clearance. Patients receiving anticancer therapies often have comorbidities that require drug therapy or cancer-related issues that require supportive care (e.g., prophylactic antimicrobials or treatment of symptoms related to cancer therapy). Undue restrictions to concomitant medications may result in hindered trial enrollment, as the average patient with cancer takes five chronic non-cancer medications, not including those that may be used to manage adverse events associated with anticancer therapy.[8] The prevalence of comorbidities and associated polypharmacy are more common in older patients, and exclusion of specific concomitant medications could result in preferentially excluding older patients from cancer clinical trials.[9] Exclusion of specific concomitant medications should be scientifically and clinically justified in the context of the known drug profile. Sponsors should consider removing exclusions carried over from earlier trials as increased drug metabolism, clearance, and drug-drug interaction information becomes available and suggests certain concomitant medications should no longer be prohibited. Sponsors may, if applicable, provide alternatives to prohibited concomitant medications in trial protocols.

III. RECOMMENDATIONS

Eligibility criteria should be tailored to the population being studied and the goals of the clinical investigation.[10] For that reason, the recommendations in this guidance reflect a general approach to broadening eligibility criteria related to washout periods and concomitant medications, rather than providing specific or prescriptive criteria. Exclusion criteria should be justified with a disease- and drug-specific scientific rationale as opposed to vague statements. For example, sponsors should avoid statements such as, "Exclude patients taking concomitant medications expected to increase the risk for a clinically significant adverse event."

Information about the PK/PD of the expected previous treatments could inform the appropriate duration of the washout period. In addition, accumulated pharmacologic information for the investigational drug should be incorporated as soon as possible in subsequent clinical trials to

[7] Harvey RD, Mileham KF, Bhatnagar V, et al, 2021, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group, Clin Cancer Res, 27(9):2400-2407.

[8] Turner JP, Shakib S, Singhal N, et al, 2014, Prevalence and Factors Associated with Polypharmacy in Older People with Cancer, Support Care Cancer, 22:1727-1734.

[9] Balducci L, Goetz-Parten D, and Steinman MA, 2013, Polypharmacy and the Management of the Older Cancer Patient, Ann Oncol, 24(7): vii36-vii40.

[10] For certain complex biological products, such as cell or gene therapy products, other considerations may apply. These should be discussed with the appropriate CBER Office.

minimize unnecessary washout periods and liberalize concomitant medication allowances. Conducting drug-drug interaction evaluations early in drug development may inform selective dosing of the investigational or co-administered drug to a subject in subsequent trials and may facilitate enrollment of more patients in mid- to late-stage clinical trials.

A. Washout Periods

- Relevant clinical and laboratory parameters, based on the characteristics of preceding therapy, 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 or acceptable baseline prior to enrollment/initiation of study treatment").

- 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 scientifically justified and relevant PK/PD of the prior therapy should be taken into consideration. If time-based washout periods are included in trial eligibility criteria, justification should be clearly specified in the protocol (e.g., provide data or justification indicating that a washout is needed so that a subject is not exposed to specific unreasonable risks). A washout period may be appropriate if prior therapy can result in delayed anti-tumor effects, if one of the objectives of a trial is an estimate of anti-tumor effects of an investigational drug.

- Depending on its relevance to the investigational drug (e.g., potential overlapping toxicity), candidate trial subjects should have recovered from clinically significant adverse events resulting from their most recent anti-cancer therapy/intervention prior to enrollment.

B. Concomitant Medications

- Patients using concomitant medications should only be excluded from trial participation when clinically relevant known or predicted drug-drug interactions and potential overlapping toxicities will impact the safety of trial subjects.

- Alternatively, instead of excluding patients using interacting concomitant medications, sponsors may also consider modification of the dosage or regimen of the investigational anti-cancer agent or the concomitant medications. These approaches should be justified and clearly specified in the protocol and other study materials. Subjects and caregivers should be adequately informed of these changes.