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IRBs and Human Subject Eligibility In Clinical Cancer Trials (#1)

A new series of recommendations for IRBs and others involved in clinical cancer trials was issued by FDA in late April. The series consists of three separate new guidances, each of which is subtitled "Draft Guidance for Industry, Institutional Review Boards, and Clinical Investigators."

The three main titles are "Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications," "Cancer Clinical Trial Eligibility Criteria: Performance Status," and "Cancer Clinical Trial Eligibility Criteria: Laboratory Values."

Although none of these new guidances exceed five pages in length, they contain considerable detail and most certainly warrant the attention of any IRB that reviews and/or monitors clinical cancer trials.

FDA is accepting comments from the public on the content of these guidances. FDA's contact information is listed at the end of this article.

"Washouts" and "Concomitant Medications"

The first guidance for which we present highlights is the one titled "Washout Periods and Concomitant Medications." We begin with a note that much of this guidance actually applies to all three documents.

> "The purposes of eligibility criteria 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.
>
> This draft guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of investigational drugs regulated by CDER and CBER for the treatment of cancer.
>
> Specifically, this draft guidance includes recommendations regarding the appropriate use of washout periods and concomitant medical exclusions and is intended to assist interested parties, including sponsors and IRBs, who are responsible for the development and oversight of clinical trials" (89 Fed. Reg. 32440-32441 at p. 32441).

As noted previously, this first guidance contains information applicable to all three guidances, but we shall present such general advice this one time only, beginning with:

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, or missing words. However, we will on occasion insert words or edit text and/or formating in brackets [ ] to make the material easier to read.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued in subsequent issues are marked at the end of the article with **{TBC}**.

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"A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population" (guidance, April, p. 1; on the Web at https://www.fda.gov/media/178016/download).

Subject Safety and Research Recruitment

"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.

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] (p. 2).

[FN #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.]

[FN #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.]" (ibid).

Presence of "Comorbidities" in Cancer Patients

"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 when a new therapy is started ....

Concomitant medications are any prescription or non-prescription medications (i.e., over-the-counter drugs and dietary supplements) a patient may be taking in addition to the investigational drug product(s). Patients receiving anticancer therapies often have comorbidities that require drug therapy or cancer-related issues that require supportive care ...." (supra at p. 3).

Minimizing the Extent of Washout Periods

Section III of the guidance ("Recommendations") presents advice to IRBs such as:

"Eligibility criteria should be tailored to the investigational treatment, patient population being studied, and the goals of the clinical investigation. 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 such as, 'Exclude patients taking a concomitant medication expected to increase the risk for a clinically significant adverse event.'

Information about the pharmacokinetics/pharmacodynamics (PK/PD) of the expected previous treatments could inform the appropriate duration of the washout period. In addition, accumulated pharmacologic information for the investigational agent should be incorporated as soon as possible in subsequent clinical trials to 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 patient in subsequent trials and may facilitate enrollment of more patients in mid- to late-stage clinical trials" (supra at pp. 3-4).

FDA is accepting public comments on this and the other two guidances until June 25. For more information about this guidance on washouts and concomitant medications, contact: Jamie Brewer of FDA's CDER at 240-402-4463.

We will present highlights from the other two guidances in future HRRs and time and new IRB developments permit. © **{TBC}**

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