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US FDA Focuses On Labs, Concomitant Medication To Avert Needless Clinical Trial Exclusions

by Sarah Karlin-Smith

The FDA is pushing sponsors away from template exclusion criteria to highly tailored drug- and trial-specific eligibility requirements in order to widen the patient pool eligible for studies.

The US Food and Drug Administration's trio of guidances on cancer trial eligibility seem to reflect an agency concern that sponsors and protocol developers have grown lazy over the years, relying on generic broad exclusion criteria for many studies rather than narrowly tailoring criteria for the medication being studied and its intended postmarket patient population.

The recently released guidances, including one on *laboratory values used as eligibility criteria* and another on *concomitant medications and washout periods*, aim to push industry in the opposite direction: assume moving forward that people are eligible for trials unless there is a scientific and clinical justification against it in the known drug profile.

A third guidance focuses on *performance status*. (*See sidebar.*)

Eligibility criteria should be re-evaluated and adjusted as a drug progresses through clinical development, and sponsors should broaden criteria if the concerns are no longer justifiable, the guidances state.

No More Templates

"The agency recognizes that some eligibility criteria may have become

Key Takeaways

- Assume people are eligible for trials. There must be a drug-specific scientific and clinical rationale for exclusion.
- Randomization should account for concerns that broader eligibility will hurt

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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," the agency said.

Lab values should be used to exclude participation "only when clearly necessary to mitigate potential safety concerns," the FDA wrote in the laboratory values guidance.

"Laboratory abnormalities occur frequently without clinical significance," the FDA added, and are more likely in individuals with cancer, but may not be of clinical significance to the treatment being studied.

Randomization should quell some sponsor concerns that broadening eligibility criteria would hurt trial results such as by increasing the rate or severity of adverse-events, the agency said.

trial results.

- Exclusion criteria should only be as restrictive as necessary.

Cancer Trials: FDA Wants Lower Performance Status Eligibility But Primary Analysis Exclusion OK

By Sarah Karlin-Smith

25 Apr 2024

New draft guidance pushes industry to broaden clinical trial eligibility criteria while offering some protection from fears it could hurt efficacy results.

Read the full article here

"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," the FDA said.

When necessary, exclusion criteria should be carefully written so it is only "as restrictive as necessary." For example, the FDA cautioned against requiring a laboratory value to be within the normal range if the safety concern is only for patients whose level would be above the normal range, not below the range.

Protocols also need to account for inter-laboratory variation in selecting eligibility criteria, potentially broadening ranges to account for variation. And they should account for natural variations in lab values among people that may be associated with race and ethnicity.

Sponsors could consider early studies to investigate alternative dosing regimens in patients with certain organ impairments if there is concern a drug may pose a safety risk to a population, but

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also is likely to be used in the population postmarket, the guidance says.

Avoid Vague Statements

Exclusion justifications due to concomitant medication use must be disease- and drug-specific, the FDA said in the guidance on that topic.

Statements like "Exclude patients taking a concomitant medication expected to increase the risk for a clinically significant adverse event," would not meet the standard.

Conducting drug-drug interaction studies early may help enroll more patients on multiple medications in later studies, the agency added.

"Use of concomitant medications may require modification of the dosage and regimen of the investigational anti-cancer agent, and this should be clearly specified in the protocol and other study materials," the guidance says.

Similarly, dosage of concomitant medications may require modification due to the investigational therapy.

Clinical and Lab-Based Washouts

If there is a safety consideration that necessitates a washout, it should be addressed by relevant clinical and laboratory parameters based on the characteristics of preceding therapy rather than a time-based washout, the agency wrote in the guidance.

When used, time-based washout periods should be scientifically justified and relevant pharmacokinetic/pharmacodynamic data of the prior therapy should be taken into consideration, the FDA said.

A time-based washout may be appropriate if prior therapy can result in delayed anti-tumor effects and one objective of a trial is to estimate the anti-tumor effects of the investigational drug.

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