Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Submitted June 23, 2024

Re: **Docket No. FDA–2024–D–1376**
Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications

To whom it may concern:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center") appreciates the opportunity to comment on the Draft Guidance by the Food and Drug Administration ("FDA") entitled, "*Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications*," published at 89 Fed. Reg. 32440-41 (Apr. 26, 2024) (the "Draft Guidance"). Guidance on this topic is timely, welcome, and important to stakeholders across the clinical research enterprise.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

The MRCT Center commends FDA efforts to increase representation in clinical trials. We offer the comments only to enhance the guidance as presented.

Comments

- The MRCT Center would recommend that FDA take a strong position that clinical trials should not use or rely on any template language; each trial should be uniquely designed with appropriate eligibility criteria for the disease, investigational product (and what is known about its metabolism, PK/PD, and toxicities, etc.) and the intended population. Optimally, Phase 3 trials should investigate the efficacy and safety of the investigational product on the population who is likely to use the product if approved for marketing authorization. We agree that eligibility criteria should be "carefully considered and be appropriate for a specific trial context" (p 2, ln 34-39).
- Note that FDA should consider replacing the word "patient" when discussing individuals enrolled in clinical trials with the word "participant," consistent with other guidance from FDA.

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- We recommend FDA clarify its use of the term "medication." Does the word medication include only prescribed medicines or also over-the-counter products, herbal medicines, nutritional supplements, infusions, injections, or implantable devices such as deep brain stimulation?
- The MRCT Center supports the general recommendation that "[e]xclusion criteria should be justified with a disease- and drug-specific scientific rationale as opposed to vague statements." (p 3, ln 91-93). While we appreciate that the Draft Guidance must remain general, we believe that more specific guidance regarding the recommendation to conduct drug-drug interaction evaluations "early in drug development" (p 4, ln 100-01) would be beneficial. Greater definition of which drug-drug interactions should be investigated, and when in the product development pathway would be helpful.
- FDA should comment on whether either the recommendations regarding concomitant medications or the washout period differ in the case of early (Phase 1/2a) versus late (Phase 3 and post-approval) trials.
- The first bullet point in the subsection on Washout Periods (p 4, ln 107-14) suggests enumerating specific justification(s) for proposed time-based washout periods in a study protocol. The Draft Guidance gives examples like "unreasonable risks" (ln 112) and "delayed anti-tumor effects" (ln 113) as possible justifications for imposing such a washout period as an eligibility criterion. For clarity, would the Agency consider simply aiming to avoid potential confounding factors in the clinical data an acceptable justification for a time-based washout period? If so, perhaps the final guidance could include this example explicitly. If not, perhaps the final guidance could expound on the FDA's position.
- We would recommend including the phrase "if possible" in the recommendation in the second bullet point (p 4, ln 116-19) to accommodate circumstances wherein a particular treatment may lack objective clinical or laboratory parameters on which to base such a determination. Moreover, it appears that the Agency prefers "relevant clinical and laboratory parameters" (p 4, ln 116) as the default method for evaluating washout rather than "time-based washout periods" (p 4, ln 107). To reflect this preference more clearly, we would recommend reordering bullet points 1 (p 4, ln 107-14) and 2 (p 4, ln 116-19). At present, FDA's preference for clinical and laboratory parameters seems secondary to the means by which time-based washout periods may be justified.
- The second bullet point under "concomitant medications" indicates that the dosage and/or regimen of the concomitant medication "may require modification." (p 4, ln 132). Are these recommendations expected to be predicated on the drug-drug interaction evaluations? If so, this recommendation underscores the need for greater clarity regarding drug-drug interaction studies. We assume that modifications should be applied uniformly across all arms of the study. Are there exceptions to that understanding? Since all potential concomitant medications cannot be evaluated, guidance from FDA regarding whether and how to design *ad hoc* modifications to the dosage or regimen of a concomitant medication would be helpful.

- Participants are often prescribed concomitant medications for chronic conditions. While some would not be predicted to impact safety or efficacy evaluations, others may. Assuming that there is no a priori reason to suggest drug-drug interactions or impact on outcomes of the trial, further guidance regarding what data to collect, whether to initiate a sub-study to isolate the evaluation of these patients, or other action would be helpful on:
    - Patients taking medications for unrelated conditions,
    - Patients on chronic medications (e.g., anti-depressants),
    - Patients on hormonal therapies (e.g., birth control, prophylaxis re breast cancer),
    - Patients on immune therapies, and
    - Patients on medications that are known to be metabolized by the cytochrome p450 family (e.g., anti-seizure medications) or medications known to prolong the QTc interval.

  How should these questions be appropriately addressed?
  Further guidance and/or specific examples would be helpful.
- What is the role of post-approval real-world evidence in further elucidating the role of concomitant medications?

The MRCT Center appreciates the opportunity to comment on this Draft Guidance, and we would welcome the opportunity to discuss it.

Please feel free to contact the MRCT Center or me (bbierer@bwh.harvard.edu) if we can be helpful.

Respectfully submitted,

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