March 21, 2024

Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

Submitted to: https://www.regulations.gov/commenton/FDA-2023-D-5259-0002

Re: Docket #FDA-2023-D-5259  
Master Protocols for Drug and Biological Product Development: Guidance for Industry

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Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance entitled, “Master Protocols for Drug and Biological Product Development: Guidance for Industry (“the Draft Guidance”) as part of its response to the rescission of its previous guidance entitled “COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention” at the conclusion of the COVID-19 Public Health Emergency.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it is an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and national drug and device regulatory agencies across the world. 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. While the MRCT Center often collaborates and interacts with regulators around the globe, we have not discussed the comments provided herein with FDA or any regulatory agency. The responsibility for this document's content rests with the MRCT Center's leadership, not with its collaborators nor with the institutions with which its authors are affiliated.\(^1\)

We share your vision for extending the Agency guidance on the use of master protocols outside the context of the COVID-19 pandemic. To that end, we would first like to thank FDA for extending this guidance and, second, to take the opportunity to provide a few comments and questions on the Draft Guidance. FDA has summarized a complex and evolving field with clarity and provided direction on the many complicated variations of master protocols. The increasing interest and use of master protocols, particularly in investigational product development programs, will provide for active collaboration and learning as the experience grows. The repeated invitation by FDA for sponsor consultation is appreciated.

---

\(^1\) Brigham and Women’s Hospital, Mass General Brigham, Ropes and Gray LLP, Harvard Medical School, and Harvard University.
The conduct of robust clinical research under a master protocol requires close scrutiny of the study methodology employed by clinical research stakeholders, and we applaud the Agency’s commitment to issuing this guidance to direct those efforts. Our comments are offered in the spirit of collegiality on which this process relies.

Commentary

Definitions

The Draft Guidance document includes the Agency’s accepted definitions of the terms “master protocol,” “sub-study,” “umbrella trial,” “platform trial,” and “basket trial.” We agree that defining these terms explicitly in the Draft Guidance was a critical step. However, we note that clarifying figures on the differences between these study designs were not included in the main text or any of the appendices, despite clarifying figures being employed elsewhere throughout the document. It would be helpful if FDA were to include graphic representations of each of the trial types named in the Draft Guidance that could “utilize a master protocol” (line 30) in an appendix.

Scope

Despite offering definitions of the terms listed above, the guidance appears to limit its focus to “randomized umbrella and platform trials” (line 51). While we support this narrowing of scope, we would suggest perhaps amending the title of the Draft Guidance to “Master Protocols for Randomized Umbrella and Platform Trials” to reflect this scope more accurately and to avoid confusion. Alternatively, substantive differences between randomized umbrella and platform trials and other trial types, if they exist, could be more clearly explained. Examples, as have been included in Appendix, are particularly helpful.

Applicability to Rare Disease Trials

The section on “Considerations on Design and Analysis” (Section III) advises sponsors to employ only concurrent control group data whenever feasible (subsection III-B) but specifically acknowledges “trials in rare diseases with feasibility constraints” (line 209) as a scenario in which the inclusion of nonconcurrent control data may be appropriate. The guidance rightly recommends early consultation with the Agency. Given the frequency of rare disease trials for which master protocols would be relevant, we would ask FDA to clarify whether there are additional considerations to those that appear on lines 213-218, and whether the items included on this list are to be weighted differently by FDA.
We note throughout that the remainder of the guidance document beyond Section III-B would likely benefit from more focused and substantial guidance specific to umbrella trials for in the rare disease space.

**Informed consent**

We believe that further exploration of informed consent issues is warranted. Accepting the detailed guidance which FDA offered in August 2023, the paragraph (beginning line 256) that specifically recommends against sub-study consent is challenging. In the case of a master protocol with four drugs and one control (as represented in Figure 1), each with somewhat different potential risks. In the scenario envisioned by FDA, the investigator would be asked to explain all the risks (benefits and burdens) of each of the five alternatives. We would ask whether this is the correct interpretation of FDA’s position. If so, that would appear burdensome in settings in which any given participant may not be eligible for one or more of the five alternatives, given their own individual co-morbidities (e.g., impaired renal function). This would render a complex informed consent discussion that is already difficult and almost incomprehensible to the prospective participants. Further, to explain to the participant options that are unavailable to that participant appears deceptive.

A similar concern is introduced in the scenario represented in Figure 1 in that the approved informed consent that includes Drug D will necessarily be different than the informed consent used at the beginning of the trial, as different potential risks and the possibility of being randomized to four drugs (and not two or three) will need to be explained. Yet the contemporaneous controls for groups in Drug A and B would still be included in the control group with the Drug D group, despite consenting to a different informed consent—presenting a parallel challenge that is not addressed in the Draft Guidance.

Both patients/participants and investigators generally prefer two-level consent, and we suggest that FDA further explore these concerns prior to the finalization of the guidance.

One additional question is whether there are considerations specific to master protocols involving children (e.g., assent, one or two parent requirements, etc.) that should be mentioned.

**Safety**

It would be helpful for FDA to explain what “additional sources” means in the sentence, “The data from a master protocol can be considered as part of the overall safety database and benefit-risk assessment but data from additional sources may be needed to support approval.” (lines 416-
418). Does FDA mean safety data from additional trials beyond the master protocol or something else?

**Data Sharing and Trial Oversight**

Further clarification of this section appears warranted. The risks to trial integrity (e.g., through the dissemination of trial information of one arm in an ongoing master protocol, thus implicitly revealing information about other arms) are well described, but mitigation strategies are not apparent. FDA should offer guidance on what and how to communicate the various eventualities that are described. Among the questions that should be addressed are whether, if a trial arm is discontinued, that should be kept confidential, and if so, whether this would be consistent with public or participant expectations of transparency. Certain situations, such as a safety concern in one arm of the trial, have patient safety implications and must be communicated. Compliance with Clinicaltrials.gov reporting should also be explained in that any registered sub-study (or arm of the master protocol) must be reported within one year of last patient last visit.

Additional explanation would also be helpful in regard to how to manage commercially confidential information and how such data-sharing agreements could help to maintain data integrity in the trial.

**Additional comments**

There are a few additional questions that arise in the planning of master protocols for which FDA guidance would be helpful:

- If a participant completes, is withdrawn from, or withdraws from a study but remains eligible for the master protocol, can they be (re-)randomized after an appropriate time interval?
- An underlying assumption throughout the Draft Guidance appears to be a single control type (e.g., placebo control or active control). However, there may be instances in which more than one type of control is preferred. How would that affect the randomization scheme and the eCTD?
- Are there special considerations in multi-national master protocols in terms of protocol study design and/or conduct? For instance, the comparator control may or may not be available in all regions. There may be additional demographic and non-demographic differences between and among potential participants that would impact the randomization parameters.
- In the event of a serious event that requires FDA to place a clinical hold on enrollment or on further trial conduct with respect to one drug, will that clinical hold apply to the entire
master protocol or only to the specific arm of the study? If the latter, will that communication then threaten data integrity in the trial?

• The Draft Guidance did not expand on issues related to the introduction of a new arm.

• As noted, master protocols have significant advantages of efficiencies, reduction in the number of participants, and shared infrastructure. The paradigm has been underutilized in settings where multiple sponsors with similar (competitive) investigational products are involved. Is there FDA guidance to help optimize utilization? Are there best practices to which FDA can refer?

• Are there learnings from the COVID-19 pandemic experience that should be illuminated in this guidance or additional FAQs?

Conclusion

We appreciate the opportunity to comment on this proposal. It is a difficult and nuanced undertaking, and we value FDA commitment to providing such helpful guidance.

Please feel free to contact the MRCT Center (bbierer@bwh.harvard.edu; sawhite@bwh.harvard.edu; or mark.barnes@ropesgray.com) if we can be helpful or if you wish to discuss.

Respectfully submitted,

Barbara E Bierer, MD
Faculty Director, MRCT Center

Sarah A White, MPH
Executive Director

Mark Barnes, JD, LLM
Faculty Co-Director