March 21, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: FDA-2023-D-5259-0002
Filed electronically at http://www.regulations.gov

Dear Commissioner Califf,

Thank you for the opportunity to provide comments to the Food and Drug Administration (FDA) on the following draft guidance issued in December 2023:

• Master Protocols for Drug and Biological Product Development

Arnold Ventures is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. We work to develop evidence to drive reform across a range of issues including health care, education, and criminal justice. Our work within the health care sector is driven by the recognition that the system costs too much and fails to adequately care for the people it serves.

We believe that clinical trials need to be carefully designed, reviewed, and monitored to ensure transparency and accountability in approving drugs and biologics that are beneficial to patients. This ensures that approvals are evidence-based, so that patients, providers, and payers have complete clinical trial evidence of clinically meaningful patient outcomes for medical products. Clinical trial data is considered incomplete for evidence-based decisions when it lacks appropriate controls, relies on indirect measures of health, or derives conclusions from narrow study populations that do not represent the patients who will ultimately use the product.

Background

The Food and Drug Omnibus Reform Act of 2022 requires FDA to provide new or updated guidance to streamline the logistics of clinical trials and facilitate the efficient collection and analysis of clinical trial data. A clinical trial master protocol, when designed, conducted, and analyzed rigorously, can coordinate multiple clinical research objectives, for multiple drugs, in various drug-disease pairings. Examples of trial types that could use a master protocol include umbrella trials (testing multiple products for a single disease) and platform trials (testing multiple products throughout many stages of a disease). This has advantages over the evaluation of a single medical product for a single disease or condition, including:

• Multiple investigational new drugs relying on a single control group;
• Analyzing comparisons between drugs (for comparative effectiveness); and
• Utilizing statistical power in the trial that is stronger than in single independent trials when there are separate comparisons or no comparisons at all.

We recommend the following changes to this draft guidance that address the use of a master protocol as well as obtain better clinical trials for clinical research:
1. Describe conditions in which a master protocol design is appropriate and the process to design a master protocol update.

2. Provide advice that improves conduct for double-blinded trials and decreases emphasis on partially blinded trials.

3. Expand discussion on appropriate clinical trial data analysis of comparative results from one investigational product while another remains under evaluation.

We present specific points of comment below for each issue area.

Recommendations

1. *Describe conditions in which a master protocol design is appropriate and the process to design a master protocol update.*

We recommend that final guidance strengthen the reliance on randomization of clinical trial participants on master protocols. Master protocol design must include randomization based on similar selection criteria for participants in both the test and control groups, which allows for random assignment. FDA clearly expects that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies. Therefore, master protocols should be advanced in settings where better evidence can be obtained more efficiently to improve patient outcomes.

The mission of FDA is to be responsible for protecting public health by ensuring the safety and efficacy of drugs and to get the public accurate, science-based information from adequate and well-controlled clinical trials. Clinical trials lack proper controls for systemic bias when trial participants are not randomly assigned. While not the only control for bias in clinical trial design, randomization improves comparability among clinical trial participants. Without randomization there may be differences between groups that make the treatment effects indistinguishable. This leaves observed results unexplained by the interventions under study.

FDA acknowledges this draft guidance is focused on master protocols that include randomization to a concurrent control group. However, final guidance should require concurrent control groups with sufficiently robust clinical trial design elements to create the conditions for well-powered analyses of comparable data between participants. The limitations of non-concurrent and external control groups are already outlined in International Conference on Harmonisation Guidance accepted by FDA and pharmaceutical companies (ICH E10). We recommend acknowledging in final guidance that master protocols must include randomization to an internal control group because it preserves the integrity of randomized comparisons and ensures valid inference from clinical trial results.

2. *Provide advice that improves clinical trial conduct for double-blinded trials and decreases emphasis on partially blinded trials.*

We recommend that FDA be more balanced in the final guidance and include more narrative discussion, schematics, and probability tables to facilitate conduct of multiple-dummy approaches. Randomization in clinical trial design must be accompanied by blinding in trial conduct to ensure concealment of group assignment. These principles work to avoid selection bias that can weaken interpretation of trial results. Schulz and Grimes (2002) explained that trials conducted with such inadequacies tend to overestimate treatment effects, which is particularly relevant as outcome measures become less objective.
The considerations in draft guidance spent on partial blinding specifically, relative to complete blinding, could be misinterpreted by industry and other stakeholders as an endorsement for partial blinding at the expense of trial integrity. Conducting clinical trials on master protocols with the use of blinding of participants, sponsors, and investigators to the assigned treatment or control arms is the optimal way to avoid bias.

Finally, research participants are central to clinical trial conduct. To this end, the informed consent process within a platform trial is more complex and should be approached in a patient-centric manner. We recommend that FDA include in final guidance how master protocol sponsors can provide clinical trial participants with informed consent processes that are continuously updated as the master protocol changes the level of participant risk exposure.

3. Expanding discussion on appropriate clinical trial data analysis of comparative results from one investigational product while another remains under evaluation.

We recommend that final guidance set clearer expectations for clinical trial data analysis to provide for updates to the control arm or additions of background therapy to the control arm of a master protocol. Specifically, the final guidance should include how to develop and execute a statistical analysis plan that includes interim analysis. This is important because Data Monitoring Committees would consider interim results and should be consulted earlier in stages of master protocol design to prepare change control procedures for the analysis plan.

Finally, this draft guidance only generally recommends limiting analysis to concurrently randomized participants for primary endpoint comparison in a master protocol. We recommend that the final guidance make clear that such comparisons are required between those control participants who were concurrently enrolled and could have been randomized to that drug. FDA must maintain valid inferences to evaluate whether analysis of clinical trial results demonstrate substantial evidence of effectiveness for the population intended to use the drug. Non-concurrent control groups have the same potential biases as external control groups as outlined in ICH E10.

Conclusion

Thank you again for the opportunity to comment and for your important work ensuring the safety and efficacy of human drugs and biological products. We are prepared to assist with any additional information needed to address these comments in final guidance to industry. Comments were prepared by Katherine Szarama, Ph.D. Director of Health Care at Arnold Ventures, with assistance from John Powers, MD.

Please contact Mark E. Miller, Ph.D. Executive Vice President of Health Care at Arnold Ventures at mmiller@arnoldventures.org or Andrea Noda, MPP, Vice President of Health Care at anoda@arnoldventures.org with any questions.

Sincerely,

Andrea Noda

2. Prasad and Berger, Mayo Clinic’s Proc. 2015 Sep; 90(9):1171-5. doi: 10.1016/j.mayocp.2015.05.006
See International Conference on Harmonisation E10 guidance on Choice of Control Group and Related Issues in Clinical Trials (ICH E10)