November 28, 2018

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

RE: ACRO Comment on
Docket No. FDA–2018–D–3292
Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; Draft Guidance for Industry

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, preclinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world, ACRO members advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually.

General comments:
ACRO thanks the FDA for producing a detailed and helpful draft guidance on the use of master protocols to expedite the development of oncology drugs and biologics by providing an approach to increase the flexibility and efficiency of oncology medicines development. In particular, ACRO welcomes the flexibility shown in the draft guidance with regard to suitable approaches for IRB oversight, given the additional challenges inherent in a master protocol trial design. We do note, however, that there is little discussion of clinical endpoints in the draft guidance. We recommend that a clear statement should be included in the Final Guidance as to whether or not FDA considers it appropriate to evaluate different endpoints in the different sub-studies.

Specific Line Comments:

Lines 128-158:
Section IV.A of the Draft Guidance discusses basket trial designs and notes that the sub-studies within basket trials are usually designed as single-arm activity-estimating trials with overall response rate (ORR) as the primary endpoint.

It is not clear what role, if any, there is for a control group in a basket trial and ACRO recommends that this should be clarified. ACRO asks the Agency to consider including this discussion in the Final Guidance.

Lines 220-221:

The text recommends that the control arm should be the current SOC so that the trial results will be interpretable in the context of U.S. medical practice.

For clarity, and to prevent confusion in international trials, we recommend that this should read "the current SOC recognized in the United States . . . . "

Lines 221-225:
Section V.A notes that changes in SOC for the target population can occur during the conduct of the trial, because of either a new drug approval or new scientific evidence, making it no longer ethical to randomize patients to the previous SOC and, in that case, the sponsor should suspend patient enrollment until the protocol, the SAP, and the protocol informed consent document are modified to include the new SOC as control.

We ask the Agency to consider adding a new discussion in Section VII to provide guidance on the statistical implications of such a change.

Lines 231-254:
Section V.B addresses novel combinations of new investigational drugs.

It would be helpful to include a discussion in the Final Guidance on the preferred design. For example, cross-over vs. factorial vs. some other design that would allow the sponsor to assess the impact of each compound both individually and in combination.

Lines 282-298:
In studies that explore multiple indications and multiple, unrelated endpoints, DMC participants may not have expertise in all areas of the study, e.g. where endpoints include both tumor reduction and pain reduction or other QOL measures for a broad population of both solid tumor and lymphoma patients. It would be helpful to include guidance on whether the sponsor should simply increase the size of the DMC as needed, to ensure that all expertise is covered, or whether a second DMC may be established to examine a particular subset or portion of a study.

Lines 329-349:
We recommend that Section VII should provide more guidance about how the analysis of the sub-studies should be addressed in the SAP and control of alpha.

Lines 348-349:
We recommend that Section VII.B should include more detail about expectations for the SAP. For instance, guidance on balancing indications across treatment groups in a complex study that includes both multiple indications and an active control would be helpful. If the randomization is stratified by indication, the control population may need to be inflated. However, if there is no stratification and the intent is to compare

subgroups by indication, there may be only a small sample or no representation for an indication within the control group.

ACRO thanks the Agency for the opportunity to comment on this Draft Guidance on Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. Please do not hesitate to contact ACRO if we can answer any questions or provide additional details.

Respectfully submitted,

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