ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

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–3124
Adaptive Designs for Clinical Trials of Drugs and Biologics; Draft Guidance for Industry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ACRO congratulates the FDA on producing a detailed, comprehensive and helpful draft guidance on adaptive designs for clinical trials of drugs and biologics. ACRO has a small number of specific comments on the text (see below) and also offers the following general comments:

- The terms ‘subject’ and ‘patient’ are used across the document. We recommend harmonizing the use of these terms.

- The use of the terms “effectiveness” and “efficacy” seems not to be aligned with the guidance to use effectiveness for real world evidence and efficacy for study results based on a restricted study population.

- We note that the draft guidance contains multiple references to ICH E9 on Statistical Principles for Clinical Trials, which for the most part endorse the ICH guidance (which forms official FDA guidance). We are concerned, therefore, to note that the definition of an interim analysis in the current draft guidance differs from that in ICH E9 and believe that this may result in confusion for sponsors. We understand, and agree with, FDA’s reasons for this but (as noted in our comment on lines 52-54, below) recommend the use of a different term in this context in order to avoid confusion.

- Section IV seems to be a repeat of the definition of non-comparative data given in section II, with added examples. We recommend that the advantages / disadvantages of adaptive designs based on non-comparative data are stated instead of repeating the definition (more or less) together with examples but without guidance.

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Specific Line Comments

Lines 25-28
Current text:
"The primary focus of this guidance is on adaptive designs for clinical trials intended to support the effectiveness and safety of drugs. The concepts contained in this guidance are also useful for early-phase or exploratory clinical trials as well as trials conducted to satisfy post-marketing commitments or requirements."

ACRO's concerns:
This introductory statement makes a distinction between adaptive designs in exploratory trials and in trials used to support efficacy and safety. The inference is that an adaptive trial design covering both exploratory and confirmatory clinical aspects should not be used. Only in lines 636-639 is it stated that "In general, seamless designs that incorporate both dose selection and confirmation of efficacy of a selected dose (based on data from the entire trial) can be considered if the principles outlined in section III are followed." For clarity, we recommend that this statement is added to the introduction.

Suggested alternative text for the Final Guidance:
"The primary focus of this guidance is on adaptive designs for clinical trials intended to support the effectiveness and safety of drugs. The concepts contained in this guidance are also useful for early-phase or exploratory clinical trials as well as trials conducted to satisfy post-marketing commitments or requirements. In general, seamless designs that incorporate both dose selection and confirmation of efficacy of a selected dose (based on data from the entire trial) can be considered if the principles outlined in section III are followed."

Lines 52-54
Current text:
"An interim analysis is any examination of data obtained from subjects in a trial while that trial is ongoing, and is not restricted to cases in which there are formal between-group comparisons."

ACRO's concerns:
As made clear in the footnote in the draft guidance, this differs from the ICH definition of an interim analysis. In order to avoid confusion, especially as FDA is a long-standing member of ICH, we recommend the use of a different term (e.g., intermediate analysis) by FDA in this context. Appropriate changes would need to be made throughout the draft guidance wherever the term interim is currently used.

Suggested alternative text for the Final Guidance:
"An intermediate analysis is any examination of data obtained from subjects in a trial while that trial is ongoing, and is not restricted to cases in which there are formal between-group comparisons. This includes an interim analysis as defined in the FDA International Council for Harmonization (ICH) guidance for industry E9 Statistical Principles for Clinical Trials (ICH E9). The term intermediate analysis accommodates the wide range of analyses of accumulating data that can be used to determine trial adaptations."

The corresponding footnote could be deleted.

Lines 353-355

Current text:

"If investigators are provided access to comparative results from an early interim analysis, knowledge of a small or unfavorable estimated treatment effect based on unreliable data could be misinterpreted as reliable evidence of no effect . . ."

ACRO's concerns:

If the interim analysis provides unreliable data, the study is questionable in any case. We recommend using a less misleading wording like 'uncertain.'

Suggested alternative text for the Final Guidance:

"If investigators are provided access to comparative results from an early interim analysis, knowledge of a small or unfavorable estimated treatment effect based on uncertain data could be misinterpreted as reliable evidence of no effect . . . "

Lines 483-484

Current text:

"Note also that some DMCs may prefer the flexibility of nonbinding futility guidelines."

ACRO's concerns:

Reasons for binding or unbinding futility rules are given in the paragraph. It is our opinion that this last sentence adds more confusion than clarity.

Suggested alternative text for the Final Guidance:

ACRO recommends that the Agency consider deleting the example altogether.

Lines 663-665

Current text:

"These techniques can increase the predictability of treatment assignment relative to simple randomization, but this predictability can be mitigated with an additional random component to prevent perfectly deterministic treatment assignment."

ACRO's concerns:

This sentence reads like it is also acceptable to have a deterministic treatment assignment and it is just an option to avoid this. We believe the first choice should be to avoid it and accept it only if it is not possible to avoid.

Suggested alternative text for the Final Guidance:

These techniques can increase the predictability of treatment assignment relative to simple randomization. Therefore, this predictability should be mitigated with an additional random component to prevent perfectly deterministic treatment assignment.

Lines 1017-1018
Current text:
"This latter model might best be reserved for group sequential designs and other straightforward adaptive designs with simple adaptation algorithms."

ACRO's concerns:
When combining the committee to review comparative data (e.g., for safety proposes) and efficacy interim analysis, the most important thing is that the decision rules are clearly pre-specified, not necessarily simple. (See also comment on line 330ff).

Suggested alternative text for the Final Guidance:
This latter model might best be reserved for group sequential designs and other straightforward adaptive designs with simple explicit adaptation algorithms.

Lines 1230-1231
Current text:
"In addition to the typical content of an NDA or a BLA, the application should include:"

ACRO's concerns:
The draft guidance does not state where in the application this additional information should be provided.

Suggested addition for the Final Guidance:
It would be helpful for the Agency to clarify the location of this information in the application.

ACRO thanks the Agency for the opportunity to comment on this Draft Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics. Please do not hesitate to contact ACRO if we can answer any questions or provide additional details.

Respectfully submitted,

Karen A. Noonan
Vice President, Global Regulatory Policy
knoonan@acrohealth.org