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November 24, 2025

Gregory Levin, Center for Drug Evaluation and Research
Phillip Kurs, Center for Biologics Evaluation and Research
Grace R. Graham, Deputy Commissioner for Policy, Legislation, and International Affairs
Food and Drug Administration

RE: ACRO comment on *ICH E20: Adaptive Designs for Clinical Trials*
        Docket (FDA-2025-D-3023)

Dear Mr. Levin, Mr. Kurs, and Ms. Graham,

Founded in 2001, the Association of Clinical Research Organizations (ACRO) is a non-profit trade association representing the world's leading clinical research and technology organizations, which provide specialized services that are integral to the development of drugs, biologics and medical devices that enable patients to live longer, healthier, and more productive lives. ACRO members provide a wide range of services and digital technologies across the entire spectrum of development – from pre-clinical, proof of concept, and first in human studies through post-approval, pharmacovigilance, and health data research. ACRO member companies employ nearly 400,000 people worldwide and conduct research in every global region.

General Comments

ACRO supports the goal of establishing harmonized principles that encourage innovation while maintaining scientific rigor and trial integrity. Industry has long adopted adaptive designs but the absence of an international guideline setting the regulatory framework and main acceptance criteria of adaptive designs has been a hurdle for innovative clinical research. This E20 guideline provides clarity and will enable discussions about planning for adaptive designs. We appreciate that the guideline provides assurance that planning, intentionality, and mid-stream mitigating effort is relevant, as this will help to embed novel design considerations throughout the stages of clinical development, trial conduct, and the product lifecycle.

ACRO recommends that the final E20 guideline encourage innovation in trial design and execution while maintaining methodological integrity and patient safety. Adaptive designs, when appropriately pre-specified, can improve efficiency, ethical balance, and decision-making without compromising statistical validity. ACRO recommends providing additional clarity in the final guideline to ensure both scientific rigor and operational feasibility. In particular, the final guideline would benefit from:

- A clear definition of "interim analysis."
- Clearer expectations for digital system validation, version control and auditability, consistent with modern data governance standards.
- Explicit recognition of advanced adaptive methods, including platform, basket, and biomarker-driven trial models increasingly used in complex research programs.
- Further illustrative examples to support understanding and expectation, per subsection.

- Explicit cross-referencing to related guidelines, including ICH E6(R3), E8(R1), E9, M11, and M13 to promote consistent terminology, system validation expectations, and documentation standards across the development lifecycle.

The documentation requirements outlined in E20 are thorough but risk creating redundancy across regions. We recommend harmonizing expectations with ICH M11 and regional data submission templates, ensuring that required documentation reflects structured, digital formats rather than duplicative narrative reports – similar to the restructuring in ICH's M4Q(R2). This would strengthen transparency, support automation, and align with ICH's broader modernization strategy.

Specific Comments

Section One, Lines 2-20
Challenge:
The definition of an "adaptive design" here may be too restrictive by excluding certain data-driven adaptations that are operationally pre-specified but may not meet a strict "prospectively planned" definition. This could unintentionally exclude valid adaptive elements implemented via automated or pre-defined decision rules.

Recommendation:
We recommend clarifying that adaptive elements may include structured responses to emerging data trends when pre-defined within the protocol or statistical analysis plan. This approach maintains scientific integrity while reflecting the realities of modern, digitally enabled adaptive trials.

We suggest the addition of the following text: *"Digitally enabling modern clinical trials may change data distributions in unforeseen ways. Therefore, consideration may be given to pre-specification of adaptive design elements in protocols and/or statistical analysis plans, which allow for data-driven changes to study conduct or analysis."*

Section Two, Lines 63-65
Challenge:
E20 effectively outlines the conceptual advantages of adaptive design but underestimates the practical barriers sponsors face, particularly small or mid-sized organizations, when comparing multiple candidate designs.

Recommendation:
We encourage the inclusion of language emphasizing proportionality, ensuring that comparative evaluation should be commensurate with the adaptation's scale and impact, focusing on rationale for the chosen design, rather than exhaustive alternatives.

We suggest addition of the following text: *"Comparative evaluation should be commensurate with the adaptation's scale and impact, focusing on the rationale for the chosen design rather than benchmarking against alternatives."*

Section Two, Lines 22-83
Challenge:
There are several examples provided here, but all are high level and effectively hidden within the text.

Recommendation:
More in-depth examples, in a more structured format, would be useful. In Section 2, there are five or more uses of "For example" with examples given. These illustrative case examples could be extracted from the main text and expanded with more detailed information to clarify the scenarios discussed. An appendix may be useful for this purpose.

Section Three, Lines 84-307
Challenge:
The five foundational principles are well-structured but would benefit from stronger operational linkage to existing ICH guidelines.

Recommendation:
Specifically, Principle 3.5: "Maintenance of Trial Integrity" should explicitly reference the digital controls, audit trails, and system validation practices detailed in ICH E6(R3) and E8(R1). Reinforcing these cross-references will ensure that adaptive trials uphold integrity and transparency across digital data systems.

Section 3.2, Lines 132-137
Challenge:
Consideration should also be given to any digital technology used in the trial and the capabilities of the system to 'adapt' as needed in accordance with the trial. Modifications to technology can take time and may not be able to be built in advance, so, careful consideration must be given as to how new or different features are turned on/off and released along with the adaptive trial schedule.

Recommendation:
ACRO recommends addition of the following statement to ensure the technological aspects are appropriately considered: *"Use of any digital technology must be appropriately planned for. This should include consideration of development and implementation of any modifications to the digital technology within the adaptive trial schedule."*

Section 3.5, Lines 249-253
ACRO welcomes the inclusion of this sentence.

Section 4, Lines 308-560
Challenge:
In addition to the examples in the draft guideline, ACRO recommends that the guideline explicitly recognize adaptive designs used in platform, basket, and umbrella trials, as well as biomarker-driven studies that rely on dynamic patient stratification. Inclusion of these examples would align E20 with the evolving design

landscape and ensure harmonization with regulatory guidances such as FDA's 2019 *Adaptive Design Guidance* and EMA's 2022 *Reflection Paper*.

Recommendation:
ACRO recommends use of the term 'master protocols' under which to consider platform, basket & umbrella trials, as discussed in the FDA Guidance: *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, Guidance for Industry*, March 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and?trk=public_post_comment-text

Specifically, we recommend the addition of a new sentence in line 313: "*Adaptations may include adaptive designs implemented under master protocols (e.g., platform, basket, umbrella trials) and biomarker-driven studies employing dynamic stratification.*"

Section 4.1, Lines 338
ACRO supports the emphasis on ensuring adequate sample size when considering the timing of interim analysis in order to support safety analyses.

Section 4.3, Lines 484-486
Challenge:
This section would benefit from an example about how to precisely define the ranges/thresholds of "continuous" baseline characteristics of subpopulations.

Recommendation:
At the end of line 486, we suggest adding: "*Real-world data can be explored, in the planning phase, to determine the common ranges of such continuous/non-binary characteristics (e.g. age ranges, lab values, etc.) in subpopulations of interest, which could help refine respective eligibility criteria in order to optimize benefit-risk profile, and estimate feasible and indicative subpopulation sample sizes for such adaptive designs.*"

Section 5, Lines 561-880
Challenge:
While comprehensive, this section is not forward-looking enough for emerging digital and analytical methods.

Recommendation:
ACRO suggests adding a discussion of machine-learning-assisted modeling and multi-protocol adaptation with the addition of subsections or examples covering:
- Machine learning–assisted response modeling and real-time data integration as permissible within pre-specified adaptive frameworks.
- Adaptive sub-study modifications within multi-protocol (master protocol) settings, referencing FDA 2022 and ICH E11A (model-informed drug development) for alignment.

This ensures E20 anticipates future analytical and digital methodologies while maintaining rigor through pre-specification.

Section 5, Lines 726-824
ACRO supports the inclusion of Bayesian and time-to-event methods, but this would benefit from further elaboration.

Recommendation:
ACRO recommends that E20 could be more forward-looking by acknowledging emerging analytic frameworks such as machine learning-assisted response modeling and real-time data integration. The guideline should consider how future adaptive methodologies can be evaluated under the same principles of pre-specification and statistical rigor, drawing lessons from ICH M15 Guideline on general principles for model-informed drug development.

Section 5.3, Lines 726-785
Challenge:
ACRO notes that much of discussion in this section is focused on prior distribution considerations that are not specific to adaptive designs.

Recommendation:
ACRO suggests providing guidance on reporting of Bayesian results, including justifying sensitivity analyses for selected prior choices and handling posterior probability thresholds for decision-making.

Section 5.3, Lines 756-759
Challenge:
This sentence claims ensuring a "Bayesian prior" reflects relevant available information introduces additional uncertainties beyond those associated with frequentist inference. However, this statement is incomplete. An uncertainty in frequentist inference – but not Bayesian analysis (which is rarely discussed) – is what does a probability about data given a hypothesis tell us about the hypothesis itself? For example, a p-value is a statement about possible data that could come from a hypothetical repetition of the clinical trial, assuming the tested hypothesis (e.g. the hypothesis of no effect). Therefore, when a p-value is reported in a trial, what does it tell us about that hypothesis (leaving aside the more fundamental question of whether that hypothesis is of interest in the first place)? Outside of the Bayesian paradigm, the latter uncertainty is more difficult to overcome.

Recommendation:
We suggest the following refined language for the final guideline:
"Ensuring that a prior accurately reflects relevant available information and addressing the potential for conflict between prior and current trial data introduces additional uncertainties that are not present when using frequentist analyses with no borrowing. However, Bayesian analyses are more suitable for evaluating hypotheses, as they directly measure the degree to which data support or undermine hypotheses and probabilities of hypotheses."

Section 5.3, Line 772
Challenge:
The discussion of borrowing from external data and trial success is unclear.

Recommendation:
ACRO recommends highlighting the main types/methods/examples of acceptable borrowing of external information in the context of adaptive designs using the Bayesian Borrowing method. It would be helpful to add examples for different extents/amounts of borrowing external data such as hybrid control arms and/or full external comparator/control arms. We suggest the following additional text at the end of line 772:
"The amount of borrowed external data could range from complementary prior data to current trial control arm (i.e. hybrid control arms) to full external comparator/control arms."

Section 5.5, Lines 832
Challenge:
ACRO notes that simulation studies, as described in section 5.2, are also applicable. As simulation studies may help to refine and optimize exploratory trials, it would be helpful to add this into this section.

Recommendation:
We suggest this additional sentence for the final guideline: *"Simulations can help limit/reduce the number of adaptations required in such early/exploratory trials."*

Section 6.1, Lines 882-928
Challenge:
The section is thorough but risks creating redundant documentation across regulatory regions. There should be reassurance that adaptive details can be incorporated into existing core trial documents, not as a separate new deliverable.

Recommendation:
We recommend the addition of new sentence in line 922:
"Details regarding adaptive elements should be included within the appropriate existing study documentation - such as the protocol, statistical analysis plan (SAP), or data management plan (DMP) - rather than requiring a new standalone 'Adaptive Design Plan.'"

Section 6.1, Lines 882-928
Challenge:
The section could better align with ongoing ICH digital harmonization efforts (M11 protocol template, M13 data submission standards).

Recommendation:
We suggest the addition of new sentence in line 920: *"Documentation expectations should be harmonized with ICH M11 and regional data standards to support structured, digital transparency and reduce duplication across submissions."*

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ACRO thanks FDA for the opportunity to provide input on this draft guideline. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions.

Respectfully submitted,

Karen Noonan

Karen Noonan
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