ACRO Innovate Advocate Collaborate

August 31, 2023

Amy Chi, Center for Drug Evaluation and Research
Diane Maloney, Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6334
Silver Spring, MD 20993–0002

RE: ACRO comment submission:
E6(R3) Guideline for Good Clinical Practice; International Council for Harmonisation; Draft Guidance for Industry
[FDA Docket No. FDA–2023–D–1955]

Dear Ms. Chi and Ms. Maloney,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical-sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

General Comments:

ACRO welcomes the flexible framework for clinical trial conduct provided in the draft guidance. As global companies delivering clinical trials worldwide, ACRO members note that it is now common practice for clinical trials to include one or more decentralized elements. This means that the discussion of decentralized trials in the yet-to-be-released Annex 2 will be critical to the practice of many clinical trials. Moreover, without the ability to review Annex 2, the operational impact of ICH E6 (R3) is unclear at this time. The planned content for Annex 2 may have a significant operational impact in terms of the change management required to implement ICH E6 (R3) across the industry. We therefore welcome the release of the draft of Annex 2 as soon as possible in order to understand ICH E6 (R3) in its entirety.

ACRO thanks the ICH Expert Working Group for the discussion of training in the draft guidance. In particular, we would welcome training by the ICH E6 R3 working group on how risk proportionality will be approached during inspections.

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Line-Specific Comments:

Lines 59-65:

ACRO welcomes the emphasis on stakeholder engagement to help with feasibility and protocol design to decrease study burden. However, we believe this could be strengthened in two ways. First, we recommend that the guidance be explicit about the need for this engagement to begin as early as possible – including the protocol development stage – and to continue throughout the planning process. This will ensure meaningful impact in early planning. One approach could be the use of committees composed of patients (and/or their caregivers) who have experience with a given disease and with clinical trials to review protocols and provide comments on how to lessen the participant burden. Second, ACRO welcomes the acknowledgement that the use of innovative clinical trial design and technologies may help include diverse patient populations. However, ACRO would welcome further emphasis in the draft on the importance of ensuring diversity of patients in order to ensure that trial outcomes are relevant to a wider set of patients, in line with principle 1.4.

In addition to a dedicated discussion of the need for stakeholder and trial participant engagement early in the planning and design process, we ask the ICH Expert Working Group to consider adding "feasibility" and "for diverse communities" in lines 60-62:
"The design of the trial, to ensure feasibility, appropriate quality and meaningful trial outcomes for diverse communities, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers."

Lines 92-98:

ACRO welcomes the discussion in this section of the importance of the participant selection process so as not to unnecessarily exclude particular participant populations. ACRO asks the ICH Expert Working Group to consider additional language in the final guidance on the importance of considering a diversity of study sites in order to ensure accessibility and availability of the trial to patients from diverse communities.

We ask the ICH Expert Working Group to consider adding the following text into the final guidance:
"Consideration should be given to ensuring diversity of location and type of study sites in order to support representation of the anticipated study population."

Lines 150-152:

ACRO notes the inclusion of a requirement for a periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed. In order to encourage a proportionate approach to conducting and documenting the periodic review, ACRO welcomes clarification in the final guidance by incorporating the word "appropriate:" "*There should be appropriate periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.*"

Lines 935-936:

ACRO welcomes the acknowledgment that the use of innovative clinical trial design and technologies may help with inclusion of diverse patient populations. However, ACRO would welcome further emphasis in the final guidance on the importance of ensuring diversity of patients so that trial outcomes are relevant to a wider set of communities.

We request that the ICH Expert Working Group consider adding "from diverse communities" to this section:
"Sponsors should consider inputs from a wide variety of stakeholders, for example, healthcare professionals and patients from diverse communities, to support the development plan and clinical trial protocols as described in ICH E8(R1) and when developing the informed consent material and any other participant-facing information."

Lines 1001-1004:
ACRO members have global experience of translating sponsor oversight into practical actions. ACRO believes that the current language in the draft guidance regarding sponsor oversight of providers could inadvertently be interpreted in a way that constrains the quality management role of the service provider. We therefore ask the ICH Expert Working Group to consider providing greater clarity in the final guidance through inclusion of the phrase "and/or regulatory or ethics committees as required:"
"Any service provider used for clinical trial activities should implement appropriate quality management and report to the sponsor, and/or regulatory or ethics committees as required, any incidents that might have an impact on the safety of trial participants or/and trial results."

Lines 1102-1403:
ACRO notes that there is no reference to Quality Tolerance Limits (QTLs) within the R3 draft, a change that has been made since R2. When applied as intended, QTLs are a valuable tool to detect systemic issues earlier than they would otherwise be flagged. QTLs are an important risk management and oversight tool, and regulatory support of the adoption of QTLs should be demonstrated clearly in guidance.

ACRO recognizes that after the release of R2, there was confusion in the industry around QTLs and adoption generally lagged behind where we thought it should be. The distinctions between KRIs, KPIs and QTLs were not always defined, therefore companies had difficulties establishing QTLs. However, in recent years, this began to shift as companies became more and more comfortable implementing QTLs. ACRO is concerned that the proposed change in terminology will further add to any hesitancy to adopt these valuable tools.

A landscape analysis of over 4,000 clinical trials conducted by ACRO showed a slow but steady increase in the uptake. In 2019, 10% of the studies within our dataset had utilized QTLs and by 2022, that had increased to 29%. This demonstrates that while adoption has been slow, the industry is just starting to utilize QTLs. ACRO is therefore disappointed to see that at this junction, QTLs have been subsequently inexplicably removed from the R3 draft.

In addition, QTLs are included in ICH M11 section 11.1 and ACRO believes that consistency between M11 and E6(R3) is essential to avoid any unnecessary confusion in the industry.

ACRO suggests that ICH add QTLs back into the guidance document. The general consensus among ACRO members is that the new verbiage of "acceptable ranges" should be interpreted as a QTL-equivalent. However, further regulatory clarity on this definition would be valuable to ensure that industry is consistently interpreting the terms as intended by the regulators. ACRO also asks for clarity around whether acceptable ranges should go into the CSR, as QTLs did.

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Thank you for this opportunity to comment on the ICH E6(R3) draft guidance. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can answer questions or provide additional detail.

Respectfully submitted,

Karen A. Noonan

Karen Noonan
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