ACRO Innovate Advocate Collaborate

February 26, 2025

P. Ritu Nalubola, Associate Commissioner for Policy
Amy Chi, Center for Drug Evaluation and Research
James Myers, 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 on ***ICH Draft Guideline for Good Clinical Practice E6(R3): Annex 2***
[FDA-2024-D-5601-0002]

Dear Dr. Nalubola, Ms. Chi, and Mr. Myers,

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.

ACRO thanks the ICH for the *Draft Guideline for Good Clinical Practice E6(R3) Annex 2.* The objective of this draft guideline is to address the application of GCP in an increasingly complex clinical trial enterprise characterized by a growing range of technological advances, design elements, and data sources. The draft guideline focuses on three specific advances in clinical research:[1]

- Decentralized elements – defined as *"those trial-related activities conducted outside the investigator's location (e.g., trial visit is conducted in the trial participant's home, local healthcare centre or mobile medical units or when data acquisition is performed remotely using digital health technologies (DHTs))"*

- Pragmatic elements – defined as *"those that integrate aspects of clinical practice into the design and conduct of the trial (e.g., simplified protocols with streamlined data collection)."*

- Real-world data (RWD) – this is contrasted with "primary data" (data generated specifically in a trial) and defined as *"data obtained from sources external to the trial that are collected for other purposes (secondary data use). RWD incorporated in clinical trials include the use of data relating to patient health status collected from a variety of sources outside of clinical trials (e.g., electronic health records (EHRs), registries, claims data). These data from RWD sources may be used in various ways, including, but not limited to, ascertaining endpoints or outcomes or serving as an external control."*

[1] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
Lines 19-31

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ACRO's comment is divided into three sections. The first section discusses how the draft guideline could go further in facilitating trials with decentralized elements (including facilitating the use of local healthcare providers (HCPs); clarifying investigator oversight of HCPs; clarifying safety reporting; and acknowledging vulnerable populations). The second section offers recommendations regarding the discussion of data variability in the draft guideline. The final section offers suggestions for strengthening participant engagement.

## I: The draft guideline could go further to enable trials with decentralized elements

ACRO welcomes the extensive discussion of real-world data (RWD) in the draft guideline, which receives dedicated discussion in Section 3.5.1.[2] However, we believe the draft guideline could go much further in facilitating and enabling trials with decentralized elements.

### *Facilitating the use of local health care providers (HCPs)*

In its consideration of investigational product management, the draft guideline discusses the appropriate use of local pharmacists:

> *The investigational product may be dispensed or supplied to the participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local pharmacist).*[3]

Local HCPs are a valuable resource for decentralized trials. However, in the Annex 2 draft guideline, the use of local HCPs in decentralized trials is referenced in just one sentence: "Healthcare professionals may be involved in performing trial-related activities that are part of clinical practice."[4] The FDA's Final Guidance on *Conducting Clinical Trials with Decentralized Elements*[5] provides a helpful summary of both the benefits of using local HCPs in decentralized trials and also the appropriately limited scope of a local HCP's contributions to a decentralized trial.

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[2] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
pages 8-9

[3] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
Lines 73 to 77

[4] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 110-111

[5] FDA final guidance on Conducting Clinical Trials with Decentralized Elements
https://www.fda.gov/media/167696/download

The use of HCPs in a decentralized trial has the potential to increase the representativeness of participants:

> *The clinical trial population should reflect the intended patient population for the medical product being studied, including with respect to race, ethnicity, age, sex, and geographic location, as applicable. Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of participants with diverse demographic characteristics more reflective of the intended patient population in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants who have challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may further improve engagement, recruitment, and retention of a more representative participant population and reduce cultural or linguistic barriers to participation in clinical trials.*[6]

The scope of the HCP's contributions differs from that of trial personnel:

> *Depending on the trial protocol, in-person visits and trial-related activities may also be conducted by HCPs who are located close to trial participants' homes. Investigators may use these local HCPs (such as doctors or nurses) to perform certain trial-related activities; for example, on a fee-for-service basis. The trial-related activities local HCPs perform should not differ from those that they are qualified to perform in clinical practice and should not require a detailed knowledge of the protocol, investigator's brochure, or IP (e.g., performing physical examinations or obtaining vital signs). These local HCPs would not be considered trial personnel, nor would they be considered subinvestigators in a drug trial.*[7]

It would be valuable to see greater discussion of the benefit and scope of HCPs in the final guidance.

The FDA draft guidance on *Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice*[8] further clarifies the role that local HCPs can play in modernized clinical trials. According to this draft guidance, the use of local HCPs is appropriate when:

- the HCP's tasks do not differ from those that they are qualified to perform in routine clinical practice
- the HCP's tasks require only limited instructions to ensure that they are performed as required

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[6] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
page 7

[7] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
Pages 4-5

[8] *FDA draft guidance on Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice*
https://www.fda.gov/media/181871/download
Lines 201-243, 177-185 and 203-208

- the HCP's tasks do not:
  - contribute directly and significantly to trial data
  - require trial-specific knowledge
  - require trial-specific training
  - require research expertise
  - require a detailed knowledge of the protocol
  - require a detailed knowledge of the investigational product
  - require a detailed knowledge of the investigator's brochure

We ask ICH to consider including discussion of the valuable role of local HCPs in innovative trials such as trials with decentralized elements.

***Further clarifying investigator oversight in a decentralized trial***

The Annex 2 draft guideline does address the role of investigator oversight of individuals such as local HCPs:

> *For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents, appropriate arrangements and appropriate investigator oversight should be in place. Such arrangements should address plans for making relevant information and records available to the investigator.*[9]
>
> *The level of investigator oversight of the trial-related activities should depend on the nature of the activities and be proportionate to the risks to trial participant safety and data reliability, and the importance of the data being collected. Such oversight should ensure that the resulting records meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial participant safety and appropriate decision-making.*[10]

However, we believe this discussion of investigator oversight would benefit from further clarification. The FDA Final Guidance on Decentralized Trials provides an enriched discussion of the investigator oversight role which we ask ICH to incorporate into the Annex 2 final guidance:

> *Investigators are responsible for the conduct of the DCT and for protecting the rights, safety, and welfare of subjects under their care. Investigators must also maintain accurate records of each subject's case history, including observations and other data pertinent to the investigation. Consistent with these responsibilities, investigators should review data from other trial personnel and local HCPs, as applicable, and follow up on any data that are missing, concerning, or appear to be in error.*

[9] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 116-120

[10] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 121-125

> *Investigators must also ensure assessments are being completed consistent with the protocol and confirm that participants have received the IP. When permitted by the protocol, investigators can delegate trial-related activities to appropriate local HCPs. Investigators can work with enrolled participants to identify such providers when appropriate. Investigators must ensure that trial-related activities delegated to local HCPs are conducted according to the investigational plan and applicable regulations and remain responsible for the adequate supervision of those to whom they have delegated these activities.*[11]
>
> *Investigators do not need to maintain a log of local HCPs performing trial-related activities. However, as part of preparing and maintaining adequate case histories, investigators should ensure that reports from local HCPs include the name of the local HCP and the date when activities were performed*.[12]

***Acknowledgement of vulnerable populations***

The section on the investigator and "Informed Consent Considerations" (Section 2.2.2) of the Annex 2 draft guideline states:

> *The characteristics of the trial population (e.g., participants may lack familiarity with electronic systems) and the appropriateness of the method and tools used to obtain consent should be taken into consideration when developing the informed consent materials and process. Trial participants may be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, should they prefer this.*[13]

Since decentralized trials have great potential to benefit vulnerable populations in particular, due to their flexibility, ACRO would recommend incorporating a final sentence into this paragraph acknowledging the needs of vulnerable populations with an additional sentence such as: "The needs of vulnerable populations should be considered."

***Safety reporting in decentralized trials***

Section 2.5 on "Safety Assessment and Reporting" would benefit from greater clarity. In decentralized trials, the connection between investigator and trial participants must be clearly defined to ensure safety reporting. This should include details of safety assessment and how the patient will communicate with the investigator. Given its importance, ACRO recommends including a specific sentence in section 2.5 about the investigator's responsibility to explain safety related procedures and communication channels to the patient. We believe that, once again, the FDA Final Guidance provides valuable language that could be incorporated into the final version of the Annex 2 draft guideline:

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[11] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
pages 8-9

[12] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
page 10

[13] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 60-64

> *As in any clinical trial, the safety monitoring plan should describe how participants are expected to respond to and report adverse events, including where to seek medical assistance locally when necessary and where to receive follow-up care*.[14]
>
> *Trial participants should have clear instructions about how to contact trial personnel to report adverse events and to have pertinent questions answered. Trial participants should also be able to arrange for an unscheduled visit with trial personnel using telehealth or an in-person visit, as appropriate (see section III.B).*[15]

**II: Data variability concerns are not unique to innovative trial designs**

ACRO welcomes the draft guidance's recommendations regarding six potential issues to consider when using secondary data such as RWD – namely:

- Data format variability – due to differing terminologies and standards across a variety of sources
- Data collection timing variability – due to a lack of standardization in the timing and frequency of clinical assessments
- Data quality variability – due to the variety of routine care data sources
- De-identification variability – due to differing methodologies for data protection
- Validation status variability – due to the variety of routine care data sources
- Missing data

Many of these considerations also apply to pragmatic trials. However, we note that decentralized trials are distinct from both trials incorporating RWD and those with pragmatic elements, as decentralized trials frequently generate *primary* data. The only mention of data variability outside of RWD is in Section 3.2.2 of the discussion of sponsor responsibilities. The draft guideline states:

> *Since data may originate from different sources or various practice settings (e.g., sources with different timing of data collection), there may be data variability within and/or between data sources/settings. The impact of such data variability should be considered in the trial design and discussed in the protocol or protocol-related documents (e.g., statistical analysis plan).*[16]

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[14] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
page 15

[15] *FDA final guidance on Conducting Clinical Trials with Decentralized Elements*
https://www.fda.gov/media/167696/download
page 16

[16] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 170-174

We ask ICH to clarify this paragraph in the final guidance to explicitly state that data variability is not a concern unique to decentralized trials. Data variability is also a feature of conventional trials, as highlighted by ACRO in its 2023 comment letter to FDA.[17] An excellent example of this is seen in an analysis of variability among clinicians when performing clinician reported outcomes (ClinROs).[18] Clinical trials today often involve global, multi-site studies. Data variability exists, and can be thoughtfully addressed, in both decentralized and conventional trials. Moreover, a recent article notes that variability analysis as a key element in data collection.[19]

In a conventional, multi-site trial – where no decentralized elements are used – the sheer number of investigator sites around the globe (and multiple parties involved in assessments) introduces the possibility of data variability. In a decentralized trial, where data may be collected remotely, data variability can occur because various parties are conducting multiple, trial-related activities – including patients themselves. Data quality and integrity may, in some cases, be improved via the continuous data flows that decentralized elements such as wearables or sensors can offer.[20] However, such methods may not be appropriate for all trials or participants. To mitigate potential data variability in a decentralized trial, ACRO has previously discussed options such as the implementation of Risk-Based Quality Management (RBQM), data flow mapping, and differentiated analysis/reporting of data from distinct data streams.[21] It is notable that these approaches are no different from those presently being applied by sponsors and CROs in conventional clinical trials to manage the risks associated with data variability. Therefore, ACRO asks that ICH consider modifying the Annex 2 final guidance to clearly state that:

- data variability is a key consideration in both conventional and decentralized trials
- currently, we have no empirical data or evidence that the variability and precision of the data obtained in a decentralized trial differs from the data in a traditional site-based clinical trial
- a risk-based quality management approach should be used in all trials

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[17] ACRO comment submission to FDA on *Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders* [FDA-2022-D-2870]
https://www.acrohealth.org/wp-content/uploads/2023/11/ACRO-Final-Comment-on-DCTs.pdf

[18] "Clinician-Reported Outcome Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force," Value Health. 2017 Jan; 20(1): 2–14. Published online 2017 Jan 10. doi: 10.1016/j.jval.2016.11.005
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5379997/

[19] "Variability in clinical data is often more useful than the mean: illustration of concept and simple methods of assessment," Int J Clin Pharmacol Ther. 2005 Nov;43(11):536-42. doi: 10.5414/cpp43536.
https://pubmed.ncbi.nlm.nih.gov/16300169/

[20] Examples include:

- the potential for objective, longitudinal data capture without a subjective interpretation on the part of a site clinician or other HCP (e.g., the six-minute walk test) to mitigate data variability
- the potential for gathering continuous data rather than the "point-in-time" data gathered at the investigator site
- the potential to gather data in the trial participant's natural, real-world setting (vs investigator site)
- the potential for the availability of continuous data (e.g., temperature) via the wearable sensor to facilitate the capture of safety issues, with the potential for more timely corrective action by trial personnel

[21] "Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials" Association of Clinical Research Organizations (ACRO)
https://www.acrohealth.org/wp-content/uploads/2023/11/ACRO_DCTResource_PAGES-1.pdf

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**III. Strengthening patient engagement**

Annex 2 Section 3.1.1 (Engagement and Communication) encourages patient engagement in the development of protocols:

> *Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure the successful integration and implementation of various operational approaches and data sources in trials. For example, involving patients early in the design of the trial may help ensure the suitability of DHTs (e.g., mobile apps, wearables) used in trials with decentralised elements. This engagement may bring attention to areas where additional training or support may be needed (e.g., digital literacy, physical ability or lack of access to technology that may require the use of alternative approaches, specialized training or the provision of technology).*[22]

This is an important step forward but does not go far enough. ACRO recommends adding the following language to the final version of Annex 2 at the end of this existing paragraph (immediately after line 144):

> Across the clinical trial enterprise, we must pair innovative science with a fit-for-purpose participant communications program that effectively informs and engages participants in language that is easily understandable to them, with communications throughout the life cycle of the trial. Easily understandable, fit-for-purpose participant communication programs aim to effectively explain trials, investigational products, and trial findings. They help encourage participation in trials, support improved engagement, and increase scientific literacy – embracing the spirit of patient-centricity-by-design and enabling patients to be partners in trials from beginning to end.

We thank ICH for the opportunity to provide these comments on *Draft Guideline for Good Clinical Practice E6(R3:) Annex 2.* Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.

Respectfully submitted,

Karen Noonan

Karen Noonan
Senior Vice President, Global Regulatory Policy

[22] *ICH E6(R3) Guideline for Good Clinical Practice – Annex 2*
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6r3-guideline-good-clinical-practice-annex-2-step-2b_en.pdf
lines 137-144