Decentralized Trials & Research Alliance

Response to ICH Harmonised Guideline Good Clinical Practice (GCP) E6 (R3) Annex 2

(Notice #FDA-2024-D-5601
Submitted to the Food and Drug Administration (FDA)
Submitted on behalf of the Decentralized Trials & Research Alliance (DTRA)
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Background

The Decentralized Trials and Research Alliance (DTRA) is a non-profit collaboration with over 50 member organizations working together to ease the global adoption of decentralized research methods. DTRA members represent bio-pharmaceutical companies, technology and service providers, site networks and research centers, advocacy groups, and government agencies.

DTRA workstreams have produced a number of valuable resources which we encourage the FDA to leverage as they consider the implementation of DCTs. Examples include a glossary of DCT terms, best practices handbook, patient journey maps, and evidence of DCT impact. DTRA also remains actively engaged with interested parties who are seeking more information about decentralized clinical trials and their enabling elements.

DTRA has engaged with multiple stakeholders to improve understanding and uptake of decentralized methods in clinical studies including:

- A Listening Session in 2023 for the NIH/NCATS RFI on Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials. A recording of this listening session is available for review[1]. A copy of our response to the RFI is also available for review.[2]
- A listening session in 2023 for the FDA Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability and drafted a response of comments from our

[1] NIH/NCATS Listening Session - https://vimeo.com/820603329/6aa02fe714?share=copy

[2] Response to Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials - https://shorturl.at/YCLP9

collective membership. A recording of this listening session is available for review.[3] A copy of our response to the RFI is available here.[4]

- Round table sessions were held in 2024 to discuss draft guidance that intersects with the implementation of DCT elements in trials:
  Diversity Action Plans To Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidance for Industry and **Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice; Draft Guidance for Industry.** The output of these roundtables were comments on each of the draft guidances to support the intent and suggest revisions to further enable patient access to trials.
- Speaking engagements with FDA and EMA leaders (e.g BIO 2024, DIA 2024 Annual Global Meeting, ASCO to discuss the value of DCT elements to support patient access to trials)

"ICH E6 (R3) Annex 2 addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources. Annex 2 provides additional GCP considerations, focusing on examples of trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD)." As these topics align directly with DTRA's areas of focus and mission, we welcome the opportunity to share our membership's unique perspective and suggestions regarding international guidance to improve the decentralized trial research infrastructure .

General Comments

Our membership is encouraged by and eager to adopt the framework outlined in Annex 2. We are delighted that Annex 2 supports the inclusion of health care professionals (HCPs) beyond the clinical trial investigator as essential participants in clinical trial conduct. However, we note that:

- Challenges remain in documentation and oversight of expanded roles
- Goal is to decrease patient/site burden while maintaining data integrity

Investigational Product Management

We are encouraged by the details and examples included in Annex 2 to clarify expectations of investigator oversight of investigational product (IP) use and distribution while creating clarity that direct to patient (or caregiver) IP shipments are appropriate in certain settings. This was an area of GCP that sponsors and other stakeholders struggled with especially while trying to adapt to decentralized approaches during the pandemic. Having clarity in the ICH guidelines will go a long way in helping

[3] DCT Draft Guidance Listening Session - https://vimeo.com/845089324/3ee09b1bfa?share=copy
[4] DCT Draft Guidance Response from DTRA Members - https://shorturl.at/TXCcj

reassure the entire clinical trial eco-system that shipping IP to patients is an acceptable approach that is still compliant with GCP.

Investigator Oversight:

We especially appreciate the fit for purpose approach to investigator oversight described in Annex 2. We believe that decreasing the need for protocol-specific training, regulatory documentation and direct oversight for activities standard in routine clinical care settings will increase the will and ability of HCPs to participate in clinical trials, while enabling patient access at their trusted care centers.

We note that this is critically important to expand the use of DCT approaches and make trial participation more accessible to patients. This will also enable the clinical trial community to be creative and expand their thinking about embedding clinical trials into routine care to create the ultimate learning healthcare ecosystem.

Sponsor Responsibilities:

Engagement and Communication:

Annex 2's inclusion of a clear expectation for cross-stakeholder (patients, caregivers, research sites) engagement during protocol design is very helpful. However, we respectfully suggest that this is repositioned as a best-practice in protocol design rather than a recommendation, and that it be expanded to include technology and digital health tool vendors and providers. Mutual understanding across the clinical trial stakeholders would improve significantly by embedding a collaborative design approach in clinical trial development, better ensuring suitability and fit-for-purpose use of modern clinical trial methods and tools.

We support the recommendation to seek advice from regulators early in trial design and planning. We request that regulators consider sharing case studies and lessons learned from inspections and regulatory agency review. This will help drive the appropriate adoption of modern clinical trial methods, digital devices, and new data collection modalities by helping provide useful examples to the drug development ecosystem. Sponsors are more comfortable implementing methods that have already been used in industry, especially if regulatory advice about best practices is available. To our knowledge, this is not a practice across regulatory agencies. DTRA offers to help coordinate these lessons learned, through an appropriate public-private partnership, to support knowledge management across the industry.

Data Considerations

Technology Implementation & Fit-for-Purpose Approach

We appreciate the ICHe6R3 Annex 2 draft's recognition of the rapidly evolving technological landscape in clinical research and its efforts to provide a framework for managing increasingly complex data ecosystems. The guidance demonstrates awareness

that traditional validation approaches must evolve to accommodate novel data collection methods and emerging technologies. However, we believe additional clarity is needed regarding the practical implementation of validation requirements, particularly in contexts where multiple data sources and systems interact. While rigorous validation remains essential for ensuring data integrity, the guidance should consider a risk-based approach that balances thoroughness with operational feasibility.

Of particular concern is the current ambiguity surrounding sponsor oversight responsibilities for site-selected and HCP-selected vendors and systems. As research sites increasingly utilize their own electronic systems and third-party solutions, sponsors require clearer direction on the scope and depth of required vendor oversight, system validation reviews, and ongoing monitoring activities. Furthermore, the interconnected nature of modern clinical trial data systems presents significant data governance challenges that merit additional consideration. Specific guidance is needed on managing data lineage, reconciliation processes, and quality control measures when integrating data from multiple sources, each potentially operating under different standards and governance frameworks. While more clarity would be helpful so expectations can be met, we also recognize and support the need for flexibility to enable innovation across the clinical trial landscape. We would support a call to action from regulators to define cross-industry standards to enable data interoperability at global scale. This would drive more rapid adoption of these methods and tools while ensuring the rigor and data integrity commensurate with clinical trial conduct.

Summary

In conclusion, while we strongly support the progressive framework outlined in ICH E6(R3) Annex 2 and its recognition of evolving clinical trial methodologies, several areas would benefit from additional clarity and guidance. The Annex makes important strides in recognizing expanded healthcare professional roles, supporting direct-to-patient approaches, and acknowledging the complex technology landscape of modern trials. However, to fully enable innovation while maintaining quality and compliance, we recommend: developing best-practices for sponsor oversight of site-selected vendors, developing cross-industry standards for data interoperability, sharing regulatory case studies of successful implementations, and making and expanded stakeholder engagement a key consideration of protocol design. These enhancements would help strike the crucial balance between enabling innovation and ensuring appropriate rigor in clinical trial conduct, while supporting the broader adoption of modern trial approaches across the global research ecosystem.

Prepared by:
Regulatory Affairs Council, DTRA

- Rasika Kalamegham, Chair, Genentech, A Member of the Roche Group

Amir Kalali MD, Co-Chair, DTRA (amir.kalali@dtra.org)
Craig Lipset, Co-Chair, DTRA (craig.lipset@dtra.org)
*Jane Myles, Program Director, DTRA (jane.myles@dtra.org)
**corresponding author*

For any inquiries, contact secretariat@dtra.org