ACRO Innovate Advocate Collaborate

April 19, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO comment submission:
FDA (CDER) – Enhancing Adoption of Innovative Clinical Trial Approaches
[FDA-2023-N-4489-0001]

To Whom It May Concern:

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 CDER for asking for comments on the barriers and facilitators to incorporating successful or promising innovative clinical trial approaches in drug development programs. ACRO is pleased to offer four recommendations for facilitating clinical trial innovation.

Recommendation One:
Expanding the Use of Digital Health Technologies (DHTs) through Enhanced Transparency and Communication

The ACRO Decentralized Clinical Trial (DCT) Working Party has created a DCT Toolkit to facilitate greater adoption of decentralized elements in clinical trials. The Toolkit is composed of a Quality-by-Design Manual; a Risk Assessment Considerations Tool; Data Flow Maps; and a Change Management Q-and-A resource. Together these resources are designed to be build trust and confidence in decentralized elements and tackle change management and risk aversion challenges.[1]

Digital health technologies (DHTs) are a key part of DCTs as they can lower participation burden (e.g. through wearables) and enable collection of more patient centric evidence (e.g. subjective quality of life data). By using digital technologies in a DCT – such as collecting ePRO subjective quality of life data and augmenting it with objective data that can be captured through sensors and wearables – the study collects data that can play a role in supporting measurement of the patient experience.

However, uptake of DHTs remains limited, as recently reported by Marra and Stern.[2] This means that the opportunities for better patient focus in development are not being realized. One reason for industry hesitance around the use of DHTs is the concern that certain types of data and collection methods may not be accepted at regulatory review. Existing guidance documents[3] do provide helpful clarity to industry to support the use of DHTs and mitigate industry hesitance. Unfortunately, there are two key sections of the draft guidance on *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* (May 2023) which may have actually exacerbated and increased industry hesitance:

> *The variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial. This would not affect the validity of a finding of superiority in a trial using such data (although it could reduce the effect size), but it could affect the validity of a finding of non-inferiority. Remote assessments may differ from on-site assessments, particularly when trial participants are responsible for performing their own physiological tests (e.g., home spirometry). Assessments performed by local HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel. In non-inferiority trials, when the effect size of an active control drug, for example, has only been determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT. This may present challenges in calculating a non-inferiority margin. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting" (Lines 98-110).*
>
> *A critical consideration in a DCT when delegating trial-related activities to local HCPs is the potential for variability in the approach across different practices (e.g., documenting vital signs, physical examinations, and evaluation of adverse events). Quality control measures should be in place to help reduce variability, including regular review by investigators of participant data entered by local HCPs, to assess consistency and completeness of the required procedures. The type and scope of quality control measures should be tailored to the criticality of the data and the complexity of procedures done by the local HCPs" (Lines 291-298).*

Data variability is not a concern unique to decentralized trials – as evidenced by an analysis of variability among clinicians when performing clinician reported outcomes (ClinROs).[4] Clinical trials today involve global, multi-site studies. Data variability exists, and can be thoughtfully addressed, in both DCTs and conventional trials. Moreover, a recent article notes that variability analysis as a key element in data collection.[5]

In a conventional, multi-site trial – where no DCT 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 DCT, 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.[6] However, such methods may not be appropriate for all trials or participants. In terms of mitigating potential data variability in a DCT, 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.[7] It is notable that these approaches are no different from those presently being applied by industry in *conventional* clinical trials to manage the risks associated with data variability. We believe CDER could facilitate innovative approaches to clinical trials such as DCTs and DHTs by clarifying 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 DCT differs from the data in a traditional site-based clinical trial
- a risk-based quality management approach should be used in all trials

To facilitate innovation and the use of DHTs, there are two additional paths we believe CDER could pursue to promote innovation and facilitate greater use of DHTs: namely, (1) enhanced transparency and (2) enhanced communication.

Enhancing Transparency

First, it would help promote innovative uses of DHTs if CDER could provide more transparency by publicly sharing, on a recurring basis, a handful of select, de-identified case studies where DHTs have been used in clinical trials *which have subsequently been accepted within the regulatory review of a new drug.* Of course, this would require DHT data to be clearly identified in an NDA or BLA. A potential template for implementation might be the FDA Oncology Center of Excellence's data flagging initiative, where sponsors are asked, voluntarily, to indicate if trial data was gathered remotely or in-person, with the objective of fostering the use of decentralized elements.[8] If implemented as a voluntary data-flagging initiative, it would provide the needed data to begin to actually characterize the differences, if any, between data gathered remotely vs in person.

Enhancing Communication

Second, enhanced communication opportunities between industry and CDER could help accelerate the use of innovative approaches – not just for DCTs and DHTs, but also the use of artificial intelligence/machine learning and real-world data/real-world evidence. With the current pace of innovation, the opportunity for earlier and regular dialogue with regulators – at the upstream, protocol development stage could help accelerate innovation by mitigating industry hesitance.

Recommendation Two:
Enabling Sites to Embrace Clinical Trial Innovation by Improving Clarity around Investigator Responsibility and Oversight in DCTs

One key element of innovative approaches to clinical trials is the flexibility that DCTs offer to patients to have clinical trial assessments and procedures take place at a wide variety of locations to minimize travel. However, this same migration of trial activities and assessments away from the central investigator site that provides flexibility to patients can creates site burden due to the need for investigator oversight in an increasingly complex trial environment. ACRO provides a recommendation for clarifying investigator oversight by examining the *FDA draft guidance on Decentralized Clinical Trials for Drugs, Biological Products.*

This Draft Guidance on Decentralized Trials discusses *"The Investigator and Delegation of Trial-Related Activities.*" This section of the draft guidance recognizes that *"A key difference between DCTs and traditional site-based clinical trials is the extent to which the investigator uses telehealth, trial personnel working remotely, local HCPs, and/or DHTs in the conduct of the trial."*

However, this discussion does not address important concerns for stakeholders today regarding the practical operationalization of investigator oversight and responsibility within the complex DCT matrix of the multiple parties involved in aspects of a decentralized clinical study – many of whom are not direct employees of the investigator. This lack of clarity regarding how investigator oversight and responsibility works on a daily, operational basis impedes innovation and greater adoption of DCTs. To provide much-need clarity, it is helpful to examine the regulations and the 2009 guidance on Investigator Responsibilities.

21 CFR Part 312.60 enumerates four general responsibilities of the investigator.[9] An investigator is responsible for:

1) ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations
2) protecting the rights, safety, and welfare of subjects under the investigator's care
3) the control of drugs under investigation
4) obtaining the informed consent of each human subject to whom the drug is administered, except as provided in Section 50.23 or Section 50.24

Further clarification of investigator responsibilities, oversight, and appropriate delegation of study-related tasks can be found in the 2009 guidance *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects.*[10]

The 2009 guidance discusses three different parties that can be involved in aspects of a clinical study:

1) Study staff that are in the direct employ of the investigator

2) Study staff that are <u>not</u> in the direct employ of the investigator
   these staff are involved directly in the conduct of a clinical investigation, but are not in the direct employ of the investigator
   (e.g., Investigators and/or other staff hired by an SMO)
   "A sponsor who retains an SMO shares responsibility for the quality of the work performed by the SMO."

3) Parties other than study staff
   (e.g., critical aspects of a study performed by parties not involved directly in patient care or contact and not under the direct control of the clinical investigator, such as radiological services)
   "Because the activities of these parties are critical to the outcome of the study and because the sponsor retains the services of the facility, the sponsor is responsible for ensuring that these parties are competent to fulfill and are fulfilling their responsibilities to the study."

It is important to note that the 2009 guidance discusses *shared responsibility* (between investigator and sponsor) for both "Study staff that are not in the direct employ of the investigator" and also for "Parties other than study staff." For "Study staff that are not in the direct employ of the investigator," the guidance notes that *"A sponsor who retains an SMO shares responsibility for the quality of the work performed by the SMO."* For "Parties other than study staff," the guidance notes *"Because the activities of these parties are critical to the outcome of the study and because the sponsor retains the services of the facility, the sponsor is responsible for ensuring that these parties are competent to fulfill and are fulfilling their responsibilities to the study."*

This concept of sponsors and investigators having shared responsibility, from the 2009 guidance, should apply to DCTs – specifically (1) remote trial personnel contracted by the sponsor and (2) local health care providers (HCPs) contracted by the sponsor.

The *FDA draft guidance on Decentralized Clinical Trials for Drugs, Biological Products, and Devices* distinguishes between "trial personnel" (including both "on site" and "remote" trial personnel), on the one hand, and local health care providers (HCPs), on the other. Local HCPs are defined as follows:

> *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 but are not part of the trial personnel. These local HCPs (such as doctors or nurses) may be used by sponsors or investigators to perform certain trial-related activities; for example, on a fee for-service basis. The trial-related services that they provide should not differ from those that they are qualified to perform in clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs). These services should not require a detailed knowledge of the protocol or the IP.*[11]

The local HCP is not a part of trial personnel, but provides trial-related services that are part of routine clinical practice. These HCPs are contracted *"to provide trial-related services that are part of routine clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs*)."[12]

In the same way that the 2009 guidance notes shared responsibly for study staff that are not in the direct employ of the investigator and for parties other than study staff, ACRO asks CDER to consider explicitly clarifying the notion of shared responsibility, within a DCT, for local HCPs contracted by the sponsor and remote trial personnel contracted by the sponsor. Providing clarity around investigator responsibility and oversight in DCTs will enable sites to embrace this innovative approach to clinical trials.

Recommendation 3:
Enabling Innovation and Form 1572

FDA outlines the purpose and scope of Form 1572 – and in particular on Section #6 on "Names of the Sub-investigators Who Will Be Assisting the Investigator in the Conduct of the Investigation(s)" – in its 2010 guidance which states: "The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data."[13]

The current language regarding "direct and significant contribution to the data" can be misinterpreted in a manner that exceeds regulatory requirements, resulting in a Christmas-tree-like approach to the form. As one observer commented, the Form 1572 has become "a data-collection tool for cataloging medical providers and ancillary facilities."[14] This creates challenges for clinical trials in general – and for decentralized clinical trials in particular.

To address challenges and ambiguities related to the FDA Form 1572 – particularly in the context of decentralized clinical trials (DCTs) – ACRO recommends specific language revisions to enhance clarity and reduce compliance uncertainties. The current definition of "Sub-Investigator" and the criteria for listing individuals in Section #6, which captures those making a direct and significant contribution to trial data, needs clearer demarcation.

The current 2010 guidance states regarding "Section #6: Names of Sub-Investigators":

> *"Sub-Investigator" includes any other individual member of that team." 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "a list of the names of the sub-investigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s)." The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572.*[15]

We suggest that the FDA refine the term "Sub-Investigator" to explicitly include only those individuals who perform specific protocol tasks that are distinct from routine care. Additionally, we recommend revising the phrase "contribution to data" to "interpretation of data and/or clinical results" to more accurately reflect the roles that warrant inclusion on the form. This modification will help delineate the responsibilities of team members in a DCT setting, ensuring that only those directly involved in data interpretation or critical clinical activities are listed. Implementing these changes will reduce the administrative burden on sponsors and principal investigators by clarifying the delegation and oversight responsibilities across multiple locations, thus fostering greater confidence in adopting innovative trial models like DCTs without fear of regulatory repercussions.[16]

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Recommendation 4:
Considerations for the Impact of Innovative Clinical Trial Approaches on Underrepresented Populations

Finally, it is important to consider the relationship between digital and technological innovation, on the one hand, and diversity, equity, and inclusion goals, on the other. To expand clinical trials to underrepresented populations, access to decentralized clinical trials and digital health technologies should be more equitable for all populations. Digital technologies frequently require access to devices and broadband connections to which some populations lack access. It is important to consider ways to help ensure access to such technology is equitable for all participants to avoid inadvertently creating barriers for underrepresented populations in clinical trials.

ACRO thanks the Agency for this opportunity to comment on Enhancing Adoption of Innovative Clinical Trial Approaches. Please do not hesitate to contact ACRO if we can provide further details or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

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End Notes

[1] ACRO Decentralized Clinical Trials (DCT) Toolkit
https://www.acrohealth.org/initiatives-hub/decentralized-trials/

[2] Marra, C. and Stern, A.D. (2024), Tepid Uptake of Digital Health Technologies in Clinical Trials by Pharmaceutical and Medical Device Firms. Clin Pharmacol Ther. https://doi.org/10.1002/cpt.3192

[3] Decentralized Clinical Trials for Drugs, Biological Products, and Devices – Guidance for Industry
https://www.fda.gov/media/167696/download

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations – Guidance for Industry
https://www.fda.gov/media/155022/download

[4] "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/

[5] "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/

[6] 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 the 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

[7] "Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials"
Association of Clinical Research Organizations (ACRO)
https://www.acrohealth.org/dctqanda/

[8] "US FDA Oncology Center Wants Trial Datasets Flagged as Remote or In-Person Assessments," Pink Sheet Citeline Regulatory, 14 Apr 2021, Sue Sutter
https://pink.citeline.com/PS144152/US-FDA-Oncology-Center-Wants-Trial-Datasets-Flagged-As-Remote-Or-In-Person-Assessments

"FDA Asks Oncology Trials to Flag COVID-Era Remote Datasets," CenterWatch, April 19, 2021
https://www.centerwatch.com/articles/25562-fda-asks-oncology-trials-to-flag-covid-era-remote-datasets

[9] electronic CFR
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-D/section-312.60

[10] Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects
https://www.fda.gov/media/77765/download
pages 5 to 7.

[11] Decentralized Clinical Trials for Drugs, Biological Products, and Devices: Guidance for Industry, Investigators, and Other Stakeholders
https://www.fda.gov/media/167696/download
Page 4

[12] Decentralized Clinical Trials for Drugs, Biological Products, and Devices: Guidance for Industry, Investigators, and Other Stakeholders
https://www.fda.gov/media/167696/download
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[13] Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572), May 2010
https://www.fda.gov/media/78830/download
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[14] "A call to action to advance patient-focused and decentralized clinical trials," R. Donald Harvey and Therica M. Miller et al., 09 January 2024, *Cancer: An Interdisciplinary Journal of the American Cancer Society*
https://doi.org/10.1002/cncr.35145

[15] Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572), May 2010
https://www.fda.gov/media/78830/download
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[16] A separate issue within the topic of investigator oversight – in addition to the Form 1572 – should be noted here. The FDA draft guidance on *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* introduces a brand new requirement that that local health care providers (HCPs) should be listed in a task log.
https://www.fda.gov/media/167696/download
ACRO argues in its comment to FDA on this draft guidance that the introduction of the task log is not only a *new* requirement for DCTs, but also creates a *different* requirement for DCTs compared to conventional trials – holding DCTs to a separate standard. DCTs should be regulated in the same way as non-DCTs. We suggest that the task log is an expansion of oversight beyond current practice in conventional trials, where study staff operating within the scope of their license to provide routine care related to a trial are not listed on the Delegation of Authority (DOA). In addition, the task log introduces a new burden for investigators without improving patient safety. We ask the Agency to consider removing the task log requirement from the final guidance.
ACRO comment letter (August 1, 2023)
https://www.acrohealth.org/wp-content/uploads/2023/11/ACRO-Final-Comment-on-DCTs.pdf