



May 12, 2023

Christopher M Hartshorn, Ph.D.
Erica Rosemond, Ph.D.
National Center for Advancing Translational Sciences
6701 Democracy Boulevard
Bethesda MD 20892-4874

RE: ACRO Response:
NCATS Request for Information (RFI): Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials
Notice Number: NOT-TR-23-006

Dear Dr. Hartshorn and Dr. Rosemond,

The Association of Clinical Research Organizations (ACRO) represents the world’s leading clinical research and 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-man studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficacy, and safety of biomedical research.

ACRO thanks NCATS for this RFI which invites stakeholders to comment on how DCTs may be designed to be more effective, efficient and equitable to bring more interventions to all people, faster. Rather than attempting to address the full list of suggested topics in the RFI, ACRO has focused on the four following topics.

***I. Resources, Infrastructure, and Enabling Technologies:
Identifying available resources, tools, or technologies used, or useful, for DCTs and technological needs for the future as well as common operational challenges in deploying and running DCTs***

A key component of a robust infrastructure for DCTs has been frequent stakeholder conversations regarding the value of clarifying the language and definitions used to describe DCTs. Numerous stakeholders have contributed to the need for precise language.¹

In late 2019, ACRO established a new committee – the ACRO DCT Working Party – to develop resources to support and advance DCTs. The ACRO DCT Toolkit is available to all stakeholders on the ACRO website.² The Toolkit includes five distinct resources – the Quality-by-Design Manual for DCTs; the Risk Assessment Considerations Tool; the Data Flow Maps; a Quick Reference Guide to the QbD Manual; and a Change Management Tool. In the Change Management Tool (*Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials*), we describe how the most efficient way to define and characterize DCTs is to think about DCT “elements” or “components.” Within the Change

Management Tool, ACRO operationalizes the definition of DCTs as those studies that contain one or more of eleven core DCT components, which are defined in the Change Management Tool and listed here:³

- eSignature
- eConsent
- Electronic Screening
- Remote Patient ID Verification
- Direct-to-patient (and direct-from-patient) shipment
- Home health visits (HHVs) and Home Healthcare (HHC) professionals
- Telemedicine
- eCOA and ePRO
- Connected devices and digital endpoints
- Local community or mobile labs
- EMRs/EHRs

II. Data Integration, Quality, Accessibility, and Reproducibility

- ***Maintaining data consistency and quality relative to digital health technologies and/or Bring-Your-Own-Device (BYOD) approaches in the context of a DCT***
- ***Analyzing, and reporting, disparate data generated from both the centralized and DCT results***

ACRO has examined issues of data consistency and quality in DCTs in two of the ACRO DCT Toolkit resources: (1) the Data Flow Maps⁴ and (2) the Change Management Tool⁵. The ACRO DCT Data Flow Maps are designed to build confidence and trust in decentralized clinical trials by providing transparency and visibility into data flow, data controls, and data traceability within a DCT to illustrate how a decentralized model guards data quality and integrity.

While wearables and monitoring devices may capture minute-by-minute information, study design and statistical analysis define the relevant time points that are most appropriate for the research effort and the volume of information that will be included in study submission data. Recent FDA draft guidance on the use of digital health technology points out this consideration in the discussion of general-purpose computing platforms versus the durable electronic trial data repository.⁶ Moreover, the FDA's guidance on real-world data and real-world evidence highlights that planned analyses should be documented and any algorithm changes tracked to help ensure that the volume of data collected and analyzed is appropriate as the trial progresses.⁷

As more types of data become available and can be readily collected by both passive (e.g., sensors) and active (e.g., ePRO) methods during a clinical trial, researchers may face challenges in designing and limiting data collection. Continuous monitoring provides a more immediate and real-world view of patients, and it permits monitoring of large volumes of data that look not just at the protocol endpoints, but also at study performance trends, patient adherence, and early signals. With continuous data collection – from sensors and wearables as well as frequent patient-reported data – a significantly larger amount of data is collected compared to a CRF.

Sponsors and CROs should have processes in place to capture only those data necessary to support the study design and endpoints, in the least burdensome way for patients. In this way, it is possible to have a clear understanding of what the data will be used for and minimize any risk of gathering excess data. The protocol is the starting point for defining what information is gathered; the purpose of gathering the information; and how data will be used to support the research effort and its endpoints. Good governance on protocol design should include input and feedback from the scientific community as well as from patients regarding data collection. Key questions include:

- What are the endpoints that are appropriate for the trial?
- What are the most effective and efficient methods for collecting the data for these endpoints?
- What are the burdens on the site/PI/patient in collecting these data?
- What are the burdens on our infrastructure and data management resources in collecting and analyzing these data?
- What are the risks of collecting and storing the data?

DCTs have resulted in the collection of more data; more types of data; and more complex data. Once the appropriate endpoints and methods for collecting the trial data are established, the tools that are used should be configured appropriately to enable good governance. Using technology to interrogate the full data set, irrespective of origin, as well as appropriate filtering for increasing volumes of data is appropriate.

In addition, appropriate guardrails should be in place to help ensure that the data collected have checksums (sequences of numbers and letters used to check data for errors) for active data so that invalid data points cannot be collected (e.g., a patient cannot manually enter a body temperature of 198.6). Filters should be in place to help ensure that passive data that falls outside of normal ranges can be identified for notifications to the PI, site or monitor to follow up in order to protect patient safety. For example, an elevated heartrate of 190 BPM when, two minutes earlier, the resting heartrate was 72 may be a device malfunction or adjustment of the sensor by the patient and should be screened or filtered appropriately. Collection methods and specific endpoint objectives should be clearly defined in the protocol and IRBs and ethics committees should be trained to look for excessive data collection that goes beyond the premise or purpose of the research. Monitors should also be following up with data points that are being collected outside of the primary and secondary endpoints to help ensure that appropriate measures are being followed by the PI and site staff.

III. Study Participation and Adherence

Developing the methods, tools, resources, and platforms to efficiently, safely, and securely screen, consent, enroll and follow up with DCT research participants

One of the main sections of ACRO's Change Management Tool for DCTs is focused on patient safety and patient-centricity. Indeed, Question #1 of the Change Management Tool is: *"How are DCTs designed to protect patient safety?"*⁸

The Change Management Tool emphasizes that – regardless of whether the trial design is conventional or decentralized – the principal investigator has responsibility to oversee patient safety per International Council for Harmonization Good Clinical Practice (ICH GCP). The medical care given to, and medical decisions made on behalf of, subjects in a clinical trial should always be the responsibility of a qualified physician.

A key challenge in planning a DCT, is determining how PI oversight and responsibility are maintained when patient interactions and assessments occur outside the investigator site. Each study needs to have a detailed operational plan for professional roles that clearly explains safeguards and processes including (but not limited to) the following elements outlined in the ACRO Change Management Tool:⁹

- A protocol outlining how PI oversight and responsibility will be maintained
- CRA processes to confirm tasks are completed and documented
- Triggers for tele-visits and/or home nurse visits to assess the patient
- Processes for safety monitoring for sites
- Processes for safety monitoring for HHC nurses in order to conduct study procedures in an off-site, local setting as instructed under the oversight and responsibility of the PI
- Clear training for sites on how safety monitoring is completed for patients in a DCT
- Clear processes for sites to use to review and approve HHC nurses who will be utilized as an extension of the site (including but not limited to):
 - Clear delegation (via a documented Delegation Of Authority) to HHC
 - Training for HHC professionals on safety monitoring and reporting back to PI
- Mobile clinician credentialing, clinical research, protocol and GCP-specific training, as well as AE/SAE identification, management and communication with the PI
- Clear education for patients (including but not limited to):
 - Processes for patient to go to urgent care; follow standard of care, as needed; and then provide information back to virtual study site staff
 - Processes for how to report safety events as soon as aware to virtual study site staff and to home nurse during visit

The RFI asks about study participation and adherence. An important factor here is whether DCTs create burdens for patients. Question #7 of the ACRO Change Management Tool asks: *“Will DCTs create increased burden and responsibilities on patients?”*¹⁰

ACRO identifies several ways to anticipate and mitigate potential patient burdens:

- ensuring that patients feel properly educated about DCTs (the content)
- ensuring that the most appropriate vehicles are used for conveying educational material – which will vary from patient to patient (information delivery media)
- working to develop DCT tools and technology that are intuitive and empathetic

Our examination of studies of patient experience revealed the promise of DCTs for patient adherence. In a recent survey, oncology patients were asked about their views on participating in DCTs. They expressed their comfort in replacing trial site visits with DCT solutions as a part of a clinical trial and many DCT tools – wearable sensors, home nursing, and telemedicine – were rated highly as options.¹¹

***IV. Workforce Development:
Identifying and developing a clinical research workforce with knowledge, skills, and abilities to administer a DCT***

An important consideration in any workforce discussion is the potential that DCTs might create burdens for clinical research sites and to examine potential ways to mitigate such burdens. One of the objectives of the ACRO Change Management Tool is to begin to address potential site workforce burdens.

The Change Management Tool is organized in a question-and-answer format. Question 6 asks: *“Will DCTs create increased operational burden on the sites/PIs that could be difficult to manage (e.g., multiple platforms and sign-ons)?”*¹²

ACRO’s review of research on site burdens, including surveys of site personnel, revealed four key issues:

- the multiplicity of systems and log-in credentials for eClinical technologies¹³
- disparate technologies, while intended to help sites streamline their data collection, often have the opposite effect and become burdensome (technology may alleviate an existing burden, but introduce a brand new one)¹⁴
- site capabilities with new technologies are one of the primary barriers to successful implementation of DCTs¹⁵
- one element of alleviating these burdens is for sites to have access to adequate logistical and technical training and support¹⁶

Thank you for this opportunity to provide feedback, and please do not hesitate to reach out to ACRO if we can provide additional information or answer any questions.

Respectfully submitted,

Karen Noonan
Senior Vice President, Global Regulatory Policy
ACRO
Email: knoonan@acrohealth.org

End Notes

¹ Please see:

Innovative Medicines Initiative (IMI) Trials@Home Glossary of terms and definitions used

<https://trialsathome.com/trialshome-glossary/>

TransCelerate White Paper “BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT,” TransCelerate Biopharma Inc. 2020

https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/08/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

Clinical Trials Transformation Initiative (CTTI) Glossary for the Digital Health Trials Recommendations

https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Digital_Health_Technologies_Glossary.pdf

Decentralized Trials and Research Alliance Glossary

<https://www.dtra.org/1a-glossary>

² The ACRO DCT Toolkit is available on the ACRO website at:

<https://www.acrohealth.org/dct/>

³ The ACRO DCT Toolkit Change Management Tool can be downloaded here:

Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials (2022)

<https://www.acrohealth.org/dctqanda/>

⁴ The Data Flow Maps can be found on ACRO’s website here:

<https://www.acrohealth.org/dctdataflow/>

⁵ The ACRO DCT Toolkit Change Management Tool can be downloaded here:

Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials (2022)

<https://www.acrohealth.org/dctqanda/>

⁶ FDA Draft Guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations Guidance for Industry, Investigators, and Other Stakeholders (December 2021)

<https://www.fda.gov/media/155022/download>

⁷ FDA Draft Guidance on Considerations for the Use of Real-World Data and RealWorld Evidence to Support Regulatory Decision-Making for Drug and Biological Products (December 2021)

<https://www.fda.gov/media/154714/download>

⁸ The ACRO DCT Toolkit Change Management Tool can be downloaded here:

Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials (2022)

<https://www.acrohealth.org/dctqanda/>

page 11

⁹ The ACRO DCT Toolkit Change Management Tool can be downloaded here:

Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials (2022)

<https://www.acrohealth.org/dctqanda/>

page 11

¹⁰ The ACRO DCT Toolkit Change Management Tool can be downloaded here:

[Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials \(2022\)](#)

<https://www.acrohealth.org/dctqanda/>

page 15

¹¹ Role of decentralized clinical trials in cancer drug development: Results from a survey of oncologists and patients, Digital Health, Volume 8: 1–24

<https://pubmed.ncbi.nlm.nih.gov/35646380/>

¹² The ACRO DCT Toolkit Change Management Tool can be downloaded here:

[Navigating Change During Rapid Transformation: A Question-and-Answer Resource for Decentralized Clinical Trials \(2022\)](#)

<https://www.acrohealth.org/dctqanda/>

page 14

¹³ SCRS Releases Research Report on the Impact of eClinical Technologies and Related Initiatives on Sites, October 3, 2019, SCRS

<https://myscrs.org/uncategorized/scrs-releases-research-report-on-the-impact-of-eclinical-technologies-and-related-initiatives-on-sites/>

¹⁴ Sites Speak Out on Clinical Trial Technology Overload, SCRS White Paper in Collaboration with IQVIA, July 2020

<https://myscrs.org/learning-campus/white-papers/>

¹⁵ The Impact of Decentralized and Hybrid Trials on Sponsor and CRO Collaborations July 27, 2022, [Applied Clinical Trials](#)

<https://www.appliedclinicaltrials.com/view/the-impact-of-decentralized-and-hybrid-trials-on-sponsor-and-cro-collaborations>

¹⁶ No place like home? Stepping up the decentralization of clinical trials, June 10, 2021, McKinsey

<https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials>