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Diane Maloney, Center for Biologics Evaluation and Research
Paul Kluetz, Oncology Center of Excellence
Soma Kalb, Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 3342
Silver Spring, MD 20993

RE: ACRO comment submission:
Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders
[FDA-2022-D-2870]

Dear Dr. Robinson, Ms. Maloney, Dr. Kluetz, and Dr. Kalb,

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ACRO thanks the Agency for releasing this draft guidance on *Decentralized Clinical Trials for Drugs, Biological Products, and Devices*. ACRO is pleased to provide the following feedback.

General Comments and Recommendations:

ACRO offers general comments on four topics:

- Investigator oversight
- New task log requirement
- Data variability
- DCTs and clinical trial diversity

In addition to suggesting further discussion of these four topics in the final guidance, ACRO asks the Agency to consider holding a public workshop with stakeholders to further address these topics, given their complexity and importance for decentralized trials.

I. Investigator Responsibility and Oversight in DCTs: ACRO Recommendations for Improved Clarity

Section III (D) (2) of the Draft Guidance on Decentralized Trials discusses *“The Investigator and Delegation of Trial-Related Activities.”* This section of the draft guidance recognizes that *“A key difference between DCTs and traditional site-based clinical trials is the extent to which the investigator uses telehealth, trial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 greater adoption of DCTs. To provide much-needed 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.¹ 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.*²

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 not 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 notes 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.”

ACRO suggests that the Agency discuss in the final guidance how this concept of shared responsibility from the 2009 guidance applies 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: Guidance for Industry, Investigators, and Other Stakeholders* 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.³

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).”⁴

In the same way that the 2009 guidance notes shared responsibility for study staff that are not in the direct employ of the investigator and for parties other than study staff, ACRO asks the Agency to consider the notion of shared responsibility for local HCPs contracted by the sponsor and remote trial personnel contracted by the sponsor.

II. New Task Log Requirement

The draft guidance discusses local health care providers (HCPs) and describes their role as follows:

- local HCPs perform assessments as part of **routine clinical practice** (e.g., evaluation of symptoms, performing physical examinations, reading radiographs, obtaining vital signs) (lines 103-104 and lines 274-276 – emphasis added)

- located close to trial participants' homes but are not part of the trial personnel (lines 127-128)
- 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 (lines 128-130)
- The trial-related services that HCPs 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) (lines 130-132)
- These HCP services should not require a detailed knowledge of the protocol or the investigational product or the investigator's brochure (lines 132-133 and lines 276-277)

The draft guidance requires local HCPs to be listed in a task log, as noted in lines 300-309:

As part of preparing and maintaining adequate case histories, investigators must maintain a task log of local HCPs who perform trial-related activities.

- *The task log should include (1) the names and affiliations of the local HCPs, (2) a description of their roles and assigned tasks, (3) the dates these local HCPs are added to the log, and (4) the locations where these activities are conducted.*
- *The task log should be dated and signed by the investigator when initially created and updated when new local HCPs are added. The task log should be available to FDA during inspections.*

Local HCPs perform assessments as part of routine clinical practice; that are within their license; and that do not require a detailed knowledge of the protocol, investigational product, or the investigator's brochure. Therefore, the introduction of a new requirement that these HCPs be listed in a task log stands in contrast to – and represents a significant departure from – other guidance on investigator responsibilities. Both the 2009 FDA guidance on Investigator Responsibilities⁵ and the ICH E6(R3) Draft Guideline on Good Clinical Practice (GCP) state that the investigator should maintain a record of the appropriately qualified persons to whom *significant* trial-related duties have been delegated. ICH E6(R3) section 2.3 “Responsibilities,” subsection 2.3.3 states:⁶

*The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated **significant** trial-related activities. **In situations where the clinical trial activities are performed in accordance with routine clinical care, delegation documentation may not be required.** [emphasis added]*
(lines 474-477)

ACRO believes 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. 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). We need to think of decentralized trials as simply clinical trials (especially given that an increasing number of trials contain decentralized elements and, therefore, the distinction between DCTs and conventional trials becomes blurred). And, DCTs should be regulated in the

same way as non-DCTs. In addition, the task log introduces a new burden for investigators without improving patient safety. As noted in the draft guidance, the trial-related services that HCPs provide should not differ from those that they are qualified to perform in clinical practice and should not require a detailed knowledge of the protocol or the investigational product or the investigator's brochure. In the case of oncology or other similarly complex indications, the requirement of a task log for routine care related to a trial adds a significant number of providers who have little to no involvement with the protocol, IMP, or IB. We ask the Agency to consider removing this requirement from the final guidance.

III. Data Variability

The topic of data variability is discussed in two key sections of the draft guidance.

“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).⁷ 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.⁸

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.⁹ 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.¹⁰ 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 the Agency consider modifying the final guidance discussion of data variability 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 DCT differs from the data in a traditional site-based clinical trial
- a risk-based quality management approach should be used in all trials

IV. DCTs and Diversity, Equity, and Inclusion

DCTs are a powerful tool to support the Agency’s diversity goals, and we ask the Agency for further discussion – in the final guidance and in a public workshop – of how DCTs support clinical trial diversity goals.

Several global surveys confirm that DCTs, with their digital and mobile options, are welcomed by participants. The global 2021 CISCRP Survey on 11,793 individuals founds that individuals from diverse communities are *“less willing to attend in-person clinic visits regardless of location type,”* and that there is a *“general high receptivity to decentralized clinical trials, with most generally comfortable using technology as part of a clinical trial.”* In addition, the survey found that *“respondents who identified as Black and/or Hispanic were more likely to cite home study visits and mobile app availability as important clinical study aspects compared to White respondents.”*¹¹

One of the main benefits of the digital and mobile solutions within a DCT are to reduce or remove the geographical boundaries to research participation. The 2021 Pharma Intelligence Report with 921 respondents confirmed that almost 50% of patients that had not participated in a study cited that distance to a site was a barrier to their participation.¹²

Finally, in 2022, the Life Sciences Strategy Group conducted a global survey on 800 respondents consisting of the general population and those that have participated in trials found that *“in-home treatment and use of familiar technology have the greatest, positive impact on trial participants’ willingness to participate in a future clinical trial”* and that *“traveling consistently ranks lowest for ease of use, beneficial impact on experience, positive influence on continuation of participation, and future willingness to participate.”* In addition, *“general population respondents who have not participated in clinical trials are attracted to trials with flexible, convenient, at-home options’ with ‘inflexible requirements’ being the third reason for non-participation in research.”*¹³

Line-specific Comments and Recommendations:

Lines 22-27:

The current text states:

In fully decentralized clinical trials, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants. In hybrid DCTs, some trial

activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes.

ACRO recommends expanding this description of where decentralized trial activities take place to more fully reflect current practice by inserting the following underlined additional language in the final guidance:

In fully decentralized clinical trials, all activities take place at locations other than traditional trial sites. These trial-related activities may take place at the homes of trial participants or in local health care facilities (such as local community health centers, retail pharmacies, and mobile facilities) that are convenient for trial participants. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical trial sites, and other activities are conducted at locations other than traditional clinical trial sites, such as participants' homes, local community health centers, retail pharmacies, and mobile facilities.

Lines 49-52:

The current text reads: “Many clinical trials already include decentralized elements such that not all trial-related activities involving participants take place at traditional clinical trial sites. For example, laboratory tests are often conducted by clinical laboratory facilities at locations remote from traditional trial sites.”

ACRO believes there is an opportunity to refine this text to better reflect current practice by incorporating the following underlined additional language in the final guidance:

Many clinical trials already include decentralized elements such that not all trial-related activities involving participants take place at traditional clinical trial sites. For example, laboratory tests are often conducted by clinical laboratory facilities at remote locations or via remote sampling taken by local HCPs or by participants themselves.

Lines 187-196:

The draft guidance states:

“Sponsors should strive for diversity and inclusiveness in trial populations.¹⁹ 187 Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of diverse participants in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes, including through the use of DHTs, may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may improve engagement, recruitment, and retention of diverse participants (e.g., race, ethnicity, age, sex, and geographic location). Further, the use of local HCPs may reduce cultural or linguistic barriers to participation in clinical trials.”

In order to facilitate participation in a DCTs, the use of BYOD devices should be included, and we recommend the following underlined addition in the final guidance:

Sponsors should strive for diversity and inclusiveness in trial populations.¹⁹ 187 Outreach

through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of diverse participants in areas where there are limited or no traditional clinical trial sites. Bringing trial-related activities to participants' homes, including through the use of DHTs, may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites. The use of local HCPs close to potential participants' homes may improve engagement, recruitment, and retention of diverse participants (e.g., race, ethnicity, age, sex, and geographic location). Further, the use of local HCPs may reduce cultural or linguistic barriers to participation in clinical trials. The option of participants to use their own devices – "Bring Your Own Device" (BYOD) – should be considered within study trial designs to optimize accessibility or inclusiveness in trial populations.

Omissions in Draft Guidance:

We ask the Agency to consider including new sections on monitoring and patient-focused drug development and to consider expanding the current "Glossary" section.

Monitoring:

The draft guidance is largely silent on monitoring in a DCT. We ask the Agency to consider including a short section on monitoring, and we recommend the principles outlined in Section 7 ("Trial Monitoring") of the *HMA/European Commission/EMA Recommendation Paper on Decentralised Elements in Clinical Trials* (2022).¹⁴

DCTs and Patient-Focused Drug Development:

ACRO would like to see further discussion in the final guidance of how DCTs can potentially play a role in supporting the FDA's priorities for patient-focused drug development (PFDD). We believe this would be a good topic for the public workshop requested earlier in this comment. As noted by the Agency, the primary goal of PFDD is to better incorporate the patient's voice in drug development and evaluation, including but not limited to:

- Facilitating and advancing use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making
- Encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimizing the burden of patient participation in clinical trials
- Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of trade-offs between treatment benefit and risk outcomes
- Identifying the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision-making

A recent study helps clarify how Patient-Focused Drug Development can be measured by identifying the meaningful aspects of health which they describe as the aspect of a disease that the patient a) does not want to become worse b) wants to improve or c) wants to prevent.¹⁵ By using the 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 can play a role in supporting measurement of the patient experience.

Glossary:

Before turning to the glossary itself, we wish to recognize the challenges in finding the best language to describe the rapid modernization of clinical trials. ACRO members note that it is increasingly common for clinical trials to include one or more decentralized elements. Because the embedding of digital technologies and remote flexibilities into clinical trials is becoming more routine, the distinction between “decentralized trials” and “conventional trials” is blurred. Given this convergence of DCTs and conventional trials, we argue that the term “decentralized trial” may have outlived its usefulness because it ends up obfuscating – instead of accurately capturing – the way studies are actually conducted today. It is time to consider shedding the bifurcation of trials as “decentralized” or “conventional.” Instead, we should think more broadly about modernized clinical trials (which may contain one or more “decentralized elements”). The concept of decentralized “elements” or “components” or “methods” is used in the *HMA/European Commission/EMA Recommendation Paper on Decentralised Elements in Clinical Trials (2022)*¹⁶ and also by ACRO in its change management tool for DCTs.¹⁷

Regarding the glossary itself, ACRO asks the Agency to consider expanding the glossary to incorporate some key terms that are missing (e.g., “local HCP,” “on-site trial personnel,” “remote trial personnel,” and “mobile nurses”). In addition, it would be helpful to use the glossary section to clarify any differences between the related terms “telehealth,” “videoconferencing,” and “real-time video interactions.” Finally, the phrase “traditional clinical trial site” (or “traditional trial site”) is used throughout the draft guidance. To improve clarity, we ask the Agency to consider the alternative term “investigator site.”

ACRO thanks the Agency for this opportunity to comment on this draft guidance on *Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders*, and we would welcome the opportunity to further discuss these issues in a DCT public workshop. Please do not hesitate to contact ACRO if we can provide further details or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

Karen Noonan
Senior Vice President, Global Regulatory Policy, ACRO

End Notes

¹ electronic CFR

<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-D/section-312.60>

² *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.

³ *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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⁴ *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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⁵ *Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*

<https://www.fda.gov/media/77765/download>

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⁶ ICH E6(R3) Draft Guideline on Good Clinical Practice (GCP)

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

⁷ “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/>

⁸ “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/>

⁹ 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

¹⁰ “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/>

¹¹ CISC RP, 2021 Perceptions and Insights Study, 15th September 2021

<https://www.ciscrp.org/services/research-services/perceptions-and-insights-study/>

¹² Pharma Intelligence Patient Perspectives on Clinical Trial Participation Report

<https://pharmaintelligence.informa.com/resources/product-content/patient-perspectives-on-clinical-trial-participation-report>

¹³ Decentralized Clinical Trial (DCT) Strategies to Enhance Patient Satisfaction and Future Participation, Life Sciences Strategy Group, September 2022.

<https://lifesciencestrategy.com/publications>

¹⁴ HMA/European Commission/EMA Recommendation Paper on Decentralised Elements in Clinical Trials (2022)

https://health.ec.europa.eu/latest-updates/recommendation-paper-decentralised-elements-clinical-trials-2022-12-14_en

¹⁵ “Developing and Selecting Digital Clinical Measures That Matter To Patients”

Digital Medicine Society (DiME)

<https://dimesociety.org/developing-and-selecting-digital-clinical-measures-that-matter-to-patients/#:~:text=A%20meaningful%20aspect%20of%20health,or%20c%20want%20to%20prevent>

¹⁶ HMA/European Commission/EMA Recommendation Paper on Decentralised Elements in Clinical Trials (2022)

https://health.ec.europa.eu/latest-updates/recommendation-paper-decentralised-elements-clinical-trials-2022-12-14_en

¹⁷ “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/>