

Decentralizing Clinical Trials

A New Quality-by-Design, Risk-Based Framework



Introduction

Clinical trials play a vital role in the development of new therapies, with positive trial outcomes helping pave the way for regulatory approval and market entry. Traditionally, trial activities have been centered around trial sites, locations where patients receive treatment or an investigational medical product (IMP) and are evaluated to determine the safety and efficacy of the intervention. Such “conventional” or “traditional” clinical trials require patient travel, which may be time-consuming, inconvenient, or costly and could restrict access for individuals who live far away from a trial site, have limited mobility, or cannot spare the time away from work. Any unnecessary burden on patients could make it difficult to enroll and retain a sufficient number of participants in the trial.

Innovations in clinical trial design are leveraging emerging mobile technologies and increased connectivity to transcend some limitations of conventional trials by incorporating decentralized, patient-centric approaches. Because of their expertise in clinical trial innovation and clinical trial technology, the clinical research and technology companies of the Association of Clinical Research Organizations (ACRO) (www.acrohealth.org) have paved the way in designing, executing, and refining decentralized clinical trials (DCTs).

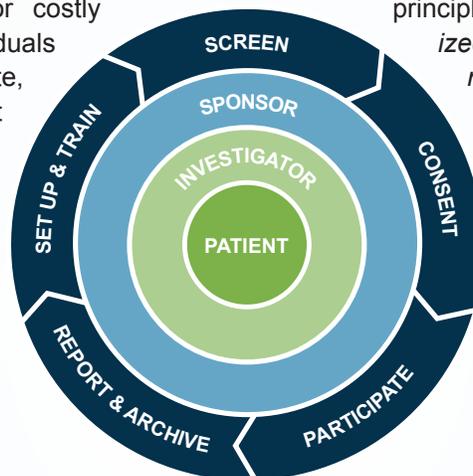
To facilitate adoption of DCTs, ACRO—an industry trade association of leading, global clinical research and technology companies—established a new committee in 2019 composed of ACRO member company experts, the ACRO Decentralized Clinical Trials Working Party, to examine the unique benefits and challenges of DCTs, with the aim of creating tools to mitigate the uncertainty around creating and implementing DCTs.

The ACRO DCT Working Party’s analysis of the beginning-to-end steps in creating and implementing a DCT resulted in two assets: *Bringing the Trial to the Patient: A Quality-by-Design Manual for Decentralized Clinical Trials* contrasts a conventional trial with a DCT in order to examine the unique issues and challenges within a DCT, providing a framework for ensuring that quality is incorporated into each step and decision in the construction of a DCT as a guiding principle¹. The accompanying *Decentralized Clinical Trials (DCT) Risk Assessment Considerations* spreadsheet is

designed to complement (rather than replace) an organization’s current risk assessment tools². It provides questions, considerations, and potential mitigations to facilitate a quality-by-design and risk management approach to decentralized trial design. The spreadsheet is intended to supplement an organization’s existing risk assessment process by providing DCT-specific questions, which can be added to an existing risk management workbook. The ACRO Quality-by-Design Manual and Risk Assessment Considerations

spreadsheet can both be found on the Decentralized Clinical Trials page of the ACRO website: www.acrohealth.org/dct.

As a leading voice for safe and ethical clinical trials, ACRO works with stakeholders globally to promote a better and more efficient clinical trial process. According to Fiona Maini, Principal – Global Compliance and Strategy at Medidata and Chair of the ACRO DTC Working Party, “The mission of the Quality-by-Design Manual is to provide considerations criteria and a risk assessment for determining whether a trial can be fully or partially decentralized, or if it should proceed via a conventional model.”



Virtualizing Clinical Trials: A New Quality-by-Design, Risk-Based Framework

Overview of DCTs

The ACRO Quality-by-Design Manual defines a DCT as a trial design focused on “bringing the trial to the patient by utilizing local healthcare providers, optimizing digital health technologies, and enabling the voice of the patient in order to accelerate medicinal product development, speed delivery of therapies to patients, and create efficiencies across clinical research processes.” Although other DCT definitions have been developed by organizations such as the Clinical Trials Transformation Initiative (CTTI), the U.S. Food and Drug Administration (FDA), and the Medicines and Healthcare Products Regulatory Agency (MHRA), these share two basic elements with ACRO’s definition: (1) use of telemedicine/digital health technologies and (2) having some or all trial activities take place outside of traditional trial sites^{3,4}.

The DCT approach is supported by major regulatory bodies around the world; however, acceptance of DCTs has been slow because many industry sponsors and trial investigators are wary of deviating from established trial protocols due to a perception of increased operational requirements, business risk, and regulatory hurdles^{3,5-7}. But as COVID-19 swept across the globe, many clinical trials were delayed or halted due to travel restrictions and the risk that trial participants might be exposed to the virus [**Case Study 1: PPD—Rescuing a Pandemic-disrupted Trial**]. As a result, the pandemic has become an accelerator for development and adoption of DCTs, given their potential to bring the trial directly to the patient [**Case Study 2: IQVIA—Converting On-site Trial to a Remote DCT**]⁹⁻¹¹. The ACRO Quality-by-Design Manual and Risk Assessment Considerations spreadsheet provide principles for determining the appropriateness of decentralization and how best to implement it.

When considering a decentralized clinical trial design, the ACRO DCT Working Party recommends thinking of decentralization as a verb—instead of as an adjective—in order to describe precisely which elements of a clinical trial are being considered for decentralization. In practice, there are very few fully decentralized trials. As Fiona Maini explains, “For certain trials, it’s

Case Study 1

PPD—Rescuing a Pandemic-disrupted Trial⁸

- Dermatology trial under way as COVID-19 emerged in Italy, one of the hardest hit countries early in the pandemic
- Travel restrictions prevented some patient visits
- Italian Ministry of Health released guidance supporting rapid adaptation of trial protocol
- PPD[®] Digital, coordinating with investigators, deployed visual communication tool TeleVisit in record time so that patient assessments were not disrupted
- Trial rescued by decentralization in a matter of days



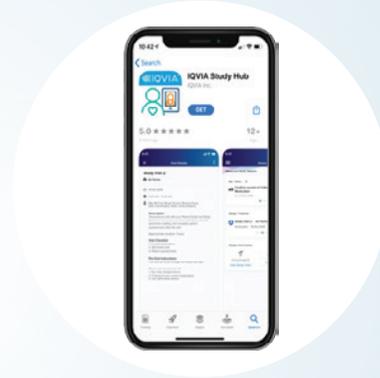
impossible to do 100% decentralization, but you can decentralize parts of the trial. This already happens today. For example, you could have a situation where the trial participants come to a site to learn about the study, take documentation home for review and then provide informed consent electronically. Once enrolled, the drug product is sent directly to the participant, and a mobile health care professional does a home visit to administer it. But the patient goes to the site again for tests that are impossible to do remotely, such as medical imaging like an MRI or an X-ray.”

Most trials labeled as DCTs are in fact “hybrid trials” that include traditional trial elements as well as DCT

Case Study 2

IQVIA—Converting On-site Trial to a Remote DCT¹²

- Highly complex study using 100% traditional on-site assessments and procedures
- Assessments halted as COVID-19 struck
- Trial converted into a remote DCT (rDCT)
- Study drug shipped to patients without delay
- Home health personnel administered drug, drew blood, shipped samples to lab
- Study Hub technology ensured continuity of contact between patient and site
- Study fully converted to an rDCT within 1 week and continued uninterrupted



Remote DCT

methods. Far from undercutting the DCT concept, however, partial decentralization may be a way for sponsors and investigators to add DCT methods to traditional trial protocols—stepping into decentralization without completely redesigning existing clinical trial models.

The concept of trial decentralization is actually fairly mature, as many of the methods and technologies characteristic of DCTs have long been in use. According to Fiona Maini, “Decentralizing trials is not a new concept and has been going on for over a decade. Many trials today are hybrids. The ACRO member group believes that end-to-end guidance could be very beneficial for greater adoption of DCTs.”

There are, however, situations where decentralization is generally not appropriate. The expense, effort, and time required to implement a DCT would likely be prohibitive for phase 1 trials or other studies with small numbers of patients and very short follow-up times. Safety concerns also make the DCT model less suitable for early phase trials or any study using an IMP that does not have an established safety profile, since in-person supervision and quick access to medical care in case of an adverse event may be advisable. Likewise, studies involving in-hospital care or procedures only available at clinical sites are not good candidates for decentralization.

Advantages of DCTs

When asked to name the main advantages of a DCT, the ACRO experts interviewed for this white paper all cited patient-centricity first. Increasing patient engagement by (1) gathering input during the trial development process from patients or patient organizations, (2) providing more information about the trial directly to patients, and (3) using patient-reported outcomes as study endpoints all enrich the patient experience, increasing retention

rates and potentially generating new types of data that better inform care. Helen Howitt, Senior Director, Quality Management at Syneos Health and a member of the ACRO DCT Working Party, says, “The patient voice is very important. As an industry, we mustn’t assume that a particular decentralized approach is a good idea and that the target patient population will want to engage with the things we’re suggesting.”

Other efforts at increasing patient-centricity focus on making trial participation more convenient. To this end, DCTs often incorporate telemedicine technology or home visits to reduce the need for patient travel, a significant burden as highlighted in a survey that found the average one-way distance between patient and trial site was 25 miles (40 kilometers)¹³. “It’s about bringing the trial to the patient and making it easier for participants to join clinical research, not only for their own health but also for the benefit of others with a similar condition,” says Fiona Maini.

When used appropriately, DCTs also offer sponsors and investigators enhanced efficiency, long-term cost savings, and faster collection of data [**Case Study 3: Covance—Practicing Patient Centricity, One Patient at a Time**]. Risk-based monitoring for DCTs, where potential problems are identified during the trial design phase and strategies for detecting them through study data are built into the trial protocol, is less time consuming than on-site monitoring and can be done remotely, decreasing the burden on sites and potentially reducing costs. Decentralized data collection allows individuals or mobile healthcare providers to enter data

on their own devices, with the information then flowing directly to the study’s data repository. With faster and more direct electronic data capture, study personnel can identify and address issues in real time.

Another major advantage of DCTs is that they can incorporate new and different types of data collection, such as continuous monitoring of vital signs and other status assessments by wearable devices, as well as direct data input from the patient using mobile devices or questionnaires accessed through online patient portals [**Case Study 4: PRA—Implementing a Fully Decentralized Trial Pre-COVID**]. “I believe the application of technology allows for real-time data insights and will modernize the way clinical trials are performed, thus decreasing the burden for sites and patients to participate,” says Carrye Nibbelink, Senior Director Of Operations and Innovation at PRA Health Sciences and a member of the ACRO DCT Working Party.

These advances in decentralized data collection allow large amounts of data to be collected in real-world settings—even in trials enrolling thousands of patients—potentially providing new insights that are

Case Study 3

Covance—Practicing Patient Centricity, One Patient at a Time¹³

- Trial participant living in Miami had to make an unexpected trip to New York City
- While trying to schedule an appointment, patient concierge team realized participant would miss a blood draw
- Risk that participant would have to drop out of study
- Alternate LabCorp Patient Service Center in NYC located by trial personnel
- Patient had blood drawn in NYC
- Sample shipped to Covance Central Laboratory Services in Indianapolis and processed within 24 hours
- Participant remained enrolled, sparing the study sponsor the effort and expense of enrolling a replacement—at an estimated cost of \$10,000-\$25,000—as well as a potential delay in completing the trial



Image repurposed with permission from Covance.

Case Study 4

PRA—Implementing a Fully Decentralized Trial Pre-COVID¹⁴

- Phase IIIb randomized, double-blind, placebo-controlled trial in heart failure
- Participants invited from Integrated Health Networks across the US and verified for eligibility
- Compliance, tech troubleshooting, and spontaneous safety reporting managed by PRA's Virtual Coordinating Center
- Insurance claims utilized to verify eligibility and for longitudinal endpoint and safety follow-up
- Incorporated PRA's Mobile Health Platform for collecting eConsent, electronic patient-reported outcomes (ePROs), medication eDiaries, and data from wearable activity trackers
- No traditional electronic data capture tool utilized—all data endpoints collected directly from the patient, the patient's wearable device, or medical insurance claims
- Direct-to-patient IMP delivery through central depot
- Launched prior to emergence of COVID-19 and continued in midst of pandemic with no disruptions
- Recruitment rate 10× higher than in typical cardiovascular outcomes trials



more relevant to patients' daily lives [**Case Study 5: Medidata—Collecting Data from 20,000 Patients**]. As an added benefit, involving participants in data collection increases patient engagement.

In addition to reducing the burden of travel on trial participants, decentralization can make it easier to enroll patients from many different geographical

regions. This can produce a more diverse study population or expand the reach of trials for treatments of rare or orphan diseases, making it easier to meet enrollment targets. One concern with large-scale remote engagement, however, is the possibility, particularly with multinational trials, that patients in regions lacking the right communications technologies or having limited connectivity will be excluded.

DCT Implementation

The decision to decentralize a trial should be made considering many factors, a few of which have already been mentioned. Early engagement with regulatory authorities is strongly encouraged when planning a DCT, rather than waiting until the protocol has been set and changes become difficult or require protocol amendments. Sponsors and investigators should not assume DCTs will be held to substantially stricter standards than traditional trials, a view at odds with the clear regulatory support for more innovative clinical trial approaches. "I know

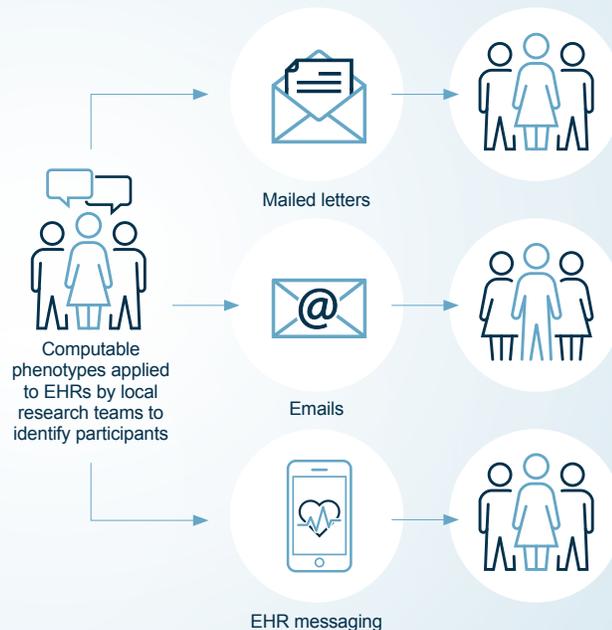
sometimes people are afraid of approaching the regulator, but it shouldn't be that way. We should be enabling new things to happen safely," says Dr. Martin O'Kane, Head of the Clinical Trials Unit at the MHRA. "There are [potential] problems in every trial, and just because there's new technology doesn't mean that we have to increase the regulatory burden. So, if they've got something brand new, and they want to incorporate it in a protocol but don't know if it will be acceptable, then they should absolutely come and speak with us."

Case Study 5

Medidata—Collecting Data from 20,000 Patients^{15,16}

- Approximately half of Americans over the age of 65 take aspirin each day to prevent blood clots that cause strokes and heart attacks
- ADAPTABLE trial goal: Determine the optimal dose of aspirin to prevent heart disease
- Patient-Centered Outcomes Research Institute (PCORI), with the assistance of the company Medidata, runs ADAPTABLE as a fully decentralized trial
- Potential participants identified by electronic health record (EHR) profile
- Participants register online and their identities are verified
- Multimedia-rich tools explain the objectives of the trial and obtain online consent
- Over a 15-month span, patients report on their use of aspirin and health outcomes
- Planned enrollment is 20,000 patients
- The low-cost, adaptable and scalable format could provide insights directly relevant to individual patients

Remote Patient Recruitment



The ACRO Quality-by-Design Manual evaluates those trial steps directly affected by decentralization through a risk assessment approach. Its companion asset, the Risk Assessment Considerations spreadsheet, which builds upon the structural categories of TransCelerate’s Risk Assessment and Categorization Tool, can be used to determine the overall risk associated with decentralization for a given trial design^{17,18}. During the development of the manual, the ACRO Working Party had discussions around the idea that “just because you can do things through a decentralized approach doesn’t necessarily mean it’s always the right thing to do,” says Helen Howitt. However, one of the factors that make creating a framework for DCT implementation challenging is that each study design is different—and that in itself requires flexibility. Says Dr. O’Kane, “Having an innovative idea’s great. Having a risk assessment is great. However, having a mapped-out approach to see how this integrates with your trial conduct is the best way to look at this.”

The ACRO DCT Working Party utilized the “Routemap” from the UK National Institute for Health Research (NIHR) Clinical Trials Toolkit as the launching pad to begin its intensive examination of the unique characteristics and requirements of DCTs¹⁹. The NIHR Routemap lists every necessary step from beginning to end that must take place in any clinical trial. The Working Party engaged in a lengthy study and examination of each clinical trial step in the comprehensive map and then divided the steps into two categories: (1) those steps where the requirements of a conventional trial and a DCT are largely the same and (2) those steps where the adoption of a DCT model creates new challenges and considerations. The ACRO Quality-by-Design Manual focuses on this second category, as illustrated by its Decentralized Clinical Trial Map based on the NIHR Routemap [Figure 1]. The analytical framework for the Quality-by-Design Manual was adapted from the CTTI Quality by Design Project—Critical to Quality

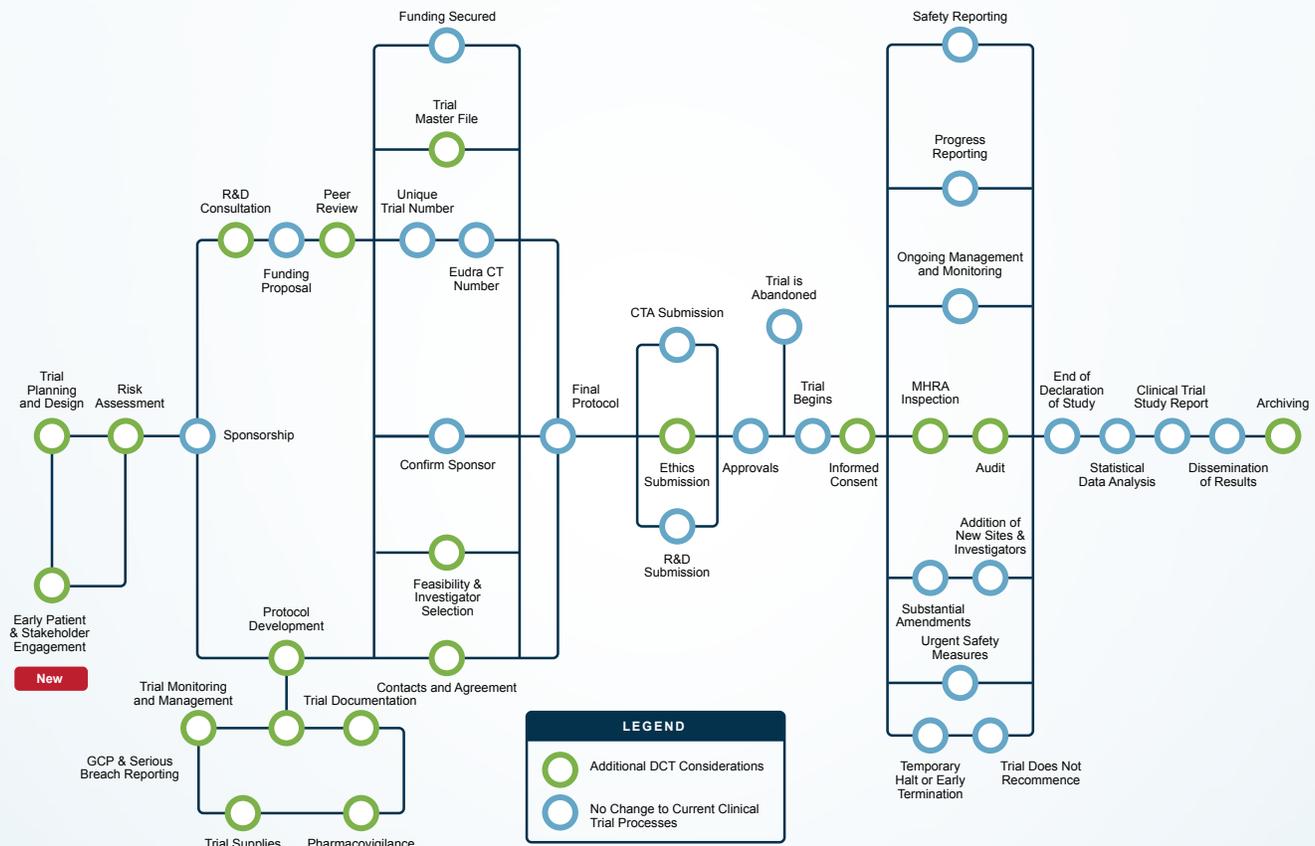
Image adapted from JAMA Cardiol. 2020;5:598-607.

(CTQ) Factors Principles²⁰. CTTI defines quality in a clinical trial as “the absence of errors that matter.”

Here, we provide a brief overview of the ACRO Quality-by-Design Manual and those clinical trial decentralization steps where a DCT model creates

new and distinct challenges, focusing on important considerations for trial planning in terms of risks specific to DCTs that should be accounted for. For more detailed guidance on DCT planning and implementation, refer to the Quality-by-Design Manual.

Figure 1 | Decentralized Clinical Trial Map



Adapted from the National Institute for Health Research (NIHR) Clinical Trials Toolkit Routemap

ACRO Quality-by-Design Manual Overview

Initial planning and early engagement

Early trial functions are heavily impacted by decentralization, as these steps lay the groundwork for all later activities. Most of these are early trial planning steps executed before the trial protocol is finalized and the clinical phase of the trial begins.

IT and Systems Considerations

IT systems infrastructure for the trial must have the flexibility to allow on-site data input as well as remote or mobile data collection and data access. The sponsor should ensure that all patients have appropriate system access as well as sufficient connectivity for reliable data input/collection. Use of trial systems by multiple parties

at a variety of sites, potentially using different interfaces, increases the risk of an external systems breach by bad actors. Security measures must take these risks into account, and systems used for DTCs must meet the same regulatory requirements as other clinical data systems.

Trial Planning and Design

Robust trial design before developing the protocol ensures that all necessary practical requirements are identified early so that the trial is both scientifically robust and operationally feasible from the perspectives of stakeholders such as trial participants, investigators, and vendors. A comprehensive study plan will help guide later planning activities and prevent protocol amendments once the study is underway.

Early Stakeholder Engagement

Patient-centricity is a key advantage of DCTs, and early engagement of patients/patient groups as important stakeholders when a trial is designed will help achieve this. Much of the technology developed for DCTs aims to reduce the burden to the patient (less travel), increase patient engagement (use of apps and tablets for data collection), and enhance compliance (real-time feedback); thus, input as to how user-friendly and convenient these technologies are can help identify problems that need to be addressed in the study design. In addition, early engagement of the investigators, CRO, and vendors by the study Sponsor should help determine whether there are other needs to be met. At this stage of DCT planning, early dialogues with regulators should be considered to help inform the study protocol and increase chances of approval.

Risk Assessment

Developing a risk assessment plan—with the aid of existing tools and ACRO's Risk Assessment Considerations spreadsheet [Table 1]—should be considered at the beginning of a project's lifecycle, and intermittent project level risk reviews should continue for the course of the trial. Key data-driven metrics should be utilized to determine success in mitigating risk, particularly in the management of data and processes considered to be critical to the overall project objectives. At this stage, it is important to determine whether the DCT methods being considered actually add value to the study. The impact of changes to the project contract, scope, timelines, vendors, and technology used should also be considered.

Defining and documenting trial practices

Decentralization also requires careful consideration of issues that could arise during trial management and monitoring, while always paying close attention to regulatory requirements. Thorough documentation of these processes should be maintained throughout the trial lifecycle.

Protocol Development/Protocol Approval

The trial protocol is an end-to-end description of all trial activities, including any DCT methods. Stakeholder engagement during initial trial design will help guide protocol development to ensure patient safety and accurate collection of any digital endpoints. Any potential risks associated with DCT methods should be addressed in the risk-benefit section of the protocol, along with suitable risk mitigation measures.

Trial Monitoring and Management

The Sponsor is responsible for putting in place robust trial management systems to ensure trial participant safety and accurate reporting of results. Risk-adapted trial management identifies critical processes and critical data for the trial and how any risks and/or vulnerabilities in these areas should be mitigated. DCT technologies can expand monitoring capabilities, allowing for data-driven decisions in real time.

Trial Supplies

Direct-to-patient shipment of IMP in DCTs can reduce the burden on patients by eliminating travel to the clinic for the collection, accountability, and return of IMP. This approach could also facilitate treatment by home healthcare providers. Careful control is required to ensure appropriate chain of custody and stability of the IMP throughout the shipment process. Tracking IMP distribution to patients and IMP use during the study as well as return or destruction of unused supplies upon study completion requires consideration and development of appropriate procedures.

Trial Documentation

Which documents are to be stored in secondary locations should be clearly detailed in the study trial master file (TMF) plan and vendor contracts, as appropriate. Sponsors must also consider how investigators will retain responsibility for the management and oversight of source documents

generated outside their direct control and which procedures are needed for maintenance and retention when documents come from local medical doctors and other local health care providers or are generated and collected at home visits by the study participants, clinical investigators, study personnel, or third-party contractors such as home healthcare providers.

Organization, administration, and consultation

Among the administrative and consultation steps that culminate in production of the final trial protocol, those related to funding, sponsorship, and trial identification (assignment of trial number) are similar in DCTs compared with traditional trials, but other documentation activities are significantly impacted by decentralization, raising important new considerations.

Trial Master File

When planning a DCT, it is important to determine who owns the documents and data required in the TMF and where these will be retained both during and after completion of the trial. The more vendors that are involved, the more complicated the process.

Contracts and Agreements

It is important to determine where contractual obligations lie within a DCT and who the appropriate signatories are. A central listing of all potential vendor types should be created, and specific criteria should be developed for qualifying DCT vendors.

Submissions and approval

The submission process itself will not change with DCTs, but it is important that the submission package clearly outlines how the trial will be conducted, including DCT methods such as telemedicine, wearable technologies, and eConsent. Preparation of the Clinical Trials Application (CTA) and R&D submission should not be significantly different for DCTs compared with traditional trials; however, special considerations apply to the ethics submission.

Ethics Submission

The Sponsor should make sure that all relevant parties are involved in the submission and that all aspects of the DCT are made available to the ethics committee. The protocol should be transparent about what is being done

remotely and who is involved in remote/decentralized activities. Any differences between an electronic document and the paper version of the same document should be explained. Data collection, storage, and access documentation should describe relevant safety and personal data protection safeguards, including methods for patient identification when remote data is being collected. The Sponsor should provide a sample of the final product of approved materials once the system is ready to go live. This will include copies of the final production video for informed consent as well as a recorded demo of the data collection tools.

Trial execution and monitoring

Much of the trial management, safety monitoring, and progress monitoring activities during the execution of the trial (i.e., the “clinical” phase) are similar for DCTs compared with traditional trials. However, there are differences in obtaining informed consent from patients and preparing for inspection and audit by regulatory authorities.

Informed Consent

Electronic Informed Consent (eConsent) can be given remotely by patients through a web portal, by e-mail, or by other means after viewing a video or reviewing a consent document online or on paper. The Sponsor, in collaboration with the investigator, should determine which methods are used to positively identify the patients, collect signatures, and assess their understanding of the consent documents. Prior to the start of the trial, the Sponsor should determine if use of eConsent is appropriate for the specific trial population. (Are they receptive to the idea? Can they access materials electronically? Do they need a face-to-face explanation?) There should be a back-up process for informed consent in case the electronic system goes down.

Inspection & Audit

Good clinical practice (GCP) inspections and their conduct will continue to evolve with greater adoption of DCTs due to increasing complexity in contractual relationships, trial design, and technology solutions, but core elements such as inspection phases, types, and locations are unlikely to change. The Sponsor should provide appropriate system access for the inspection, ensuring inspectors have complete and direct access to the TMF and that data flow and ownership are documented. For new or DCT-specific technologies, the Sponsor should consider specific

data management plans/diagrams showing data flow between all stakeholders (sponsor, participant, vendors, site staff, CRO). The protocol should describe how new technologies are assessed as fit for purpose and validated, including implications for areas such as data protection, data security, and privacy. The Sponsor should ensure availability at the site of tools used for remote activities (e.g., equipment used by mobile nurses). Inspections may also need to take place at other facilities where trial-related activities occur.

Data analysis, reporting, and archiving

This is where all of the planning outlining data collection, validation, and flow pays off. The Statistical Analysis, Clinical Trial Study Report, and Dissemination of Results

should not be significantly different for DCTs compared with traditional trials, but special consideration should be given to storage and access for study data and documentation after the trial has ended.

Archiving

This is the final step of the trial process and the last step impacted by decentralization. Data and documents must be available to the investigator and relevant teams throughout the archive period, with a process in place to ensure all documents and data in electronic systems are available to study personnel and regulatory authorities, where appropriate. The Sponsor should determine how the investigator can access the data during the trial and once the trial has closed, as well as who is responsible for archiving which data, being very clear in the contract regarding these roles and responsibilities.

Conclusion

Stakeholders within the clinical trial ecosystem have understood the benefits of DCTs for some time now. The COVID-19 pandemic further highlighted their value and illuminated the necessity for the decentralization of specific elements of the clinical trial process in order to keep trials up and running under difficult conditions. While the rationale for DCTs has been long understood, a set of general principles dedicated to the effective planning and execution of these trials has been missing from the DCT conversation. The aim of the ACRO Quality-by-Design Manual is to help provide these principles. DCTs are more important than ever, and these models

will only become more useful as technology improves. Although the COVID-19 pandemic has shone a bright spotlight on DCTs, their advantages will remain in a post-COVID world, says Dr. O’Kane: “Certainly in the UK, we’re having a look at the lessons learnt and trying to find out which parts of decentralization or virtual elements worked really well with COVID, and which would work well in a non-pandemic situation, which should almost become business as usual. You know, what could become the standard moving forward—and it’s taken something like the pandemic to make people take that leap.”

Table 1 | Excerpt From Decentralized Clinical Trials (DCT) Risk Assessment Considerations Spreadsheet

Category	Objective
Trial Planning and Design	Trial design should be considered before developing the protocol and relevant stakeholders should be consulted in these discussions.

Assessment Criteria	Considerations	Mitigation Strategies
What elements of the DCT differ from conducting the trial in a more traditional model?	Evaluate which elements of DCT methods/tools differ from a standard trial to identify new risk areas for evaluation. Include additional systems and vendors which may be in use and requirements for control and oversight	Have in place a specific data management plan/diagram for DCTs to show how the data flows and data ownership
Are there any additional safety risks associated with the planned decentralized processes?	Is it possible to conduct all protocol required assessments and IP management activities with remote alternatives? Consider that some investigations can only be done face to face	Determine and make clear in the protocol/ participant information sheet / NCA & IEC submission which elements of the trial can be decentralised
Are the proposed decentralized approaches suitable for implementation in all geographical locations / with all participants?	Some DCT activities may only be accepted (culturally or per local regulations) in some countries and/or patient populations and may necessitate a 'hybrid approach' - this may introduce unintentional bias or risk e.g. rating scale administration may not be comparable between on-site and remote delivery	Engage with all stakeholders as early as possible (see next section) to assess acceptability of proposed approaches. Consult with project biostatistician to assess the potential impact on data integrity/ interpretability of utilizing a hybrid approach
Are the proposed decentralized approaches likely to be accepted by the participant population? Taking into account the disease nature and participant population demographics?	Care needs to be taken not to unintentionally exclude subjects from accessing a clinical trial because they are unable / uncomfortable with accessing DCT methods or technologies e.g. accessibility issues in some countries; elderly engagement with technology; impact on mental health	Design communication models and scenarios; what these look like could depend on the trial, such as participant interfaces with investigators and health care professionals, call center models, video, phone, telemedicine, trial participant interacts or travels to a local site
Are there any relevant regional and/or national legal requirements and/or site requirements which may prevent implementation of proposed decentralized approaches on the trial?	Are there restrictions in planned countries for study conduct which will require a hybrid approach rather than fully decentralized approach and what is the impact of this?	Consult with National Competent Authorities / IRBs/IECs and local site authorities to confirm acceptability of proposed methods prior to finalizing strategy and country list
Is it clear how data will be collected and how it will flow between systems and parties involved in the conduct of the trial? Is a data flow diagram available to demonstrate this?	Consider who owns the data, where it will reside and who is responsible for long-term archiving of data after study completion Consider who will monitor/clean the data and how this oversight will be documented? Are there audit trails that can/should be reviewed, with a process to follow? Consider how Investigator maintains oversight and control of data related to participants from their site - Sponsor / vendor should not be able to change participant data independently from investigator and without their approval (unless an agreed self evident query) Consider who has edit/read access to data and how Investigator continued access will be assured during archiving period Consider how participant privacy is maintained e.g. requirements for firewall between investigator facing and Sponsor facing data; pseudonymization etc. Will data from all vendors be integrated into the EDC or will data exports be provided from each vendor for analysis purposes, and on what frequency?	Schedule a meeting as early as possible in trial set up as possible with all vendors to agree and map data flow requirements and confirm monitoring strategy
Are new technologies fit for purpose and validated in line with computer systems validation principles?	Consider whether technology has been developed specifically for clinical trial / medical use or whether more generic apps are being utilized? If the latter do they meet all GXP requirements (e.g use of fitness trackers)	Conduct vendor qualification audit <i>before</i> proceeding with any new technology vendor; develop a standard framework for qualification audits of vendors
Is there any potential impact of the proposed technical solutions on data protection, data security and data privacy?	Consider where data resides - is it stored on a server within country or in a third country which may have different data privacy controls? Is technology specifically developed for clinical trials and have demonstrated GXP compliance or is the technology a generic commercial offering which may not have those controls built in?	Consult regulatory authorities

Please note that the Risk Considerations Spreadsheet is a living document, designed for future refinement as needed.

References

1. Association of Clinical Research Organizations (ACRO). Bringing the Trial to the Patient: A Quality-by-Design Manual for Decentralised Clinical Trials. Published online 2020. <https://acrohealth.org/dctqbdmanual>
2. Association of Clinical Research Organizations (ACRO). Decentralised Clinical Trials (DCT) Risk Assessment Considerations [Spreadsheet]. Published online 2020. <https://acrohealth.org/dctqbdmanual>
3. Apostolaros M, Babaian D, Corneli A, et al. Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials Transformation Initiative. *Ther Innov Regul Sci*. Published online December 9, 2019. doi:10.1007/s43441-019-00006-4
4. FDA/MHRA Considerations for the Design and Conduct of Decentralised Clinical Trials: Regulatory perspectives – FDA/MHRA GCP Symposium 2020.
5. Gottlieb S. Breaking Down Barriers Between Clinical Trials and Clinical Care: Incorporating Real World Evidence into Regulatory Decision Making - 01/28/2019. FDA. Published March 4, 2019. Accessed August 7, 2020. <https://www.fda.gov/news-events/speeches-fda-officials/breaking-down-barriers-between-clinical-trials-and-clinical-care-incorporating-real-world-evidence>
6. Medicines and Healthcare Products Regulatory Agency. MHRA Position Statement and Guidance on Electronic Health Records. Published September 16, 2015. Accessed August 7, 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470228/Electronic_Health_Records_MHRA_Position_Statement.pdf
7. European Medicines Agency (EMA). EMA Regulatory Science to 2025. Published 2020. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
8. ©2020 PPD Inc. All Rights Reserved.
9. US Food and Drug Administration (FDA). FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Published July 6, 2020. Accessed August 7, 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>
10. European Medicines Agency (EMA). Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. Published April 28, 2020. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
11. Medicines and Healthcare Products Regulatory Agency. Managing clinical trials during Coronavirus (COVID-19). Published May 21, 2020. Accessed August 7, 2020. <https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19>
12. IQVIA. *Data on File*.
13. Covance Inc. Improving Patient Retention with Flexible, Patient-Centric Sample Collections. Published April 22, 2020. <https://www.covance.com/content/covance/en/latest-thinking/explore-library/pdf-viewer.html/covance/assetLibrary/casestudies/DCT-Patient-Service-Centers-CSDCT001.pdf>
14. PRA. *Data on File*.
15. Medidata Solutions, Inc. Virtualizing Clinical Trials.
16. Marquis-Gravel G, Roe MT, Robertson HR, et al. Rationale and Design of the Aspirin Dosing—A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial. *JAMA Cardiol*. 2020;5(5):598-607. doi:10.1001/jamacardio.2020.0116
17. TransCelerate BioPharma Inc. The TransCelerate Model Approach. Accessed August 11, 2020. <https://transceleratebiopharmainc.com/rbminteractiveguide/how-does-clinical-trial-site-monitoring-work-under-a-risk-based-monitoring-approach/the-transcelerate-model/>
18. TransCelerate BioPharma Inc. Risk Assessment and Categorization Tool (RACT) Template, Version 2.0. Published April 11, 2014. Accessed August 7, 2020. http://transceleratebiopharmainc.com/wp-content/uploads/2020/04/RACT_FINAL_April-2020.xlsx
19. UK National Institute for Health Research. Clinical Trials Toolkit Routemap, Version 1.1. Published August 2013. Accessed August 7, 2020. <http://www.ct-toolkit.ac.uk/routemap/>
20. Clinical Trials Transformation Initiative. CTTI Quality by Design Project—Critical to Quality (CTQ) Factors Principles Document. Published May 19, 2015. Accessed August 7, 2020. <https://www.ctti-clinicaltrials.org/toolkit/qbd/introduce-qbd/qbd-principles>