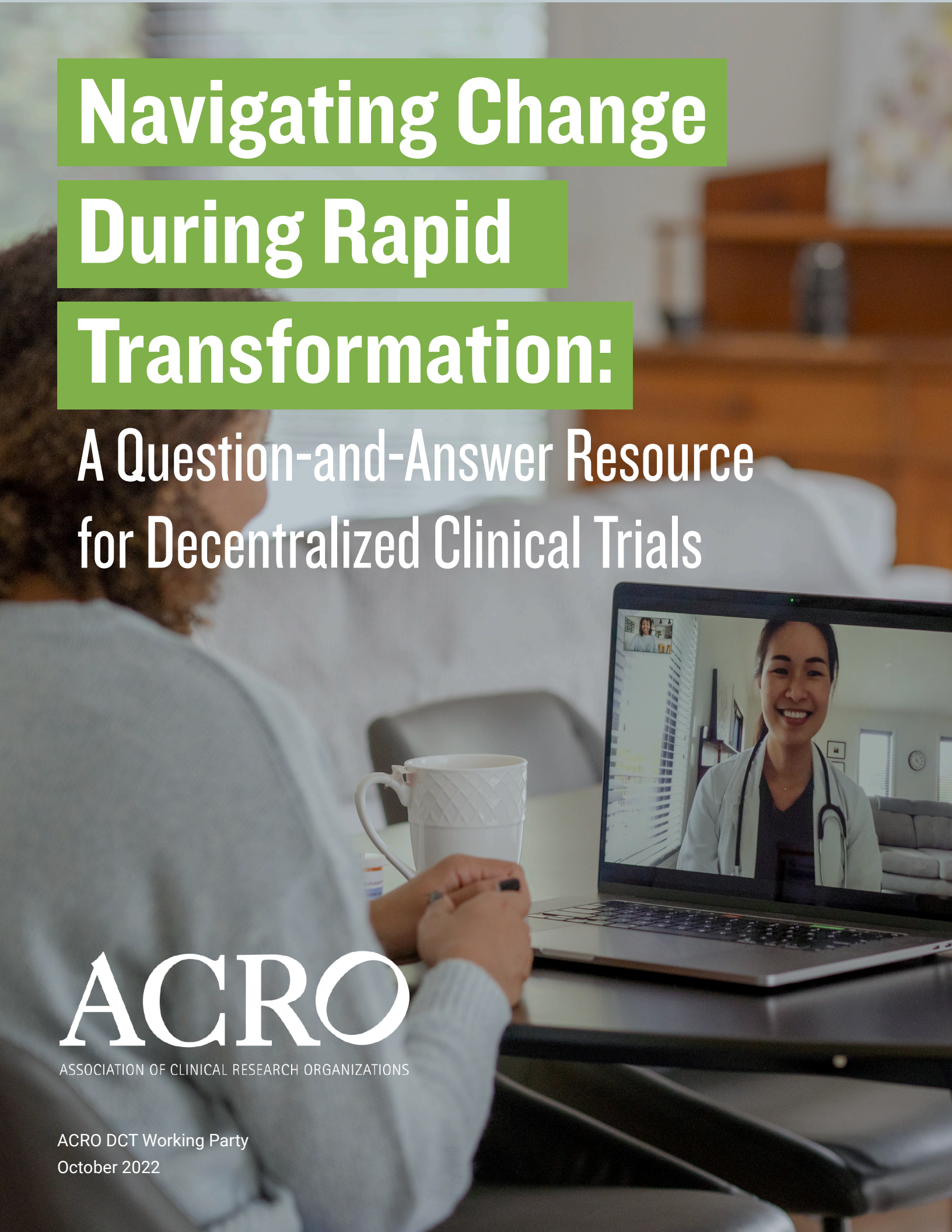
Navigating Change During Rapid Transformation:

A Question-and-Answer Resource for Decentralized Clinical Trials



ACRO

ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

ACRO DCT Working Party

October 2022

Table of Contents

Introduction: Why It is Time to Apply Change Management Principles to DCTs

We are experiencing a paradigm shift in the clinical trial enterprise from conventional clinical trials to trials where at least one or more decentralized clinical trial (DCT) components are utilized (e.g., direct-to-patient shipment; home health visits; etc.). The use of DCT components is here to stay.[1] DCTs enable patient-centricity and patient flexibility, and they are part of the solution for increasing diversity and inclusion.[2] A recent survey noted the attractiveness of DCT technology for cancer patients.[3]

This shift means some things will change and some things will remain the same. The two pillars of clinical research – patient safety and data integrity – are safeguarded in a DCT model through careful planning, intensive protocol development, and digital controls. Data flow mapping not only helps promote data integrity, but also helps maintain data protection, privacy, and confidentiality.

This Change Management Tool expands the existing tools in the ACRO DCT Toolkit. While the Quality-by-Design (QbD) Manual, Risk Considerations Tool, and Data Flow Maps focused on providing educational resources to build confidence and trust in DCTs, this tool focuses on the final hurdle to greater DCT adoption – which is the change management needed to tackle organizational and individual risk aversion and the tendency to keep doing things the way they have always been done. As noted at a recent industry conference, "Change Management is the greatest challenge. Change the way we all work – adjust behaviors, attitudes – away from preconceived ideas and interests – and on to new, better, ways of working."[4]

Definitions

Before applying change management principles to DCTs, it is important to address the question of how to define a DCT – as numerous stakeholders have recognized.[5] In September 2020, the ACRO DCT Working Party released its Quality-by-Design (QbD) Manual for DCTs, which defines a decentralized clinical trial as a study that "brings 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 medical product development, speed delivery of therapies to patients, and create efficiencies across clinical research processes."[6] In January 2021, in an effort to operationalize this definition even further (and enable the measurement of DCT adoption), the ACRO DCT Working Party further defined decentralized trials as those studies that contain one or more of eleven core DCT components.

We would like to highlight two caveats about the list of eleven DCT components included in this paper. First, it should be noted that some countries may not currently accept the use of some of these DCT components. Second, we recognize that some of these components may not be unique to DCTs. For example, one could argue that eSignatures

are not unique to DCTs, as they have been used in electronic data capture (EDC), interactive response technology (IRT), and other digital healthcare tools for some time. However, given the fact that eSignatures are a vital DCT tool, and the barriers created by the absence of universal acceptance of eSignatures, we have chosen to include this tool in our list. We have also included other components which are not unique to DCTs (e.g., remote patient ID verification) because they are valuable, digital, remote tools. This is not a list of components that are exclusive to DCTs, but, rather, a list of some of the core digital, remote capabilities that are essential to DCT success.

	DCT Component	Definition
1	**eSignature**	eSignature is a digital, paperless signature that is a legal signature. In the US, this must be compliant with FDA 21 CFR Part 11 regulations. In the European Union, the eIDAS Regulation defines three levels of electronic signature: "simple" electronic signature, "advanced" electronic signature, and "qualified" electronic signature.
2	**eConsent**	This refers to the use of electronic, online platforms for the consenting process – whether or not this is accompanied by an eSignature or a wet-ink signature. The purpose of eConsent is to convey study information & obtain/ document consent during the consenting process. This may sometimes include, for example, the use of electronic media (such as text, graphics, audio, video, podcasts, or websites) to convey information related to the study and to obtain and document informed consent.
3	**Electronic Screening**	Once a person is identified as a potential candidate for a clinical trial, they need to undergo a pre-screening process (prior to consent). eScreening methods can be implemented which allow the candidate to complete a screening questionnaire online, either via a web browser or smartphone app. This also includes patient screening throughout the trial.
4	**Remote patient ID verification**	The verification of the identity of the patient without a physical visit to site, but instead using electronic tools, such as through the use of video or audio communication or web portals.

5	**Direct-to-patient (and direct-from-patient) shipment**	Direct-to-patient (and direct-from-patient) shipment in clinical trials includes the direct shipment of investigational medicinal product (IMP), as well as other instruments such as medical sensors, wearables, and home lab kits directly to the patient's location. This includes shipping biological samples, as well as unused IMPs, devices, wearables, sensors, and study information documentation, but excludes mailing a hard copy of the ICF documentation and any electronic delivery.[7]
6	**Home health visits (HHVs) and Home Healthcare (HHC) professionals**	Home health visits allow the conduct of clinical trial assessments in the patient's residence or other location, decreasing the need for the patient to travel to the study site. Home visits can include blood draws, IMP administration, as well as other assessments which do not require the physician to be present.[8]
7	**Telemedicine**	Telemedicine is the use of telecommunications technology to deliver real-time healthcare interaction remotely. Telemedicine can take the form of a simple phone call or a video call between the investigator and patient.[9]
8	**eCOA and ePRO**	eCOA (electronic Clinical Outcome Assessments) employs technology such as handheld devices, tablets, or web to allow patients, clinicians, and caregivers to directly report outcomes, resulting in more granular endpoint data. ePRO (electronic Patient-Reported Outcome) is a health outcome reported electronically directly by the patient.
9	**Connected devices and digital endpoints**	Digital Endpoints are assessed using data captured by mobile applications typically outside of the clinic during activities of daily living. These data exclude, and should be distinguished from, eCOA and ePRO. Typically, these include hardware and/or software products that can be used to support the practice of medicine via collection, measurement, and remote transmission of data from a variety of sources (including laboratories and patients themselves). Connected devices can be used to send data to and/or from patients. Examples include patient education, patient support, reminders, calendars.[10]

10	**Local community or mobile labs**	The ability to allow the patients to have clinical assessments, including phlebotomy, imaging, and any other test procedures performed at a lab that is local to the patient -- or mobile -- as opposed to the study site.[11]
11	**EMRs/EHRs**	Electronic medical record (EMR) or health record (EHR) systems are electronic platforms that contain individual health records for patients. The benefits of EHRs for clinical research are noted in the 2018 FDA Guidance "Use of Electronic Health Record Data in Clinical Investigations"

The People Side of Change: How Individual Attitudes, Interest, and Support Impact DCT Adoption

When addressing the puzzle of why there has not been greater adoption of DCTs, it is helpful to think about the language of necessity and sufficiency. DCTs would simply not be possible without the required digital technology infrastructure (e.g., wearable sensors; telemedicine platforms; Investigational Medicinal Product (IMP) shipment logistics; et cetera). Yet, DCT adoption has been modest in spite of rapidly advancing technology. What accounts for the remaining gap between capabilities and actual adoption?

While digital technology is a necessary prerequisite for DCTs, it is not sufficient for achieving prevalent adoption of DCTs. To close the gap on DCT adoption, one must examine the human element of change management. The power of change management is that it enables greater adoption of DCTs. Change management tools enable research professionals and patients to change their ways of thinking about DCT operations, risks, and benefits.

Rescue DCTs versus Planned DCTs-by-Design

While DCT capabilities have existed for some time, they came to prominence during the COVID-19 pandemic when flexible, remote technologies were implemented, where appropriate, to keep ongoing, active trials up and running. Because the pandemic acted as a sort of natural experiment to dramatically showcase the power and value of DCT technologies as tools to rescue and maintain active, ongoing trials, two things happened. First, regulators began exploring and examining the idea of making some of the remote technology flexibilities introduced during the pandemic more permanent and enduring, where appropriate. Second, industry began pivoting to the value of DCT technologies not only as "rescue" tools during the pandemic (where DCT tools are bolted on to, or retrofitted to, a conventional trial), but also as a planned approach where a trial is planned and organized to include DCT elements from the beginning – sometimes referred to as "DCT-by-design."[12]

Change Management and Decentralized Clinical Trials

ADKAR is a school of change management that focuses on the role of individuals in successful change by supporting and enabling the individual's successful response to change via awareness, desire, knowledge, abilities, and resistance.[13] The ACRO DCT Working Party examined decentralized clinical trials via a change management lens in order to develop a Question-and-Answer resource that would be helpful to (1) sponsors, (2) IRBs/ethics committees, (3) sites, (4) patients, and (5) regulators. After several months of intensive, collaborative content development by the ACRO DCT Working Party, the committee then engaged in informal conversations across the stakeholder community – including representatives from IRBs/ethics organizations, sponsors, patients, and sites – during this document's development. Now that this work is complete, the Working Party plans to continue to hold additional informal conversations with stakeholders to share this tool, hear reactions, and welcome additional suggestions. While ACRO's thinking, and this paper, were informed, and greatly improved, by stakeholder conversations, it must be noted that these were informal discussions only. External stakeholders have not reviewed this paper. ACRO's consultation with stakeholders should not in any way be construed as a formal collaboration with, or endorsement from, any organization. ACRO is the sole author of this resource and solely responsible for its content.

The ADKAR analytical categories or steps of successful change management are (1) awareness, (2) desire, (3) knowledge, (4) abilities, and (5) resistance.[14] It is helpful to think about categories like these in order to identify potential barriers to the changes required for greater DCT adoption.

First, we should consider awareness. Are stakeholders, research professionals, and patients aware of the changes that DCTs require? The good news is that general awareness about DCTs is very high, as evidenced by the large number of DCT-focused articles in trade journals and the prevalence of DCT-focused panels at industry conferences. Discussion of DCTs is everywhere. Second, what about desire? Do stakeholders possess the desire for change that is needed to support DCTs? Like awareness, desire is robust – thanks to the often recognized benefits of DCTs (e.g., the ability to reach geographically dispersed populations; the potential for greater diversity and inclusion; reduction in travel for patients). Moreover, the desire for change will grow as resistance points are successfully addressed. Third, what about knowledge? Do stakeholders possess the theoretical knowledge about DCTs that is required for successful change? Knowledge is strong. The underlying theory, concepts, and principles of decentralization – and of specific DCT tools (e.g., direct-to-patient shipment) – are well understood. Fourth, we need to consider abilities (i.e., the practical side of knowledge). Thanks to the wide variety of "how-to" webinars, blogs, and conference panels on DCTs, stakeholders are beginning to successfully build and hone the necessary experiential skills and practical, applied tools for successful change.

Finally, what about resistance to change? What kinds of concerns, hesitation, and questions do stakeholders, professionals, and patients have that could create resistance to change and thwart broader DCT adoption? Moreover, what is the source of the resistance? The concerns and hesitance that create resistance to change are often due to unanswered questions and/or misperceptions about DCT capabilities, processes, and risk. Resistance to change may be the biggest hurdle to greater DCT adoption. Fortunately, it is possible to begin to address the gaps in knowledge and the misperceptions that generate resistance in an efficient question-and-answer framework. This ACRO change management tool adopts a Q-and-A approach to key questions about DCTs. The objective of this tool is to help demystify DCTs and to address potential points of resistance in order to remove barriers to greater DCT adoption.

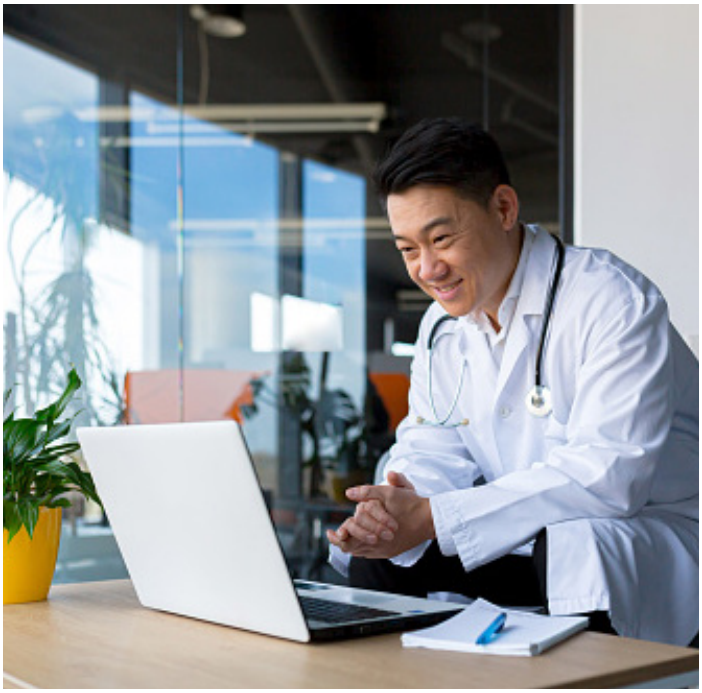
Addressing Stakeholder Hesitation and Concerns around DCTs: A Question-and-Answer Approach

Stakeholders who are comfortable with conventional, investigator-site focused trials may ask why they should take an interest in DCTs. The answer is that DCTs are here to stay – thanks, largely, to our maturing, and increasingly nuanced, understanding of patient-centricity. Patient-centricity no longer means simply engaging with patients on each step of the clinical trial, from planning and design to data sharing. True patient-centricity now means diligently avoiding a one-size-fits-all approach to clinical trials, so that patient-centricity becomes patient-flexibility. DCTs can offer the flexibility that patients need and deserve.

When patient safety and data integrity do not necessitate assessments and procedures to be done at the investigator site – and, therefore, the consideration of off-site, remote assessments and procedures is possible – patient flexibility should be taken into account. Some patients may wish to avoid both (1) the investigator site and (2) their home as options in favor of alternative locations such as local, community based facilities or mobile locations. And, for any individual patient, the preference for an investigator site, home, local, or mobile option may vary from assessment to assessment. As stakeholder commitment to – and understanding of – true patient-centricity and patient-flexibility continues to evolve, the benefits of DCTs will be further illuminated. DCTs meet the needs of today's patients, care settings, and digital world, offering numerous opportunities to all stakeholders for the benefit of patients. Such potential benefits include:

- Adaptability, agility, and flexibility in delivering research
- Inclusion of naïve and geographically dispersed populations – providing the potential for broader, diverse, and inclusive patient populations
- Improved engagement flexibility for patients throughout study lifecycle
- Mirroring standard of care and real world data settings
- Better access to real-time data (vs points-in-time) – especially valuable for safety signals and events

- Collection of direct source data – without an intermediary or transcription errors
- Enabling development/timeline efficiencies to drive accelerated development – speed to closure of studies, and, therefore, improved speed to market
- Preparedness for future potential pandemics
- Reduced study data verification (SDV), efficiencies, cost reductions



The idea that DCTs are here to stay is exemplified by the growth of regulatory guidance on the topic. DCT-specific guidance has begun to emerge at both the national and regional level. Countries which have issued DCT-specific guidance include Denmark,[15] Sweden,[16] and Switzerland[17]. Moreover, DCT-focused recommendations and guidance are expected from EU[18] and US[19] regulators by the end of 2022.

This release of US and EU-level recommendations on DCTs will address industry desire for DCT-specific guidance and will help diminish lingering industry hesitance. In addition to issuing guidance, regulators have been generally receptive to DCTs (especially when clear rationales for the use of DCT elements are carefully explained in the protocol). Moreover, because some elements of DCTs are not new to clinical research, a significant amount of guidance applicable to DCTs exists across currently available general guidelines. A recent survey of European regulators published in August 2022 offers illuminating findings on regulatory receptiveness to DCTs.[20]

The two pillars of all clinical research are patient safety and data integrity; this is true for both conventional trials and DCTs. However, after patient safety and data integrity have been thoroughly considered through planning and protocol development, there may be additional barriers to stakeholder acceptance and adoption of DCTs. One possible additional barrier is the cost of DCTs. Are DCTs too expensive? There is a dearth of data about the cost of DCTs. However, the good news is that industry stakeholders are beginning to explore this question and data are now beginning to emerge to suggest that, in some cases, DCTs can make sense financially. Two recent studies consider the issue of DCT cost – one by Tufts Center for the Study of Drug Development and Medable[21] and another by IQVIA.[22] This work is just beginning, and the jury is still out. But, it is encouraging to see that industry is working to gather data on this important question.

The Questions

The ICH E6(R3) Draft Principles state that: "Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results."[23] Section I of this paper examines DCTs and patient safety. Section II considers DCTs and data integrity.

I. Patient Safety and Patient-Centricity

QUESTION 1:

How are DCTs designed to protect patient safety?

ANSWER:

The principal investigator has responsibility to oversee patient safety per International Council for Harmonization Good Clinical Practice (ICH GCP) – regardless of whether the trial design is conventional or decentralized.[24] This is further discussed in the Answer to Question 2.

In a DCT, there may actually be the potential for enhanced monitoring to help protect patient safety through:

- Digital platforms with access to wearable/sensor data in real time which contain pre-defined parameters, inbuilt algorithms, and digital controls that can be set up to flag potential safety events and trigger alerts for further interventions (indeed, one can add devices to the study design to allow near real time collection of digital biomarkers, including vitals if required)
- New vehicles for accessing patient safety data, such as patient data dashboards that can be monitored and reviewed by the site in real time, capturing safety events
- Real-time data monitoring enables patients' health data to be monitored in an efficient manner and can trigger faster decisions if a patient requires follow-up
- Access to real-time data is complemented by other DCT tools – including tele-visits between the PI and patient to collect safety information and also home healthcare visits in the patient's home to collect safety data
- Careful planning and a focus on safety via intensive protocol development (using the resources within the ACRO DCT Toolkit[25] – such as ACRO's Quality-by-Design Manual for Decentralized Trials and the Template for Risk Assessment Considerations)

QUESTION 2:

A key element of patient safety is principal investigator (PI) regulatory responsibility and oversight. How is PI oversight maintained in a DCT when the patient may be hundreds of miles away and home health visits are used?

ANSWER:

PI responsibility to oversee patient safety is clearly detailed in ICH GCP guidance and is no different in a DCT than what it would be for a conventional trial.[26] 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.

In planning a DCT, one must consider and explain 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 an operational plan, including (but not limited to):

- 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

QUESTION 3:

What does the proposed continuum of locations for trial assessments and procedures look like?

- Will some need to be done at an investigator site?
- Will some be conducted in local community locations or mobile facilities?
- Will some be done by the patient at home with remote supervision?
- Will some be performed at home by the patient alone?

ANSWER:

Patient safety and data integrity are the primary determinants for the location of assessments and procedures and should be explained in the protocol. Additional factors to consider might include IMP formulation and stability. When patient safety and risk considerations permit flexibility, decentralized trials should take an agile approach focused on patient flexibility and choice. An agile approach will help achieve enrolment and retention of a representative and diverse patient population.

One size does not fit all. Different patients may opt for different locations for the same assessment in the same trial. Even for assessments and procedures that are not required to be done at the investigator site for safety or data quality reasons, some patients

will want some of their assessments conducted via a visit to the investigator site because of their preference for in-person, face-to-face contact with site personnel. At the other end of the continuum, in-home assessments are not attractive options to all. Some patients will wish to opt out partly – or completely – from having assessments conducted in their home for a wide variety of reasons (e.g., discomfort with strangers in the home). For these patients, the investigator site, local community facilities, and mobile facilities are an option.
An individual patient may prefer a hybrid set of options within a single trial – with some investigator-site assessments and some remote assessments (in the home and/or a local, community facility). Where safety and data-quality considerations do not preclude the consideration of a multiple location options – and where patients may not have a clear preference – early engagement with patients and sites would be beneficial.

QUESTION 4:

Medical support/communication (live person): In a DCT, how do we provide the patient with 24/7 medical support/access?

ANSWER:

DCT safety monitoring plans must be held to the same high standards as those for traditional trials. Investigators and sponsors should assess the suitability of 24/7 service providers for the specific purpose of medical contact. Moreover, out-of-hours contact arrangements should be assessed and also tested to ensure that the chain of contact is functioning as intended. As in a traditional clinical trial, it is important to ensure that access to the trial team and code-breaking arrangements are maintained at all times." A patient information card with safety contact details for site and CRO/Sponsor medical support lines helps to provide the patient with 24/7 access to a live person for medical support, as they would in a traditional trial. Moreover, DCT technology provides the opportunity for new, innovative ways to enable live medical support and communication – through access to wearable/sensor data in real time and inbuilt algorithms that can be set up to flag potential safety events and directly alert site staff and CRO/Sponsor medical teams.

What this support looks like will depend on the needs of the patient and the design of the study, but it might include a variety of services including:

- Telemedicine to support patient/investigator communication without the need for travel
- Real-time dataflow, via ePRO/ObsRO data or wearables/sensors, which can trigger alerts for further interventions based on investigator review or pre-defined parameters
- Pre-coordination between investigators and approved facilities/clinicians near the patient's location on acceptable treatment as well as feedback procedures and reporting requirements.
- Ad-hoc communication capabilities where a patient can reach out the study team for any concerns
- Providing the patient with the procedures and methods for obtaining information to address possible adverse events

QUESTION 5:

Technical (non-medical) support/communication (live person and online support): In a DCT, how do we provide the patient with 24/7 technical support/access?

ANSWER:

Technology can be utilized to facilitate reminders and to provide training video and technical guidance. Yet, technical support for patients is important, given the wide range of digital literacy in the patient population. However, it is crucial that the medical staff – the investigator site and study site staff – are not viewed as a help desk for non-medical, technical questions. In order to help ensure that the investigator site and study staff are not burdened with non-medical questions, patients must be trained on where and how to access technical support at the beginning of the study – in addition to regular check-ins to optimize comfort with use of technology. Responsibility for technical, non-medical help desk services should be clearly outlined in the protocol – e.g., a tech support 24/7 helpdesk or concierge services that the patient can contact 24/7 for support. Patients should be clear that the appropriate helpdesk or concierge service (rather than the HHC team or virtual study site staff) should be contacted for resolving issues with use of the technology. These services should be readily accessible 24/7 in a language that is clearly understood by the patient.

QUESTION 6:

Will DCTs create increased operational burden on the sites/PIs that could be difficult to manage (e.g., multiple platforms and sign-ons)?

ANSWER:

The benefit of decentralized clinical trials is that they can help alleviate existing burdens on sites. However, at the same time, they can also introduce brand new burdens. The ways DCTs can potentially improve site operations include:

- Streamlining the management of the study to enable focus on patient care
- Reducing the need for sites to collect and enter data manually
- Potential for improved recruitment, retention, and diversity of patients
- Real time data – alerting the Investigators of any potential issues or deviations that can occur during or between visits
- Reduced SDV requirements and onsite monitoring visits

The new burdens that DCTs can create for sites include:

- Technology overload – sites can be confronted with multiple, competing technologies and platforms and multiple sign-ons
- The time and resource requirements for training on all of these technologies

In a report of their 2019 survey on clinical trial technologies, SCRS noted the growth in site frustration with the multiplicity of systems and log-in credentials for eClinical technologies.[27] As noted in a 2020 White Paper,[28] disparate technologies, while intended to help sites streamline their data collection, often have the opposite effect and become burdensome. Supporting these findings, a recent Tufts survey addressing the impact of DCT adoption on sponsor-CRO collaborations found that site capabilities with new technologies are one of the primary barriers to successful implementation of DCTs.[29] To help alleviate the burden, sites need adequate logistical and technical training and support.[30]

While there are no silver bullets to ease the change management needed to mitigate site burden, there are several ways that industry and sites can work can continue to help ensure a site-focused approach:

- Early planning and communication – clear protocol design and early engagement with sites to address concerns from the beginning
- Greater site training and support from sponsors, CROs, and technology vendors
- Industry can adopt a more site-centric outlook by selecting DCT technology that is site-friendly – as noted in a recent analysis – industry can help towards alleviating sites' technology burden by utilizing industry technology (e.g., wearable sensors, eCOA, ePRO) that adapts to existing *site* technology (e.g., Investigator Site File and Clinical Trial Management System) – instead of the *sites* adapting to *industry*[31]

QUESTION 7:

Will DCTs create increased burden and responsibilities on patients?

ANSWER:

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. Many DCT tools – wearable sensors, home nursing, and telemedicine – were rated highly as options.[32]

To enable patients to have a positive experience with DCTs, industry is focused on patient education about DCTs from two angles – the content needed for adequate education and the best vehicles for conveying educational material.

As part of the continued evolution of what it means to be truly patient-centric, industry is increasingly focused on utilizing DCT tools that are intuitive and empathic.

Considerations for developing robust content for patient education include:

- Considering the variety of new roles and responsibilities patients take on in a DCT that they would not adopt in a conventional trial
- Education regarding receiving direct-to-patient shipment of the IMP
  - Is shipment to the patient residence acceptable to the patient?
  - Is there an alternative for shipment in the local community when residential shipment is not possible?
- Education and training on the care and storage of the IMP
- Training on the use of wearables, tablets, and other digital tools
- Training on the storage and care of wearables, tablets, and other digital tools
- How to use a Bring-Your-Own-Device (BYOD) tool where applicable

- When BYODs are utilized in a trial, patient questions regarding BYODs must be anticipated and answered:
  - Will the patient incur extra data costs when a BYOD is used?
  - What will the impact be on the patient's BYOD data storage limitations
  - Privacy concerns related to connecting the BYOD to the trial

Patients have varying abilities and preferences for learning and obtaining information. Consideration should be given to the wide variety of media available for conveying educational material to patients – including both electronic, online tools and printed, paper tools. Some patients may prefer visual vehicles such as video and others may be interested in a textual approach such as FAQ documents.

QUESTION 8:

Is a DCT different from a conventional trial regarding the patient standard of care?

ANSWER:

No. A DCT is not different from a conventional trial regarding the patient standard of care. However, the implementation of the standard of care may be different in a DCT, compared to a conventional trial (e.g., a questionnaire on an app may be used instead of a paper survey). Moreover, the patient's standard of care should be unaffected by their participation in a DCT. Well-designed protocols and properly applied DCT tools optimize the patient experience so that the patient's involvement in clinical research augments and complements their care pathway and patient journey.

QUESTION 9:

Is there a need for a new approach to the protocol and informed consent form (ICF) development (e.g., so that risks can be identified and mitigated)?

ANSWER:

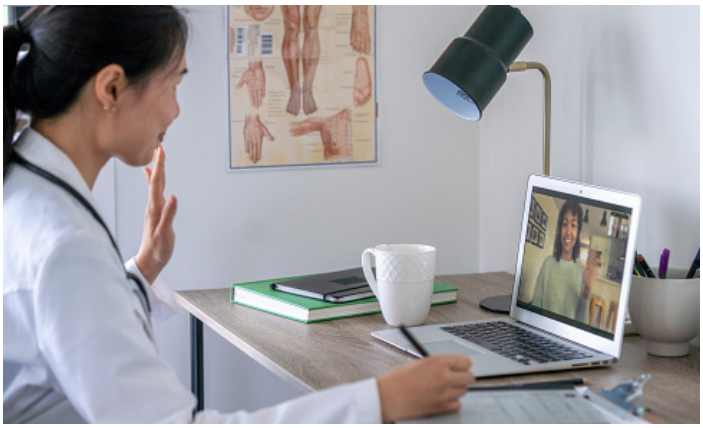
During the height of the COVID-19 pandemic, conventional trials designed for in-person patient visits at the investigator site were disrupted. Where appropriate, DCT tools were adopted to keep these active trials up and running. However, the Answer provided here pivots from DCT technologies as rescue tools to a focus on considerations for protocol development and ICF development where trials are originally planned – from the beginning – as a DCT (sometimes referred to as DCT-by-design).

The basic questions influencing protocol design for any clinical trial – whether conventional or decentralized – are the same:

- What is the research question the study seeks to answer?
- What data are needed to answer the question?

The primary focus for protocol development for a DCT will consist in embedding (1) the risk-assessment outcomes, (2) the rationale for a DCT design, and (3) an explanation of how the data will be captured (e.g., remote visits, use of telemedicine, home nurses, eConsent, Bring Your Own Device (BYOD)) into the protocol and forcing some of the operational assessments and decisions to be made earlier in the process. As in any clinical trial, each element of the protocol (including alternatives that allow for patient-centric flexibility) should be subjected to a rigorous risk assessment and inclusion of mitigation measures when a risk to patient safety, data integrity, protocol compliance or other aspects

of the conduct of the trial is identified. Clinical trial sponsors should engage fully with stakeholders during protocol development to enable the relevant risks to be identified and to include mitigation measures that are both appropriate and practical.



The patient information sheet and informed consent form (ICF) should be developed alongside the protocol and should also include engagement with appropriate stakeholders. Best practices for informed consent forms in clinical trials including DCT elements include:

- Details about which specific activities are decentralized and the responsibilities and actions that patients participating in the clinical trial will be expected to take
- For example, if eCOA or telehealth is being used, language will need to be added that describes the patient responsibility for the DCT portion, such as: *"You will be required to complete a daily diary on your personal or provisioned device."*
- Patient-centric flexibilities in study conduct (e.g., that assessments may be performed either by healthcare staff visiting the patient at home or performed at the study site) should be clearly identified in the ICF

The ACRO DCT Toolkit Quality-by-Design Manual and Risk Assessment Considerations tool can be a resource for DCT protocol development.[33]

QUESTION 10:

In addition to the protocol and ICF, might other clinical trial documents change?

ANSWER:

Just as early engagement and robust planning is necessary for a successful DCT protocol, other trial documents can benefit from thorough consideration when a decentralized trial is planned, for instance:

- Patient handouts may need to explain the use of DCT elements in the study
- Investigator leaflets may need to explain the use of DCT elements in the study
- Additional training materials may be required so that all parties contributing to the clinical trial, including patients, are able to use the required technology appropriately
- Investigator agreements should address how the PI will maintain oversight of relevant staff and services contracted centrally by the sponsor
- When protocols allow for patient-centric flexibilities, the precise workloads (nature and content) of the study site and outsourced healthcare services may be difficult to predict, therefore flexibility may also be necessary in contracts and budgets with sites and service providers
- Clinical trial reports will need to identify clearly any DCT elements that were used in the study. When the protocol allows for patient-centric flexibility, analysis of data generated by different procedures or at different sites (e.g., home visits compared with a centralized site visit) may need to be reported separately to support combining the data for the overall analysis

QUESTION 11:

How does endpoint selection work in a DCT?

ANSWER:

Endpoint selection in a DCT, as with conventional trials, is always driven by the therapeutic area and research question under investigation. Moreover, the methods used for measuring subjective and objective endpoints in a DCT should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness. Appropriate endpoint selection in DCTs is critical for a successful trial.[34] To develop novel digital endpoints, sponsors should follow the same guiding principles as when developing novel endpoints captured by other means. They should, for example, first determine whether the novel endpoint is a clinically meaningful reflection of how a patient feels, functions, or survives and whether it can be adequately captured using digital tools. There are many issues to consider, such as which endpoints can be obtained remotely and which would need to be obtained at the investigator site. This could involve redefining standard practices. For example, a physical examination can often only be performed by a physician, while specific checks may be performed by a nurse in a remote setting. Is a full physical examination needed, or can that be defined in a way that makes decentralization possible? Endpoints can be obtained through eCOAs and ePROs, and wearables can also be considered. Options should be evaluated early and clearly explained in the protocol.

In their work with the DIA Study Endpoints Community, Walton et al. describe a useful framework for the development of meaningful endpoints.[35] In essence, the process requires insights into the aspects that are most meaningful to patients – likely established through qualitative research in the patient group to identify meaningful aspects of health from which to define concepts of interest for health measurements. By understanding these valued aspects, pertinent endpoints can be defined, and an appropriate measurement approach can be identified– which may include a digital health technology.

QUESTION 12:

Do DCTs raise unique risk management considerations?

ANSWER:

GCP principles include the importance of risk management and encourage the use of technology to support this activity. Introducing DCT methods of data collection, monitoring, patient engagement through home visits, wearables, apps, and other tools may surface new risks that require mitigation. These may be different from risks seen in a traditional study, but still fall within the typical risk categories. As in any clinical trial, each element of the protocol (including alternatives that allow for patient-centric flexibility) should be subjected to a rigorous risk assessment and inclusion of mitigation measures when a risk to patient safety, data integrity, protocol compliance or other aspects of the conduct of the trial is identified. Clinical trial sponsors should engage fully with stakeholders, including regulatory agencies, patients, clinical research organizations (CROs), and experienced third-party vendors providing services such as telehealth or home health care providers, during protocol development to enable the identification of relevant risks and the development of mitigation measures that are both appropriate and practical. Key resources and tools for risk management considerations include the ICH Guideline for Good Clinical Practice E6(R2)

and E6(R3) Draft Principles,[36] the ACRO DCT Toolkit, which contains a Risk Considerations Tool dedicated to the specific risk considerations within a DCT,[37] along with ACRO's White Papers on Risk-Based Quality Management (RBQM).[38]

II. Data Integrity and Data Protection

QUESTION 13:

Because of the sheer volume of data in a DCT (e.g., via continuous monitoring), how do we aim to gather data that are fit for purpose?

ANSWER:

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?

Once the appropriate endpoints and methods for collecting the data are established, the tools that are used should be configured appropriately to enable good governance. 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.

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.[39] 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.[40]

QUESTION 14:

Do DCTs raise unique data protection concerns?

ANSWER:

The fundamentals of data protection in a DCT are no different than those required in a conventional trial. Processors and controllers (whether in the US or Europe) must adhere to the same privacy regulations and laws regardless of trial design. It is true that a DCT will include privacy considerations for telemedicine, home health visits, and electronic data capture, transfer, and monitoring. However, these tools are used outside of DCTs and have known data protection safeguards. DCTs can utilize modern data protection tools to enable a traceable path for the data.

DCTs have resulted in collection of more data; more types of data; and more complex data. A recent study by Tufts Center for the Study of Drug Development noted exponential growth in trial data, with the majority of sponsors using at least three to five data sources in their trials.[41] Given the volume and complexity of data in DCTs, data protection and data privacy are highlighted. However, the fundamentals of DCT data protection are not any different than those for data collection from devices and other systems that we have been using for many years. DCTs can apply the same rigor and protection that we have utilized for processing such as imaging and diaries.

Decentralized data collection can increase the gathering of personally identifiable or HIPAA-protected health information, thereby increasing concerns about how the data are being captured, used, stored, shared, and monitored during a trial. Moreover, globalization across world regions with diverse regulations and local requirements adds to the challenges. When implementing DCTs, the key consideration for sponsors and CROs is adherence to established, global data protection regulations. In the US, this includes FDA regulations in 21 CFR Part 11, 50, 56,[42] HIPAA,[43] and HITECH.[44] In Europe, relevant regulations include EU Annex 11,[45] the General Data Protection Regulation (GDPR),[46] guidelines from the European Data Protection Board,[47] and local legislation and regulation via DPAs.

Sponsors and CROs must assess potential DCT partners' compliance with such regulatory requirements and determine delivery approaches in global geographies to enable the minimization of data protection risks. Understanding how a proposed technology solution will process, validate, and store data is also important when vetting providers from a compliance perspective. Conducting Data Protection Impact Assessments (DPIAs)[48] is another useful way to map the data collection workflows within a proposed DCT to better understand data usage, movement, storage, and potential privacy risks.

Protocol development should include consideration of how patient data are protected when captured, transferred, and stored digitally. Moreover, it must be clear who can access the data and how it is shared and monitored. Enabling data protection across multiple geographies in a DCT can be achieved through risk assessment, upfront planning, and continuous oversight to help remove uncertainty and provide confidence that the data protection in place meets requirements and is scalable across DCT studies.

QUESTION 15:

Are there unique cybersecurity concerns in a DCT?

ANSWER:

Cybersecurity is a major concern in all digitized systems that hold and safeguard personal data, financial data, health data, and other sensitive data. DCT data are no different than data collected in conventional clinical trials using electronic or paper-based systems. The physical and logical security requirements for all of these systems have been outlined in a variety of regulations and guidance documents such as ICH GCP, 21 CFR Part 11, Annex 11, and others. DCT systems are required to follow these same guidelines and best practices, which should be further enhanced by internal and external penetration testing, quality management systems, and regular inspections to check that appropriate safeguards are in place. It is important to rely on technologies that utilize established security frameworks (e.g., application, infrastructure, and data security) and employ secure software development practices. Limiting system access to authorized individuals through adequate access control and identity management and using robust audit trails help mitigate cybersecurity risks.

While centralized cloud technologies are not exempt from risk, they can be more readily secured, with good governance systems in place, than most on-premise systems. Organizations using either on-premise or SaaS models should strive to attain the highest level of industry certifications to demonstrate that their practices and policies provide the highest level of protection and preparedness possible to promote the security of the data that they are collecting and storing. Data that are collected should be limited to data that are appropriate to document the scientific and legal aspects of the clinical trial and should only be stored for as long as is appropriate by regulation or local policy. Destruction of data should follow a standardized policy and procedure, and should be possible to demonstrate that physical media as well as logical data storage have been protected and appropriately disposed of at the end of the retention period. Additional considerations can be found in recent FDA guidance Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, specifically the section on "Risk Considerations When Using Digital Health Technologies."[49] This guidance also notes, "Sponsors should ensure security safeguards are in place to secure data at rest and in transit to prevent access by intervening or malicious parties."[50]

QUESTION 16:

What about data flow and accountability and provenance in a DCT? How do we know who has data access (and when) throughout the data flow?

ANSWER:

In a DCT, additional checks and surveillance can be implemented to verify and validate all datastreams. Data should be evaluated as it is collected, in real time, so study teams can respond proactively to correct errors, aberrations, mishandling or misuse of data. Consistency between data collected at the investigator site, through in-clinic procedures, and data collected remotely, via patient report or home health assessment, should be monitored. Telehealth visits can be used to monitor patient engagement, comprehension, safety, and compliance with decentralized activities (e.g., ePRO, wearables/ sensors). Patient adherence to protocols in a DCT requiring use of tools such as sensors and ePRO can be checked through the use of telemedicine and data analysis tools. For example, a patient who is participating in a fully decentralized trial using a sensor that measures heart rate, heart rhythm, or other vital signs can be physically observed by the principal investigator in both proper placement of the device as well as real time collection of data from the device during a telemedicine session. Using the baseline cardio rhythm, the PI is able to detect if future readings are coming from that patient or from another person based on signature rhythms, for example. Data analytic tools that are designed to identify changes or anomalies in standard vital signs or measurements can more readily detect these anomalies by screening the changes over time.

Integrated technology platforms support data aggregation and should be paired with a data review strategy employing risk based monitoring, data management, and centralized statistical monitoring. Artificial intelligence (AI) and machine learning (ML) can also be used to identify trends, patterns, or anomalies with the data and can detect and assure data integrity from wearables. AI algorithms exist to detect sensors being worn by someone (or something) else other than the patient. In tandem with these controls, it is helpful to consider how data will be securely stored and transferred among all parties collecting and receiving data during the trial. In addition, training of study staff and patient education is vital to maintain data integrity and quality.

Connected devices are aligned to specific user records as part of their provisioning process and the level of security at authentication, transit, and rest typically exceeds other methods of data capture. With connected devices, and similar direct capture methods, there are additional capabilities to enhance the level of trust in the data source in a way that exceeds the current baseline applied to other clinical eSource collection methods. Some of these options are dependent on the type of connected device, on protocol design, on the data platform capabilities. The following may apply depending on the combination of such factors:

- Connected device data are not collected in vacuum, it is often correlated to ePRO, eCOA, and similar data. For example, if the response to a quality-of-life questionnaire is that the patient experiences pain when walking but the actigraphy data shows a high number of steps, this may show a discrepancy

- Outlier detection and fraud detection tools may be available. Clinical data repositories, risk-based quality management and centralized monitoring platforms are already applied to clinical data (e.g., laboratory results, ePRO, EDC, etc.) for the detection of outliers and fraud both across patient, site, country, and study levels. The same can be applied to connected device data to trigger a clinician review

- For a DCT setting in both streaming data devices and spot data devices the data can be observed in real time for both mobile nurse visits and investigator-led telemedicine

- In real-time pattern recognition, patient baseline profiles can be individualized to each patient based on their connected device data pre-intervention. Any outliers detected post-intervention can trigger a clinical event whether that is due to fraud or due to medical reasons requiring clinical follow-up

- Some streaming devices are often applied over a duration of weeks (e.g., continuous glucose monitoring) and cannot be removed and reapplied in that interval. Therefore, there is higher confidence in the source of the data

Overall, perhaps the biggest influence for supporting data accountability is when good protocol design factors in connected devices (i.e., those fitted to the patient and which are not readily removed) as part of the design process. In such a scenario the patient or user burden is greatly minimized.

When technologies are used in the capture and transfer of data on a DCT, user access controls such as username and password combinations are required to restrict access to the appropriate users.

This can be challenging with some of the wearable and sensor technologies required on some studies. In their 2017 Draft Guidance Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR Part 11 – Questions and Answers, FDA states that:

For wearable biosensors and other portable electronic devices intended for a single study participant to wear or use (e.g., small physiologic sensors with no display screen), basic user access controls may be difficult to implement. In cases where access controls are impractical, sponsors should consider obtaining a signed declaration from the study participant confirming that the device will only be used by the study participant.[51]

In addition, the ICF would outline the expectations for the study, and the investigator would review the requirements with the patient. During this discussion any requirements about proper device use would be reviewed. Most eSource collection methods rely on an attributable user ID and authentication method. Additional measures such as two-factor authentication may be applied.

Both the Clinical Trials Transformation Initiative (CTTI)[52] and TransCelerate[53] have created resources for promoting and protecting data integrity in decentralized trials. CTTI provides a high-level data flow diagram[54] illustrating data movement from digital device collection to analysis. Additionally, ACRO has developed data flow maps for five processes central to decentralized trials, accessible in ACRO's DCT Toolkit,[55] to provide transparency and visibility into data flow, data controls, and data traceability.

End Notes

[1] Please see:

Decentralized clinical trial transformations are 'here to stay': ICON, July 6, 2022, Outsourcing Pharma https://www.outsourcing-pharma.com/Article/2022/07/06/decentralized-trial-transformations-are-here-to-stay-icon?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright

FDA Official: Decentralized Trials are 'Here to Stay', March 22, 2022, ACRP Blog https://acrpnet.org/2022/03/22/fda-official-decentralized-trials-are-here-to-stay/

Why Decentralized Clinical Trials Are the Way of the Future, April 5, 2021, Applied Clinical Trials, https://www.appliedclinicaltrialsonline.com/view/why-decentralized-clinical-trials-are-the-way-of-the-future

[2] "Opportunities and counterintuitive challenges for decentralized clinical trials to broaden participant inclusion," May 5, 2022, NPJ Digital Medicine https://www.nature.com/articles/s41746-022-00603-y

[3] "Association of Remote Technology Use and Other Decentralization Tools With Patient Likelihood to Enroll in Cancer Clinical Trials," July 5, 2022, JAMA Network https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2793869

[4] "Setting the Stage: Transforming the Clinical Trials Landscape in Europe"—PowerPoint presentation for DIA Europe 2022 DIAmond Session: #DMD06-H: Dedicated to Advancing Health Priorities: The Digital Transformation Fueling Decentralized Clinical Trials, Presented by Fergus Sweeney on 30 March 2022

[5] Please see:

Innovative Medicines Initiative (IMI) Trials@Home Glossary of terms and definitions used https://trialsathome.com/wp-content/uploads/2022/03/D2.1-Glossary-of-terms-and-definitions_-2021_V2.1final.pdf

TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/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

[6] Bringing the Trial to the Patient: A Quality-by-Design Manual for Decentralized Clinical Trials, September 2020 https://www.acrohealth.org/wp-content/uploads/2020/08/ACRO-QbD-Manual-FINAL-for-WEBSITE-UPLOAD-1.pdf

[7] This definition was adapted from, and builds upon, the TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

[8] This definition was adapted from, and builds upon, the TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

[9] This definition was adapted from, and builds upon, the TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

[10] This definition was adapted from, and builds upon, the TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

[11] This definition was adapted from, and builds upon, the TransCelerate White Paper "BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT," TransCelerate Biopharma Inc. 2020 https://www.transceleratebiopharmainc.com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf

[12] Signant Health: consider DCT design factors from the start, December 16, 2021, by Jenni Spinner HTTPS://WWW.OUTSOURCING-PHARMA.COM/

ARTICLE/2021/12/16/SIGNANT-HEALTH-CONSIDER-DCT-DESIGN-FACTORS-FROM-THE-START

[13] For more details on ADKAR, please see https://www.prosci.com/methodology/adkar

[14] For more details on ADKAR, please see https://www.prosci.com/methodology/adkar

[15] The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products," September 2021 Version 2.0, Danish Medicines Agency, https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/~/media/5A96356760ED408CBFA9F85784543B53.ashx

[16] "Decentralised and virtual interventional clinical trials Published: June 18, 2021, Last updated: January 17, 2022," Swedish Medical Products Agency, https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-and-virtual-interventional-clinical-trials

[17] "Position paper by Swissmedic and Swissethics on decentralized clinical trials (DCTs) with medicinal products," 01 November 2021, https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/publikationen.html

[18] Please see discussion on planned Recommendations Paper on DCTs on EMA website here: https://www.ema.europa.eu/en/events/act-eu-multi-stakeholder-meeting-decentralised-clinical-trials

[19] The FDA issued a draft guidance on the use of Digital Health Technologies in clinical trials in early 2022 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) and is expected to issue a draft guidance on decentralized clinical trials by the end of 2022 https://www.fda.gov/media/134778/download

[20] "Opportunities and Challenges for Decentralized Clinical Trials: European Regulators' Perspective" CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 112 NUMBER 2 | August 2022 https://ascpt.onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.2628

[21] Investment in decentralized clinical trials pays off: analysis, 28 July 2022 By Jenni Spinner, OutsourcingPharma A joint study conducted by analysts from Medable

and the Center for the Study of Drug Development points toward shorter cycle times, cost savings, and more. HTTPS://WWW.OUTSOURCING-PHARMA.COM/ARTICLE/2022/07/28/INVESTMENT-IN-DECENTRALIZED-CLINICAL-TRIALS-PAYS-OFF-ANALYSIS

[22] IQVIA White Paper -- DCTs Deliver Big ROI: New study proves that choosing decentralized clinical trials enables reduced time and cost, delivering measurable benefits for sponsors, by Bhausaheb Patil https://www.iqvia.com/library/white-papers/dcts-deliver-big-roi

[23] ICH ICH-E6(R3) Good Clinical Practice (GCP) Explanatory Note DRAFT PRINICIPLES, dated 19 April 2021 https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

[24] Please see both E6(R2) Guideline and also E6(R3) Draft Principles:

> ICH HARMONISED GUIDELINE: INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) -- Current Step 4 version, dated 9 November 2016 https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
> ICH ICH-E6(R3) Good Clinical Practice (GCP) Explanatory Note DRAFT PRINICIPLES, dated 19 April 2021 https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

[25] ACRO DCT Toolkit https://www.acrohealth.org/dct/

[26] ICH HARMONISED GUIDELINE: INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) -- Current Step 4 version, dated 9 November 2016
https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

[27] 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/

[28] Sites Speak Out on Clinical Trial Technology Overload, SCRS White Paper in Collaboration with IQVIA, July 2020
https://myscrs.org/learning-campus/white-papers/

[29] The Impact of Decentralized and Hybrid Trials on Sponsor and CRO Collaborations July 27, 2022, Applied Clinical Trials.
https://www.appliedclinicaltrialsonline.com/view/the-impact-of-decentralized-and-

hybrid-trials-on-sponsor-and-cro-collaborations

[30] 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

[31] Why Decentralized Clinical Trials Remain a Black Box to Most Research Sites, by Catherine Gregor, ContractPharma, March 18, 2022 https://www.contractpharma.com/contents/view_experts-opinion/2022-03-18/why-decentralized-clinical-trials-remain-a-black-box-to-most-research-sites/

[32] Role of decentralized clinical trials in cancer drug development: Results from a survey of oncologists and patients, Digital Health, Volume 8: 1–24, https://journals.sagepub.com/doi/pdf/10.1177/20552076221099997

[33] ACRO DCT Toolkit https://www.acrohealth.org/dct/

[34] Please see:

Utilizing DHTs for Clinical Trial Endpoints by Bill Byrom, May 14, 2021, Applied Clinical Trials https://www.appliedclinicaltrialsonline.com/view/utilizing-dhts-for-clinical-trial-endpoints
Considerations For Using Established Versus Novel Endpoints In Decentralized Trials, By Vibha Sharm, March 18, 2022, Pink Sheet https://pink.pharmaintelligence.informa.com/PS145878/Considerations-For-Using-Established-Versus-Novel-Endpoints-In-Decentralized-Trials

[35] Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials, Walton et al., Contemp Clin Trials April 2020 https://doi.org/10.1016/j.cct.2020.105962

[36] Please see both E6(R2) Guideline and also E6(R3) Draft Principles:

ICH HARMONISED GUIDELINE: INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) -- Current Step 4 version, dated 9 November 2016 https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
ICH ICH-E6(R3) Good Clinical Practice (GCP) Explanatory Note DRAFT PRINICIPLES, dated 19 April 2021 https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

[37] ACRO DCT Toolkit https://www.acrohealth.org/dct/

[38] Please see:

ACRO White Paper:
Risk Based Quality Management (RBQM) – A Collaborative Approach to Holistic Clinical Trial Oversight
https://www.acrohealth.org/oversight-rbqm-paper/
ACRO White Paper: Establishing Risk-Based Monitoring within a Quality-Based System as "Best Practice" for Clinical Studies
https://www.acrohealth.org/rbqm-report/

[39] 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

[40] 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

[41] Rising Protocol Design Complexity is Driving Rapid Growth in Clinical Trial Data Volume, Tufts Center for the Study of Drug Development IMPACT Reports, January/February Vol. 23 No. 1 https://csdd.tufts.edu/impact-reports

[42] US Code of Federal Regulations – electronic CFR -- https://www.ecfr.gov/current/title-21

[43] Health Insurance Portability and Accountability Act (HIPAA) of 1996, https://aspe.hhs.gov/reports/health-insurance-portability-accountability-act-1996

[44] The Health Information Technology for Economic and Clinical Health (HITECH) Act Enforcement Interim Final Rule https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/enforcementrule/enfifr.pdf

[45] EudraLex -- The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 11: Computerised Systems https://health.ec.europa.eu/system/files/2016-11/annex11_01-2011_en_0.pdf

[46] EU General Data Protection Regulation https://gdpr.eu/tag/gdpr/

[47] European Data Protection Board https://edpb.europa.eu/our-work-tools/general-guidance/guidelines-recommendations-best-practices_en

[48] Please see GDPR website at

https://gdpr.eu/data-protection-impact-assessment-template

[49] 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

[50] 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

[51] FDA Draft Guidance on Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR Part 11 – Questions and Answers https://www.fda.gov/media/105557/download

[52] Clinical Trials Transformation Initiative (CTTI) "Table 3: Promoting and Protecting Data Integrity" at https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Digital_Health_Technologies_Data_Integrity_Table.pdf

[53] TransCelerate "eSource Initiative: Issues Related to Non-CRF Data Practices" at http://www.transceleratebiopharmainc.com/wp-content/uploads/2018/01/eSource-Non-CRF-Data-Practices.pdf

[54] CTTI Data Flow Diagram https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Digital_Health_Technologies_Data_Flow_Diagram.pdf

[55] ACRO DCT Toolkit – Data Flow Maps https://www.acrohealth.org/dct/