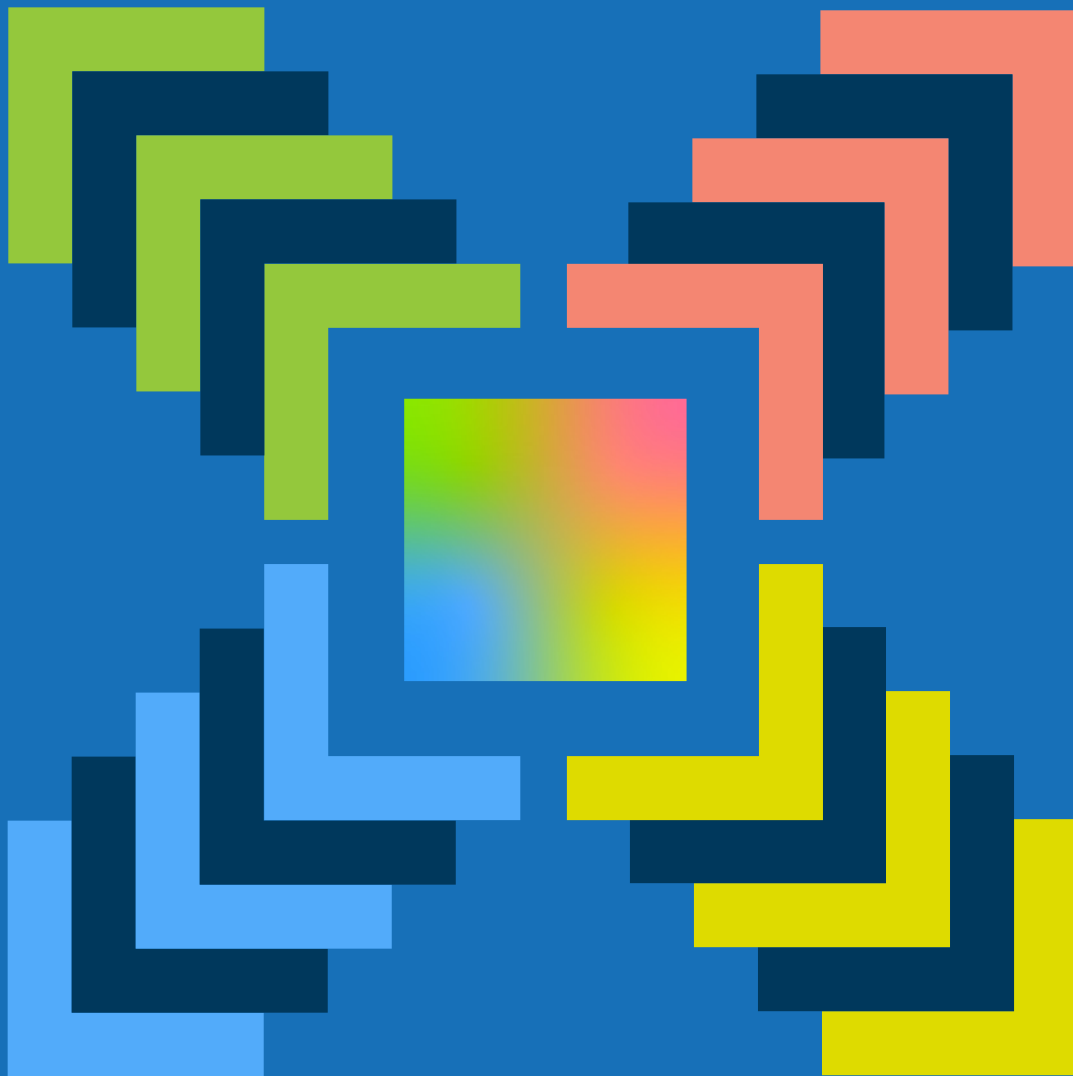


Decentralized Clinical Trials: Perspectives for Clinical Research Professionals



INTRODUCTION

This position paper presents the views of Association of Clinical Research Professionals (ACRP) Fellows about the impact of increased use of decentralized clinical trial (DCT) elements in clinical research and the evaluation of test articles. The paper describes the potential impact on subject safety, human rights, data integrity, electronic communication, and study financials, and provides guidance on the changes required to clinical research plans, facilities, equipment, and training. The wide variety of study objectives and designs that use DCT elements does not allow for the development of simple rules that fit all or even most situations. Out-of-the-box thinking is required; traditional SOPs and clinical operation practices based on site-centric assumptions must be rewritten. Adapting to the range of models is key with an emphasis on training clinical research professionals to carefully consider every study individually and customize study plans.

Assessing the impact of DCTs on both clinical trial validity and clinical research stakeholders is of pressing importance due to the increased use of DCT elements during the COVID-19 pandemic — a trend that is forecast to continue. This recent surge represented a major disruption to traditional clinical trial operational models and clinical researcher roles. As CenterWatch (December 6, 2021) writes, “Industry is approaching a watershed moment, with sponsors and CROs planning for the first time to conduct more hybrid trials than traditional site-based trials, a trend that is expected to play out across all trial phases and therapeutic areas.” The publication quotes a recent survey by Science 37, in which respondents viewed the top three advantages of hybrid trials as being better study subject experience, better patient retention and faster recruitment.²

Developing this position paper is in accordance with ACRP’s mission to promote clinical research professionalism, and its vision that clinical research must be performed ethically, responsibly, and everywhere in the world. Our commitment to the ethical tenets of our profession will be referred to within this paper, with protection of our study subjects and the collection and documentation of clean, unadulterated data during clinical trials first and foremost.

AUTHORS

This paper was researched and written by Fellows of the Association of Clinical Research Professionals, including the following lead authors:



JERI BURR
RN, PED-BC, MS, FACRP



JERRY M. STEIN
PhD, FACRP



JOY JURNACK
RN, FACRP

METHODOLOGY / DEFINITIONS


DECENTRALIZED TRIALS (DCTs): DEFINITIONS

- U.S. Food and Drug Administration (FDA) (Eric Pittman): Defines DCTs as “clinical trials using digital technologies to have remote interactions with real subjects”³
- FDA (Eric Pittman): Defines virtual trials as “preclinical trials conducted in silico or on models”
- Academic Perspective: DCTs are those that use remote technologies (mHealth, sensors, telemedicine, etc.) to interact with subjects away from central research facilities.
- Clinical Trials Transformation Initiative (CTTI): DCTs are defined as “those executed through telemedicine and mobile/local healthcare providers, using procedures that vary from the traditional clinical trial model (e.g., a study where investigational medical products are shipped directly to the trial subjects).”⁴


Decentralized approaches to clinical trials have been a topic of discussion for many years. The first U.S. Food and Drug Administration (FDA) guidance to refer to ‘remote’ informed consent and access to data was published in 2013.⁵ The 2013 FDA guidance, “... specifically encourage(d) greater use of centralized monitoring methods where appropriate.”

In most traditional studies, subjects travel to a clinic (e.g., a hospital or a practitioner’s office) where data are collected by trained site personnel or patient reported outcomes are documented. Although previous studies have frequently collected some study data away from the physical clinic (e.g., diaries completed at home), the recent surge in the proportion of data collected in this manner requires new definitions and strategies.

For purposes of this position paper, any study where most of the data originates away from the clinic utilizing virtual tools, such as video or telephone calls, or electronic sensors is considered a DCT trial. The goal of the DCT model is to provide GCP-compliant, IRB-approved, investigational study plans that rely on sponsor-designated data collection outside a traditional research site, whether as an extension of the brick-and-mortar site or as a completely decentralized trial. The key feature of a decentralized trial is that most or all



The key feature of a decentralized trial is that most or all study data are collected away from a central research facility. Hybrid DCT trials include a more balanced mix of centralized and decentralized elements. The relevant feature is the location of the subject’s interaction.



study data are collected away from a central research facility. Hybrid DCT trials include a more balanced mix of centralized and decentralized elements. The relevant feature is the location of the subject's interaction.⁶ Decentralization should not be confused with the physical method chosen to document study data and transfer the information into a database. Site personnel and study subjects can record data on paper or enter it electronically while located in the clinic, at the homes of subjects or any location as part of a traditional, clinic-based study or as part of a DCT trial.⁷


In addition to reduced access to healthcare facilities during the COVID-19 pandemic, the increase in DCT elements has been driven by several potential benefits for sponsors, study sites and subjects including (Table 1):

- A reduction in the need for sponsor resources, with fewer study subject site visits, lower professional service fee budgets, lower subject transportation costs, fewer site monitoring visits, more rapid enrollment, fewer missed visits, and overall shorter study durations
- A reduction in study site resources that need to be dedicated to clinical studies including space requirements (e.g., subject training areas and study supplies), and fewer tasks for study site personnel
- A better, more convenient study subject experience with fewer, shorter clinic visits and less frequent face-to-face contact^{7,8}


Concerns about the increase in DCT elements include:

- Potential for missed opportunities to detect safety signals
- An increase in data errors or fraudulent practices
- Increased reliance on study subject compliance

The true balance of advantages and disadvantage using DCTs will become known during the next few years as our collective experience increases. We can comfortably predict that data-based assessments of the various DCT approaches will be shared at future scientific / medical meetings concerning the performance of marketed products or validity of research findings. This ACRP position paper presents a summary of clinical research factors likely to be impacted by DCT. The discussion is divided into six sections: training, protection of human subjects, electronic communication, data integrity and Part 11 compliance, safety considerations and financial considerations.




The true balance of advantages and disadvantage using DCTs will become known during the next few years as our collective experience increases.



KEY RECOMMENDATIONS

In response to the increased use of full or hybrid decentralized clinical trial designs:



Sponsors, CROs, vendors and sites need to review and potentially customize each study plan to ensure data integrity, Part 11 compliance, protection of human subject rights, adequacy of communication tools, detection of adverse events, and mitigation of subject safety risk.

Clinical investigators need to adapt site infrastructures to conduct studies that will likely require fewer patient site visits and an increase in remote data collection locations.


Clinical research professionals (including data management specialists, study monitors, and site study coordinators) need to review their informatics skills to ensure these are sufficient to deploy and test devices/digital tools in real-world settings.

Sponsors and CROs need to modify their SOPs and study-specific plans to train study subjects, provide adequate electronic communication away from clinics and provide study subjects with access to study coordinators or coaches.

Clinical teams need to expand their memberships (including electrical engineers, computer scientists, data engineers, and informatics specialists) to support digital communication and data collection tools.

Financial aspects of clinical research (including the distribution of clinical study resources amongst sites, vendors and study subjects) need to be modified to reflect new activities, responsibilities and data collection locations.

Curricula offered by ACRP (and other educational organizations) designed to train clinical research professionals need to adapt to a wider range of new clinical operation models and roles.



KEY FACTORS IMPACTING DECENTRALIZED CLINICAL TRIALS

1. Training

Will training requirements and training plans need to change based on the increased use of DCT trials?

As part of its mission of promoting excellence in clinical research, ACRP provides a comprehensive range of educational opportunities to individuals working for sponsors, academic medical centers, study sites and ethics committees/institutional review boards (ECs/IRBs) in a variety of roles. These training programs, and ACRP's well-established clinical researcher certification processes,⁹ must be continually updated to reflect contemporary study designs, legal requirements and best practices.

Regardless of the location of the clinical study visit – whether on-site or remote – research on human subjects must consistently meet stringent standards. Clinical training curricula are based on regulations and guidance from the U.S. Food and Drug Administration (FDA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In addition, sponsor SOPs and protocol-specific training are required for certain stakeholders.

Clinical investigational plans are partially based on assumptions concerning the location of study visits where data are collected. These individual plans are commonly interrelated parts of complex systems that can be significantly impacted by the increased use of DCT elements. A change in data collection location can affect the data management plan, plan for monitoring, plan for training sites and study subjects, audit procedures and communication. For example, training designed to educate CRAs to detect database errors may require significant modification should the primary data source switch from a central clinic to electronic sensors worn by study subjects while at home. In addition to protocol-specific changes, it may be necessary for sponsors to modify general SOPs, impacting many individuals across their organizations.

In addition to protocol-specific changes, it may be necessary for sponsors to modify general SOPs, impacting many individuals across their organizations.

All procedures that typically occur at study sites have the potential to be significantly impacted by the increase in DCT elements.

Study site SOPs may also be significantly impacted, including written SOPs and more informal site practices. In many trials, study coordinators are tasked with delivering informed consent information, interfacing with study subjects at each visit, collecting efficacy and safety data and recording the data on paper case report forms or in electronic records. All procedures that typically occur at study sites have the potential to be significantly impacted by the increase in DCT elements.²⁴ If a DCT design results in a decrease in office visits, study coordinators may have fewer opportunities to monitor subject compliance and reinforce proper instructions, including those for the use of test articles. In contrast, if the DCT design includes more frequent home visits by clinical research professionals, opportunities to shape compliance might increase.²⁴ Traditional expectations and procedures based on use of a central research clinic can no longer be the default model and customization will be required for each new study.

Traditional expectations and procedures based on use of a central research clinic can no longer be the default model and customization will be required for each new study.

Training of study subjects might also be significantly impacted by DCTs. Trials with reduced clinic visits will increasingly rely on educational materials delivered electronically (e.g., via internet, telephone and video contacts). In some instances, a significant increase in subject training will be required, with higher levels of electronic accessibility to study coordinators throughout the study.

Sponsor SOPs, general and study-specific training plans, site SOPs, protocol-specific training and technology must be evaluated to assess the impact of increased DCT elements on each study.

Thus, sponsor SOPs, general and study-specific training plans, site SOPs, protocol-specific training and technology must be evaluated to assess the impact of increased DCT elements on each study. Curricula offered by ACRP designed to train individuals who design, manage or monitor studies and site personnel must adapt to these changes.

2. Protection of Human Subjects


Will requirements and procedures designed to protect study subjects need to change in view of the increased use of DCT trials?

Protection of human rights is an important tenet of ethical clinical research. Potential study subjects need to properly be informed about the nature of the study, the fact that participation is voluntary and that there are alternatives to participation. These and other factors need to be part of risk:benefit summaries presented to potential study subjects. To ensure the protection of human rights, strict adherence is required to established regulations such as 45 CFR 46,¹⁰ 21 CFR 50 and 56,¹¹ and ICH E6 (R2).¹² Implementation of these protections is typically the responsibility of study sites, with study sponsors, ethics committees (ECs) and Institutional Review Boards (IRBs) providing important ongoing oversight.


The introduction of more DCT elements will not change the basic requirements for informed consent features intended to protect the human rights of study subjects. The personal delivery of informed consent information by site personnel or the use of innovative electronic delivery methods can occur regardless of subject location.

Historically, the introduction of electronic informed consent (eConsent) was an important early element in the evolution of the DCT model. Clearly, it is essential to ensure that informed consent is effectively delivered to everyone considering participation in a study, and where appropriate, their parents or legal guardians. The information must contain the required elements and confidentiality must be addressed. Thus, personal health information (PHI) should not be sent to a shared address. Processes, procedures, and training must be put in place to ensure that all the subjects' questions can be answered regardless of their physical location, and the decision to participate can be adequately documented. Remote visits must be set up so that the identity of each participant is documented, their safety, privacy and confidentiality maintained and ad hoc questions answered. With the introduction of more DCT elements, including studies with no initial office visit, additional staff training may prove to be essential since policies and procedures for brick-and-mortar site studies may not be sufficient for DCTs. Unintended consequences are likely to occur.

Thus, sponsor, site and EC/IRB requirements and practices for protecting human rights must be carefully reviewed and modified as necessary to accommodate the increase in DCT elements.



With the introduction of more DCT elements, including studies with no initial office visit, additional staff training may prove to be essential since policies and procedures for brick-and-mortar site studies may not be sufficient for DCTs.



3. Electronic Communication


Will requirements and procedures designed to promote effective electronic communication need to change in view of the increased use of DCT trials?

Electronic communication methods and devices are essential enablers of DCTs. Considerations related to their use include:


- Development of strategies to support investigators in selecting digital tools
- Changes in privacy, ethical, and regulatory issues related to using digital tools
- Understanding study deployment and how a digital platform fits within study workflows
- Understanding the limitations of digital tools, data capture validity, and calibration
- Increased need for infrastructure to support the integration and orchestration of digital activities and data arising from such events within a study
- Educating investigators and adapting trial data systems to fully utilize multi-resolution 'big data' appropriately in their studies
- Scaling to accommodate larger and different types of studies for increased efficiency, cost-effectiveness, and reproducibility.

While sensors and other electronic devices can certainly enhance a trial, their use requires planning, oversight, and ongoing monitoring. Some research institutions are developing next generation devices and systems to address these electronic communication needs. Features being investigated include:

- A repository for metadata about the sensor device deployments and the captured data. These will enable investigators to understand how specific devices are being utilized in a study and provide context about the data being captured.^{14, 15}
- Provisioning of sensor/device information in a library to support study device selection.¹⁶
- The fact that sensors and similar devices are uniquely situated by time and space. Research information systems need to accommodate data collected over an extended timeline and in multiple locations, along with capture of study operation events, to support temporal reasoning.¹⁷




The potential for DCTs and digital technologies to create or worsen health disparities is an important consideration.




- Scaling of the information systems to support diverse study types, from those that require intense monitoring and have multiple digital devices per participant, to community or population-based studies with many subjects and few devices.
- Enabling studies that require ecological momentary assessments (repeated real-time sampling in natural environments) and Just-In-Time (adaptive) interventions (Abbreviated JITI or JITAI) that provide tailored responses to real-time data through integration of sensor data feeds, clinical data and text messaging.²¹
- Supporting other types of real-world digital studies.²²
- Exploring the use of blockchain or similar methods for privacy management.²³
- Adapting institutional SOPs, systems, workflows and other practices to recognize and leverage the increasingly ubiquitous use of digital technologies by study participants.

The potential for DCTs and digital technologies to create or worsen health disparities is an important consideration. If a study plan requires data to be collected through a subject's smartphone and needs a reliable WiFi connection, this could exclude participants who do not have access to these technologies, including people with lower socioeconomic status, rural participants, or other important cohorts. Study teams must create strategies to ensure representative sampling of patient populations.²⁴ Relatively little is known about how to make digital health tools accessible to different populations, or acceptable to participants from a cultural standpoint.²⁵ There may be other considerations regarding the use of DCTs internationally, for example the adoption of digital tools may not be consistent across regions and populations, raising questions about when DCTs are appropriate or feasible.



To ensure data quality and integrity in DCTs, it is important that study sponsors and sites focus on building quality into the entire process through proactive compliance rather than being reactive or expecting quality improvements at later stages.



4. Data Integrity and Part 11 compliance

Requirements and procedures designed to protect data integrity, including regulations such as Part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11)²⁶ that help to document security and authenticity of responses, may need to change in view of the increased use of DCT trials.²⁷

The FDA requires high quality data regardless of how this is collected. Electronically-collected data – a feature of DCTs – must comply with


21 CFR Part 11. This applies to “records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations.” DCT activities must also comply with data privacy and security regulations such as the Health Insurance Portability and Accountability Act (HIPAA).²⁸

To ensure data quality and integrity in DCTs, it is important that study sponsors and sites focus on building quality into the entire process through proactive compliance rather than being reactive or expecting quality improvements at later stages. This proactive approach should include mapping and managing data flow, user access controls, data reconciliation, and storage (which may involve multiple parties, locations and systems). The Clinical Trials Transformation Initiative (CTTI) suggests starting with the trial source data and then mapping data flow, reconciliation, and storage based on how data reliability and integrity are assured, including data control and security.



chpc.utah.edu

Academic Perspective


Clinical trial stakeholders may conflate validation of an electronic system with external certification. Not all clinical trials are regulated by the FDA. Thus, feedback on the impact on DCT designs of regulatory requirements may not be assessed until after some studies are completed. Academic medical centers and smaller research sites may not always have necessary budgets for third-party certification of Part 11 compliance for all studies (e.g., external certification of Part 11 compliance for their instances of REDCap use). Nonetheless, organizations should operate under the general principles of Part 11, be fully HIPAA compliant and have processes in place for internal validation (e.g., HIPAA-compliant servers at the Center for High Performance Computing). FDA has issued INDs, EUAs and accepted data from academic medical centers based on studies conducted using its platforms for consent, data collection, and other elements.



It is clear that the increased demand for DCT elements is changing clinical research from the old paper-based data collection methods to cutting edge eSolutions, requiring study teams to collaborate with multiple functional groups that have informatics expertise to innovatively address these new requests.



Successful DCTs will depend on a collaborative team, including non-traditional partners from electrical engineering, computer science, data engineering, and informatics to support DCTs utilizing digital communication and data collection tools.



Part 11 compliance is not the only issue related to data integrity and documenting study rigor and reproducibility. One common request for DCT elements is text messaging integration (for example, text messaging intervention compared with other intervention formats). In addition, there has been increased interest in quickly obtaining clinical data from medical records. EPIC-REDCap integration through Fast Healthcare Interoperability (FHIR) systems is being evaluated, although institutional hurdles and priorities have slowed implementation. It is clear that the increased demand for DCT elements is changing clinical research from the old paper-based data collection methods to cutting edge eSolutions, requiring study teams to collaborate with multiple functional groups that have informatics expertise to innovatively address these new requests.


Data monitoring is a key consideration in DCTs. If data are being collected remotely rather than in a clinic, the addition of many new automatic data checks should be considered, in addition to incorporating these data sources into the study workflow. Similarly, there will be statistical considerations related to data accuracy and completeness. The increased use of DCTs is predicted to benefit adoption of more sophisticated methods for central statistical monitoring.

Continued efforts are needed to scale infrastructure to support various studies seamlessly and in a cost-effective manner. Successful DCTs will depend on a collaborative team, including non-traditional partners from electrical engineering, computer science, data engineering, and informatics to support DCTs utilizing digital communication and data collection tools.


5. Safety Considerations

Will requirements and procedures designed to protect study participant safety need to change in view of the increased use of DCT trials?

Minimizing study subject safety risk is a key tenet of good clinical research. Clinical product development plans are characterized by a progression of well-designed, scientific studies used to evaluate, identify, and mitigate risk. Laboratory and pre-clinical studies and analyses are initially used to develop preliminary risk profiles based on established



When the proportion of DCT elements increases, there is potential for an adverse impact on the safety of individual clinical trial subjects. However, in view of the large variety of study designs, the opposite might also be true: subject safety might increase.



models. Next, early-phase clinical studies help identify optimal dosing regimens, appropriate subject eligibility criteria and testing strategies. The design of later-stage clinical studies (e.g., Phase III) typically includes many features that mitigate risk, including more frequent clinic visits at the beginning of dosing sequences, well-defined procedures for collecting and managing adverse events and well-designed procedures for discontinuing treatment when warranted.


Impact on study subject safety

When the proportion of DCT elements increases, there is potential for an adverse impact on the safety of individual clinical trial subjects. However, in view of the large variety of study designs, the opposite might also be true: subject safety might increase. The education and training of clinical research professionals and clinical operation methodologies are often based on the assumption that studies contain a relatively small proportion of DCT elements. The increased use of DCT elements, with its disruptive effect on this model, demands a careful assessment of the impact on individual study subject safety. Current clinical research practices may be sufficient or may require significant modification.



Increased data collection by field-based clinical research professionals (e.g., nurse practitioners) may improve the collection of safety information. If a study used this type of design, safety data could be collected more quickly and accurately compared to traditional, study site centered research models.

In view of DCT's potential impact, it will be important to carefully review and customize each study plan for monitoring safety, documenting AEs, and managing risk based on the:


- Opportunities for noncompliance by study subjects
- Intended use and safety profile of the test article
- Sponsor's experience with this or similar studies and test articles



The increased use of DCT methodologies may impact financial factors, including significant changes to overall product development costs, and the distribution of sponsor expenditures directed to vendors, sites, field-based personnel, study subjects and study site operations.




The number of independent PIs interested in conducting clinical studies may decrease due to reduced hands-on involvement and profitability.




- Site's experience with this or similar studies and test articles
- Study design (visit schedule, subject contacts)
- Treatment regimen
- Technology designed to collect safety data (novelty, reliability)
- Use of field-based clinical research professionals to collect data remotely

Long-term Impact

The accuracy of safety information derived from formal clinical studies has implications for the validity of study results. When the objective is the evaluation of a pharmaceutical, medical device or diagnostic, product labeling (e.g., indications, risk information) may be impacted. If safety information collected from research utilizing DCT elements is inaccurate or misleading, much larger patient populations may be negatively impacted.



Clinical costs and the barrier-to-entry for small and emerging companies may increase as DCT models requiring more expensive technology become the norm. These financial factors must be carefully examined for their impact on safety, human rights and data integrity.



6. Financial Considerations

Will increased use of DCT trials elements impact financial aspects of clinical studies?

The increased use of DCT methodologies may impact financial factors, including significant changes to overall product development costs, and the distribution of sponsor expenditures directed to vendors, sites, field-based personnel, study subjects and study site operations. Net expenditures may decrease as a result of this redistribution with sponsor payments and incentives directed to study subjects increasing as compensation for the increased reliance on subject-initiated activities. For example, instead of periodic study clinic visits, study subjects may be required to wear electronic monitors 24/7 or enter their own data online.

The types of individuals who are eligible to be study subjects may change under the DCT model. In one scenario, DCT may skew recruitment in favor of higher-income populations with greater access to mobile devices and better internet connectivity. However, the opposite may occur. Use of field-based staff to collect information directly from study subjects may increase the involvement of lower income groups who currently have transportation or work-related barriers that limit participation in studies. Compensation for study participation will be impacted.

Impact on study sites

Sponsor payments for study site activities may change, impacting profitability and study staffing decisions. If a sponsor shifts the management of subjects away from clinic personnel towards a central data management center, site budgets will decrease proportionately; there will be a reduction in site activities and site monitoring visits will become shorter. However, the need to interact with individual study subjects to ensure compliance will increase. If a study is sponsored or managed by a central data coordinating center (DCC), budgets to properly monitor compliance and ensure data integrity may increase if additional technologies need to be acquired. Otherwise, DCC monitoring includes less on-site monitoring and relies more on risk-based and remote monitoring approaches, which is consistent with early adoption of DCT elements.

The number of independent PIs interested in conducting clinical studies may decrease due to reduced hands-on involvement and profitability. Sites will continue to serve as sources for recruitment and assess eligibility. The characteristics of study sites and PIs may change since fewer procedures will be based in the central clinic. In some studies, there will be an increased reliance on the collection of data by field-based health care professionals who visit study subjects outside the central clinic (e.g., at private residences or institutions).

Impact on sponsors

Clinical development budgets at large sponsor companies will likely decrease or stabilize. The use of central, remote monitoring will increase, with a reciprocal decrease in on-site monitoring. This trend will be more pronounced for established, larger sponsors who own or license the technology to service larger portfolios. In contrast, clinical costs and the barrier-to-entry for small and emerging companies may increase as DCT models requiring more expensive technology become the norm. These financial factors must be carefully examined for their impact on safety, human rights and data integrity.


Impact on vendors

An increase can be expected in expenditures intended to support the automated collection of study data from remote locations. Vendors who develop or manage the use of technology designed to collect medical information may hire many more specialists to analyze device output, essentially serving as sub-contractors or sub-investigators (similar to reading centers). The use of field-based, health-care professionals (e.g., nurse practitioners) may increase.


Overall Conclusions

While there was a rapid increase in studies using DCT elements as a practical response to the COVID-19 pandemic, it also became clear that the introduction of new approaches to data collection and study designs would have long-term effects throughout the clinical trial enterprise. The pandemic impacted timelines for new studies that were in the startup phase and many institutions shut down clinical research that was not COVID-related. Research had to be decentralized to continue. The true impact of COVID on the research workforce, decentralized data collection, and many traditional clinical trial functions remains to be seen, but it is apparent that clinical research professionals will have to adapt to the requirements of these decentralized approaches. Because DCTs require increased use of data collected away from the central research site, it will be important for clinical research professionals to understand the study deployment space and how a digital platform can be utilized. In addition, electronic communication methods and tools that enable DCTs require study teams to have adequate infrastructure, support and training to utilize the appropriate digital tools (mHealth, sensors, telemedicine, etc.) when collecting and transmitting data.

New roles will likely emerge for clinical research professionals assisting with the execution of DCTs that require informatics skills and the ability to deploy and test devices/digital tools in real-world settings. The new models can potentially impact many clinical study factors including traditional human rights protections, data integrity, the administration of informed consent, the training of clinical trial professionals and study subjects, and study finances. Direct reliance on study subjects as the source of study data and for good compliance will increase. SOPs and long-held practices used by stakeholders to plan, conduct and summarize clinical research must be carefully reviewed and potentially changed to cope with the wide variety of DCT approaches.



The true impact of COVID on the research workforce, decentralized data collection, and many traditional clinical trial functions remains to be seen, but it is apparent that clinical research professionals will have to adapt to the requirements of these decentralized approaches.



What is the Potential Impact of Increasing Proportion of DCT Study Design Elements in a Randomized Controlled, Phase III Clinical Trial?

	POSITIVE IMPACT	NEGATIVE IMPACT
 <p>Safety</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • More frequent reporting of AEs in a contemporary manner. <p>Site Perspective</p> <ul style="list-style-type: none"> • Decrease in AE reporting activities <p>Subject Perspective</p> <ul style="list-style-type: none"> • Fewer visits to centralized study sites 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Increased reliance on study subject actions to report safety issues • Increase in unreported AEs <p>Site Perspective</p> <ul style="list-style-type: none"> • Fewer opportunities to observe AEs <p>Subject Perspective</p> <ul style="list-style-type: none"> • Greater chance for under-reporting of AEs
 <p>Protection of Human Subject Rights</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • More uniform IC messaging • Increased request for eSolutions <p>Site Perspective</p> <ul style="list-style-type: none"> • Decrease in IC activities • Subject Perspective • Increased standardization of the IC process 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Less in-person GCP training • Increased request for eSolutions <p>Site Perspective</p> <ul style="list-style-type: none"> • Less F2F training and reliance on eSolutions <p>Subject Perspective</p> <ul style="list-style-type: none"> • Less customized IC processes
 <p>Data Integrity and Part 11 Compliance</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Cleaner data directly from source • More timely receipt of subject data <p>Site Perspective</p> <ul style="list-style-type: none"> • Less overhead for onsite staff <p>Subject Perspective</p> <ul style="list-style-type: none"> • Convenience of mobile and wearable technologies 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Need more resources to provide validated systems • New data checks to consider <p>Site Perspective</p> <ul style="list-style-type: none"> • Need more support for digital resources <p>Subject Perspective</p> <ul style="list-style-type: none"> • Worry about loss of PHI
 <p>Electronic Communication</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Decreases travel to site to review source data • Sensors enhance regular data collection methods <p>Site Perspective</p> <ul style="list-style-type: none"> • Source data received in real time <p>Subject Perspective</p> <ul style="list-style-type: none"> • Acceptance by most study subjects of the use of digital technologies in studies 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • More resources for infrastructure to support data integration <p>Site Perspective</p> <ul style="list-style-type: none"> • More IT/informatics effort needed to support data integration <p>Subject Perspective</p> <ul style="list-style-type: none"> • Lower socioeconomic classes may be excluded that cannot access digital technologies
 <p>Training, Communication Transparency</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Training methods shift to virtual platforms instead of expensive investigator meetings <p>Site Perspective</p> <ul style="list-style-type: none"> • Opportunities to shape compliance might increase <p>Subject Perspective</p> <ul style="list-style-type: none"> • Increased opportunities to participate in research through everyday wearable devices 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • CRA training may require significant modification <p>Site Perspective</p> <ul style="list-style-type: none"> • Study site SOPs may be significantly impacted • Fewer opportunities to monitor subject compliance and reinforce proper instructions <p>Subject Perspective</p> <ul style="list-style-type: none"> • Difficulty in participating if less educated in use of DCT technologies
 <p>Financial</p>	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Decreased direct payments to sites for study procedures • Decreased monitoring expenses <p>Site Perspective</p> <ul style="list-style-type: none"> • Decreased time devoted to hosting monitors and auditors <p>Subject Perspective</p> <ul style="list-style-type: none"> • Increased compensation • Use of field-based health care assessors will increase participation of subjects with transportation and work-related barriers <p>Vendor Perspective</p> <ul style="list-style-type: none"> • Increased use of technology that automates data collection 	<p>Sponsor Perspective</p> <ul style="list-style-type: none"> • Adoption, purchase and distribution of new technologies • Greater reliance on larger number of data source locations <p>Site Perspective</p> <ul style="list-style-type: none"> • Adaption to new technologies <p>Subject Perspective</p> <ul style="list-style-type: none"> • Use of data collection devices reliant on the internet may skew enrollment to higher income individuals. • Increase requirements / actions (change from passive to active) <p>Vendor Perspective</p> <ul style="list-style-type: none"> • Requirement to be GCP trained for vendors that previously did not require this training

DEFINITIONS

mHealth: mHealth is an abbreviation for mobile health, a term used for the practice of medicine and public health supported by mobile devices. The term is most commonly used in reference to mobile communication devices, such as mobile phones, tablet computers and personal digital assistants, and wearable devices such as smart watches, for health services, information, and data collection.

'Big data': 'Big data' is a field that analyzes, systematically extracts information from, or otherwise deals with data sets that are too large or complex to be handled by traditional data-processing application software. Data with many fields offer greater statistical power, while data with higher complexity may lead to a higher false discovery rate.

Sensors: Patient-centric sensors collect data, often passively, during a person's daily activities in his or her usual environment. These devices include pulse oximeters, activity trackers, glucometers, and spirometers, among others. A decade ago, few people owned wearable technology. Today, fitness trackers and smartwatches are widespread. As public comfort with wearables has grown, sensors have become more common in clinical trials as well. Some estimates predict that in under five years, up to 70 percent of all protocols will include sensors.²⁹

eHIE: electronic health information exchange

Blockchain: A blockchain is a type of database that collects information together in groups, also known as blocks, that hold sets of information. Blocks have certain storage capacities and, when filled, are chained onto the previously filled block, forming a chain of data known as the "blockchain." All new information that follows that freshly added block is compiled into a newly formed block that will then

also be added to the chain once filled. A database structures its data into tables whereas a blockchain, as its name implies, structures its data into chunks (blocks) that are chained together. As a result, all blockchains are databases but not all databases are blockchains. This system also inherently *makes an irreversible timeline of data when implemented in a decentralized manner*. When a block is filled, it is set in stone and becomes a part of this timeline. Each block in the chain is given an exact timestamp when it is added to the chain.³⁰

EPIC: Epic Systems Corporation, or Epic, is a privately held healthcare software company. According to the company, hospitals that use its software held the medical records of 54% of patients in the United States and 2.5% of patients worldwide in 2015.³¹

FHIR: Fast Healthcare Interoperability Resources (FHIR) is a standard describing data formats and elements and an application programming interface for exchanging electronic health records. The standard was created by the Health Level Seven International health-care standards organization.³²

REDCap: REDCap is a browser-based, metadata-driven electronic data capture (EDC) software and workflow methodology for designing clinical and translational research databases developed at Vanderbilt University.³³

References

- ¹ <https://www.centerwatch.com/articles/25878-hybrid-trials-may-overtake-traditional-studies-in-2022-new-data-show>
- ² <https://science37.com/Agile-Clinical-Trial-Report>
- ³ Pittman, E. *Decentralized Clinical Trials*. in Avera Research Integrity Conference. 2021. Sioux Falls, SD, USA: The Office of Research Integrity.
- ⁴ <https://ctti-clinicaltrials.org/decentralized-clinical-trials-expert-meeting/>
- ⁵ <https://www.fda.gov/media/116754/download>
- ⁶ Faulkner, K., *Decentralized vs Digital Clinical Trials: There is a Difference*. Applied Clinical Trials, 2021. 30(12).
- ⁷ Medicine, T.N.A.o.S.E., *Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop*. 2019.
- ⁸ Medicine, T.N.A.o.S.E., *The Role of Digital Health Technologies in Drug Development - A Workshop*. 2020
- ⁹ <https://acrpnet.org/certifications/>
- ¹⁰ <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>
- ¹¹ <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50>
- ¹² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1>
- ¹³ Ramkiran Gouripeddi, P.L., Sneha Kasera, Scott Collingwood, Mollie Cummins, Julio C. Facelli, Katherine Sward, *Exposure Health Informatics Ecosystem, in Total Exposure Health*. 2020, CRC Press. p. 46.
- ¹⁴ Burnett N, G.R., Wen J, Mo P, Madsen R, Butcher R, Sward K, Facelli JC, *Harmonization of Sensor Metadata and Measurements to Support Exposomic Research, in International Society of Exposure Science 2016: Research Triangle Park, NC, USA*.
- ¹⁵ Morgan T, G.R., Sward K. , *Characterizing Metadata of e-Devices for Interventional Translational Research.*, in AMIA 2019 Informatics Summit 2019, AMIA: San Francisco, CA, USA.
- ¹⁶ Burnett N, G.R., Facelli J, Mo P, Madsen R, Butcher R, Sward K, *Development of Sensor Metadata Library for Exposomic Studies, in International Society for Environmental Epidemiology Annual Meeting*. 2018: Ottawa, Canada
- ¹⁷ Gouripeddi R, T.L.-T., Madsen R, Gangadhar T, Mo P, Burnett N, Butcher R, Sward K, Facelli J, *An Architecture for Metadata-driven Integration of Heterogeneous Sensor and Health Data for Translational Exposomic Research*, in IEEE EMBS International Conference on Biomedical & Health Informatics 2019: Chicago, USA.
- ¹⁸ Smyth JM, Jones DR, Wen CKF, Matera FT, Schneider S, Stone A. Influence of ecological momentary assessment study design features on reported willingness to participate and perceptions of potential research studies: an experimental study. *BMJ Open*. 2021;11(7):e049154. Published 2021 Jul 30. doi:10.1136/bmjopen-2021-049154

- ¹⁹ Mofsen AM, Rodebaugh TL, Nicol GE, Depp CA, Miller JP, Lenze EJ. When All Else Fails, Listen to the Patient: A Viewpoint on the Use of Ecological Momentary Assessment in Clinical Trials. *JMIR Ment Health*. 2019;6(5):e11845. Published 2019 Apr 21. doi:10.2196/11845
- ²⁰ Wang L, Miller LC. Just-in-the-Moment Adaptive Interventions (JITAI): A Meta-Analytical Review. *Health Commun*. 2020;35(12):1531-1544. doi:10.1080/10410236.2019.1652388
- ²¹ Min, K.T., et al., *Smart home air filtering system: A randomized controlled trial for performance evaluation*. *Smart Health*, 2018. 9-10: p. 62-75.
- ²² Groat, D., et al. *An Architecture to Support Real-World Studies that Investigate the Autonomic Nervous System*. 2019. Cham: Springer International Publishing.
- ²³ Sarbhai A, G.R., Lundrigan P, Chidambaram P, Saha A, Facelli JC, Sward K, Kasera SK. *Managing Sensor Metadata in Exposomic Studies Using Blockchain*. in *The Air We Breathe: A Multidisciplinary Perspective on Air Quality*. 2019. Salt Lake City, Utah, USA.
- ²⁴ Sieck, C.J., et al., *Digital inclusion as a social determinant of health*. *NPJ Digit Med*, 2021. 4(1): p. 52.
- ²⁵ Marwaha JS, Kvedar JC. Cultural adaptation: a framework for addressing an often-overlooked dimension of digital health accessibility. *NPJ Digit Med*. 2021;4(1):143. Published 2021 Oct 1. doi:10.1038/s41746-021-00516-2
- ²⁶ Curcin V. Embedding data provenance into the Learning Health System to facilitate reproducible research. *Learn Health Syst*. 2016;1(2):e10019. Published 2016 Dec 27. doi:10.1002/lrh2.10019
- ²⁷ Foley & Lardner LLP. FDA Addresses the Role of Digital Health Technology in Clinical Trials. *National Law Review*, 2022; 12(11). Accessed 1/28/2022 from <https://www.natlawreview.com/article/fda-addresses-role-digital-health-technology-clinical-trials>
- ²⁸ Apostolaros, M., 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*, 2020. 54(4): p. 779-787.
- ²⁹ Parexel. *Capitalizing on sensors in clinical trials*. 2021; Available from: https://www.parexel.com/news-events-resources/blog/capitalizing-sensors-clinical-trials#_edn1
- ³⁰ Conway, L. *Blockchain Explained*. 2021; Available from: <https://www.investopedia.com/terms/b/blockchain.asp>.
- ³¹ <https://www.epic.com/about>
- ³² HealthIT.gov. *FHIR Fact Sheets*. 2021; Available from: <https://www.healthit.gov/topic/standards-technology/standards/fhir-fact-sheets>.
- ³³ Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners*. *J Biomed Inform*, 2019. **95**: p. 103208.