



Landscape Scan for CTTI DCT Update Project

Completed 16 April 2021

Overview

This landscape scan was conducted by the Clinical Trials Transformation Initiative (CTTI) to inform ongoing work by the Decentralized Clinical Trials (DCT) Update project team. It focuses on recent insights related to operationalizing DCT solutions (i.e., remote and virtual visits, using local labs and healthcare providers, and direct-to-participant shipping), drawing primarily on publicly available sources released between March 2020 and March 2021. Please note that the approach was informal and summary findings are not intended to be exhaustive.

Contents

I. High Level Findings

II. Detailed Findings

- A. [Telemedicine](#)
- B. [Home health visits](#)
- C. [Using local labs, imaging centers and healthcare providers \(HCPs\)](#)
- D. [Direct to participant shipping](#)
- E. [Safety monitoring](#)
- F. [Remote monitoring](#)
- G. [Protocol design](#)

III. Sources

I. High Level Findings

Anticipated Benefits of DCT Solutions Adoption

- ▶ Higher participant enrollment, compliance, satisfaction and retention
- ▶ Broader geographic reach (e.g. rare disease)
- ▶ Shorter drug development timelines
- ▶ Cost savings
- ▶ Data captured in real world settings, improving the validity and generalizability of results
- ▶ Decentralized elements can be used selectively on a fit for purpose basis for a given trial

Barriers to Decentralized Clinical Trial (DCT) Solutions Adoption

- ▶ Variations in global legal and regulatory requirements and uncertainty around future change
- ▶ Technology platform variations across sites
- ▶ Lack of data demonstrating cost vs benefit
- ▶ Lack of data demonstrating impact on and preferences/needs of sites and participants
- ▶ Need for practitioners to share methods and evidence for those methods
- ▶ Need for change management within sponsor organizations
- ▶ Need for new processes and procedures to optimize implementation of DCT elements

State of DCT Solutions Adoption

- ▶ Extensive use of DCT solutions as COVID-19 mitigation measures for trials already planned
- ▶ DCT solutions not yet being routinely incorporated into new study design processes
- ▶ Evaluations of the benefits and effectiveness of DCT solutions are being conducted but are not yet available
- ▶ North America is ahead of Europe in adopting DCT due to stricter EU data privacy laws¹⁶
- ▶ Adoption varies by therapeutic area

Key Takeaways from Literature Scan and Team Input: Opportunities

- ▶ The literature scan provides a starting point for collecting learnings and emerging best practices from pandemic-mitigation implementation which can ***help the clinical trials enterprise better plan and operationalize DCT solutions in new trials going forward.***
- ▶ Evaluations of the benefits/value of DCT solution implementation are being conducted but are not yet publically available. Likewise, DCT solution

success stories are limited. Both will be important to adoption. ***Are there early evaluation results or success stories we can share to foster adoption?***

- ▶ The literature reflects key overarching questions DCT solutions give rise to and which the team has also identified:
 - Little information is available at this point on the impact of DCT solution implementation on sites. ***What will be necessary for sites to successfully adapt to and deliver increasingly hybridized trials going forward?***
 - Likewise, the role of the investigator is changing as more trial elements are managed centrally and/or conducted remotely. At this stage, ***the implications for investigators and their oversight role is still unclear.***
 - Recently reported participant perspectives on decentralized solutions are often pandemic-specific (e.g. concern about having a home healthcare professional in one's home due to COVID risks). There is evidence that the frequency, duration and time required to travel to site visits are major deterrents to clinical trials participation. There is also evidence that preferences for and feasibility of decentralized solutions vary across participants, ***supporting the need for sponsors to offer participants options when possible.***

Other Observations

- ▶ The use of local healthcare providers (HCPs) does not appear to be playing as large a role as telehealth, home health providers, direct to participant shipping and use of local labs and imaging centers in the decentralization of clinical trials.
- ▶ Telemedicine is widespread in healthcare. Data shows patients want to maintain the option of using telemedicine going forward. There is an opportunity to leverage best practices and early evidence of its efficacy. Are there issues around telehealth unique to clinical research?

II. Detailed Findings

A. Telemedicine

- ▶ **Leverage learnings from healthcare**
 - Evidence of patient preference for telemedicine in healthcare post-pandemic^{20,23}
 - Leverage best practices and tools from widespread use of telemedicine in healthcare^{19,20}
 - Evidence of the effectiveness of telehealth in child neurology care²⁰

- ▶ **Evidence of preference for or benefits of telehealth in research**
 - Emerging evidence of preference for telemedicine in clinical research post-pandemic²⁴
 - Video conferencing visits allow for more frequent and longer-term safety assessments²¹
- ▶ **Application areas and uses for telehealth**
 - Focus on therapeutic areas where telemedicine utilization is most advanced (e.g. dermatology, psychiatry, cardiology, radiology)⁴⁰
 - Assessing patient-reported outcomes that do not rely on physical exam features are amenable to remote data collection^{22,60}
 - Uses of telehealth in clinical research may include conducting assessments, collecting and documenting AEs, con meds, PROMs and secondary endpoints, supervising IMP administration or device use, assessing compliance, delivering intervention (e.g. psychology or physical therapy), making physiological measurements and guiding patient photography.^{2,4,41}
 - Patients may be referred to primary care physician (PCP) for evaluation of safety concerns identified remotely.⁴¹
 - Patients may self-assessing (temperature/blood pressure) at home and report results and method-used over phone or videoconference. Site staff record in the source document and electronic data capture (EDC) description who performed and how.⁴¹
 - Telephone used as backup in case technology fails or users experience problems.
- ▶ **Protocol design**
 - Engage patients and sites to better understand their perspectives, experiences, and preferences for telemedicine (including acceptance criteria)^{3,7,42}
 - Consult telemedicine providers in protocol development⁴⁰
 - Consider how to mitigate access disparities²³
 - Understand privacy requirements in selecting telehealth technology.^{4,42}
 - Determine language requirements and how to address them¹
 - Have a plan for handling system failures^{41,43}
 - Map data flow, data collection and data storage⁷
 - Consider recording policy for telehealth sessions⁵⁰
 - Include telemedicine in ethics submission⁷
- ▶ **Operationalizing**
 - Test run telehealth platforms^{41,42,43}
 - Train patients/caregivers and sites on platforms^{7,41,42}
 - Provide standardized training and possibly interview scripts for conducting remote assessments to minimize bias.⁶⁰
 - Put procedures in place to maintain participant privacy.⁶⁰

- Remote assessments should be conducted as similarly as possible to in-person assessments, and consistently across sites and participants to minimize data variability⁶⁰
 - Provide acceptable virtual waiting room experience in case clinician is running late²⁰
 - Train clinicians in creating human connections with participants virtually^{19,20}
 - Create an appropriate environment for telemedicine^{41,60}
 - Have a plan outlining when and how to verify participant and investigator identity^{1,4,7,60}
 - Consider giving participant flexibility to schedule trial visits during evenings, weekends or holidays (when investigator sites may be closed)¹⁵
 - Increasing availability of home health monitoring devices (e.g., blood pressure, glucose, EKG, heart rate, etc.) help enable televisits in more cases²⁶
- ▶ **Barriers/challenges**
- Unclear return on investment resulting in a lack of willingness to be a first mover³
 - Demonstration of data comparability and acceptance generated from telemedicine³
 - Cost (may need to supply device)⁴
 - Not all endpoints can be measured remotely; video may be insufficient for some purposes¹
 - Access disparity and equity/diversity implications^{23,26}
 - Can't fully replace human connection
 - Variation in telemedicine technology platforms used by sites^{1,2}
 - Connectivity of technology systems and platforms between stakeholders³
 - IT support needed for set-up and troubleshooting⁴
 - Vulnerable to broadband availability and internet connectivity issues^{4,21,26}
 - Privacy concerns⁴
 - Patient acceptance and learning curve for using telemedicine technology^{3,26}
 - No universally applied definition; telemedicine means different things to different people³
- ▶ **Legal/regulatory**
- Policies governing practitioner reimbursements for virtual visits are subject to change (*Important in healthcare; how important is this in research?*)²⁰
 - Variation of data protection and privacy laws by country and health authority^{3,4}
 - Primary Investigator (PI) licensure limitations (e.g., PI licensure in patient's 'home location' when using telemedicine)^{3,4}

- The Office of Civil Rights (OCR) within the Department of Health and Human Services (HHS) Guidance provide a list of HIPAA compliant vendors approved for telehealth.⁴¹
- “FDA considers real-time video interactions, including telemedicine, as a live exchange of information between the trial personnel and trial participants. These interactions are not considered electronic records and therefore are not subject to 21 CFR part 11.”⁶⁰

B. Home health visits

▶ Leverage learnings from healthcare

- Startup companies are using lower cost healthcare professionals rather than clinicians to reduce cost (e.g. emergency medical technicians (EMTs), paramedics, registered dietitians, etc.)²⁶
- Home healthcare can be delivered in tandem with a televisit with a physician.²⁶

▶ Evidence of preference for or benefits of using home health visits

- In a 2020 Pediatric Perceptions & Insights Study, 43% of parents indicated 'Some or all study visits conducted at my home or my office' was 'very important' to their or their child's participation in a study¹⁴
- In an April 2020 global survey of 100 pharma/biotech companies exploring *COVID mitigation solutions*, 32% had implemented home healthcare, 27% initiated but had not yet implemented, 23% planned but had not initiated, and 18% did not plan to use home healthcare.¹³
- Home visits lend themselves to providing more “real-world” data, as any drug application is occurring in the patient's home setting^{15,22}
- Home care staff could reduce the burden placed on site staff¹⁵

▶ Application areas and uses for home health visits

- Uses of home health visits in clinical research may include collecting physiological data via guided measurement, physical specimen collection, testing, collection of clinician-assessed outcomes and participant reported outcome measures (PROM), endpoint reporting and pharmacovigilance event reporting.⁴
- Home health visits used in combination with telehealth and direct to participant shipping.^{1,50}

▶ Protocol design

- Clearly define what is source data and how to get it into the database (e.g. does home health provider enter directly into EDC platform or will site enter?)²
- Communicate with investigator to ensure appropriate investigator oversight and buy-in^{1,3,7}

- The European Medicines Agency (EMA) Good Clinical Practice (GCP) Inspectors Working Group states in a Q&A that contracts with home healthcare providers should be with the investigator⁷
- Plan for the oversight of home health providers⁷
- Put drug accountability procedures in place if appropriate¹⁵
- Define triggers for key interactions and information sharing between home care provider, site and participant⁷
- ▶ **Operationalizing**
 - Prepare the vendor and participant in advance for upcoming visits to set expectations and ensure any necessary preparations are made.¹
 - Make sure home care partner carries proper insurance¹⁵
 - Ensure home care partners follow industry regulations for privacy and data security.¹⁵
 - Ensure home care partner can offer all types of clinicians required for a given trial.¹⁵
 - Ensure home care providers have the right credentials⁷
 - Plan for the management and oversight of source documents collected at home visits⁷
 - Create operating procedures to ensure consistent oversight and quality³
 - Develop training approach and materials, including who is responsible for delivery³
 - Define process for the recording of home care notes and diaries⁷
 - Ensure drug safety concerns (stability and storage) are properly managed for home investigational product administration⁹
 - Ensure verification of participant identity.^{3,4,7}
- ▶ **Barriers/challenges**
 - Maintenance of investigator oversight³
 - Investigators who don't contract with home care services may push back⁷
 - Global coverage of home health vendors³
 - Cost constraints for sponsor and/or investigator^{1,3}
 - Lack of available information/benchmark data about the typical costs for services rendered by sites and vendors for Home Health Visits³
 - Lack of modernized site agreements/budget templates including payment responsibilities³
 - Variability of home healthcare professional training related to clinical trial understanding and performing procedures
 - Scientific resistance to change or modify the approach from traditional site visits²
 - GCP compliance accountability³
 - Sourcing nurses can prove difficult³
 - Lack of evidence demonstrating impact and acceptance by patients and sites³

- Home infusion of anti-cancer therapy can introduce risk from potentially high toxicities⁹
- Variation of data protection and privacy laws by country and health authority³
- Variation of policy by country and health authority for conducting home health visit³
- Principal investigator licensure limitations³
- Drug stability and storage are concerns for home infusion applications.⁹

C. Using local labs, imaging centers and healthcare providers (HCPs)

- ▶ **Evidence of preference for or benefits of using local labs, imaging centers and HCPs**
 - Trial data is generated in a real-world setting.⁴
 - Pediatric participants and their caregivers value the involvement of their primary clinicians in any direct-to-family research model to support their participation, communicate treatment changes, and perform endpoint assessments.²²
- ▶ **Application areas for utilizing local labs & imaging centers**
 - Alternative sites are used to perform tests and assessments routinely performed in those settings (e.g., routine chemistries, blood counts, chest radiographs).⁶⁰
 - Patients receive computerized tomography (CT) scans and blood draws at local facilities.^{9,41}
 - In an April 2020 global survey of 100 pharma/biotech companies exploring *COVID mitigation solutions*, 42% had implemented remote safety lab collections, 25% initiated but had not yet implemented, 3% planned but had not initiated, and 20% did not plan to use remote safety lab collections.¹³
- ▶ **Protocol design**
 - Consult with the appropriate FDA review division if remote lab or imaging results are the basis for formal hypothesis testing (primary, secondary or safety endpoints)⁶⁰
 - Communicate with investigator to ensure investigator oversight and buy-in^{1,3,7}
 - Prespecify plan to address variability of results from local imaging center (sensitivity analysis)^{9,25}
- ▶ **Operationalizing**
 - Local providers performing routine procedures do not need to be held to higher standards (e.g. no protocol or GCP training or Form FDA 1572 required)^{40,50}
 - Create operating procedures to ensure consistent oversight and quality³

- Define procedures for managing the use of and collecting data from local labs and imaging centers^{3,9}
- If a local healthcare provider administering the IMP is not considered a sub-investigator, the investigator should secure participant consent to access medical records from the local HCP (vital signs and any symptoms or signs occurring with the infusion)⁶⁰
- Conduct baseline tests when necessary and ensure differences in reference ranges among local labs are accounted for^{25,60}
- ▶ **Barriers/challenges**
 - Consistency and quality in local specimen collection⁹
 - Process and shipping procedure for local specimen collection⁹
 - Lack of available information about the typical costs for services rendered by sites and vendors for local lab use³
 - Payment for local imaging centers, especially if across state boundaries or outside of payer network⁹
 - “Careful attention to the appropriate accreditation of local laboratories and differences in reference ranges is critical.”²⁵
 - “Subsequent transfer of source documents must be done within established timelines.”²⁵
 - Local infusion providers may not have experience with investigational agents⁹
- ▶ **Legal/regulatory**
 - Variation in lab measurements or imaging protocols will increase variability and can effect type I and II error rates.⁶⁰

D. Direct to participant shipping

- ▶ **Application areas and uses for direct to participant shipping**
 - Alternative methods used^{17,50}
 - site to patient
 - depot to patient
 - depot to local pharmacy
 - Using investigational drug service for alternative IP delivery⁴¹
 - SOPs created for shipping new clinical trial medications/devices to and unused medications from participants with signature required receipt or pre-paid shipping. ^{41,60}
 - Participants are provided a means of disposing of unused medication at their home (e.g. drug disposal pouch) and provide documentation of disposal via photo or video.⁶⁰
 - Eliminates the need for dispensing-only site visits for patients³
 - In states or countries where study drugs cannot be shipped directly to patients, the study drug can be shipped directly to the home nursing agency to deliver and administer to the patient.¹⁵

- Home health providers are able to solve for drug supply chain of custody and can provide clear documentation to help with reliability of the study data.¹⁵
- Direct to participant shipping goes beyond investigational product to trial supplies, auxiliary medicinal products, lab sample kits, mobile/wearable devices and bio-sample dispatch.⁷
- Use cases include use of a trial-specific pharmacy, postal delivery with mailbox-safe packaging, overnight courier with recorded delivery, temperature-controlled packaging, prescribing via usual healthcare provider and self-purchase by participant.⁴
- Support for home administration provided using online educational videos, hardcopy instruction and telehealth. Home health visit used to support administration and/or device use/setup.⁴
- Examples of compliance assessments include online self-reporting, postal/courier return of packaging or excess meds and blood/urine testing of a random participant sample.⁴
- In an April 2020 global survey of 100 pharma/biotech companies exploring *COVID mitigation solutions*, 26% had implemented direct to participant options, 27% initiated but had not yet implemented, 24% planned but had not initiated, and 24% did not plan to use direct to participant shipping.¹³
- In a 2020 Pediatric Perceptions & Insights Study, 49% of parents indicated 'Clinical study medication delivered to my home' was 'very important' to their or their child's participation in a study¹⁴

► Protocol design

- Consider whether study drug has well-characterized safety profile
- Perform a risk assessment evaluating the nature of the IP (e.g. could changes to storage/handling impact product quality/stability?) and potential risk to both participants and remote healthcare providers involved in administering it.⁶⁰
- Consult FDA review divisions on plans for storage, handling, and managing unused supply.⁶⁰
- Communicate with investigator to ensure investigator oversight and buy-in³
- Ensure chain of custody and supply chain are maintained and documented^{3,7,25,60}
- Ensure temperature control is maintained, monitored and recorded throughout. Ensure temperature excursions are recorded and define course of action for occurrences.^{1,2,7,25,60}
- Ensure patient privacy throughout the process (packaging, etc.)¹
- Delivery of IP from trial site to patient's homes (instead of from drug distributor or central depot) may be necessary to maintain patient privacy and data confidentiality.²⁵
- Have a plan for managing unused IP or other supplies requiring special handling, disposal, storage or administration.⁶⁰
- Plan to ensure blinding is maintained^{15,25}

- Home health provider may be able to ensure drug supply chain of custody¹⁵
- ▶ **Operationalizing**
 - Determine whether site or company contracts with courier²
 - Participants must be made aware of storage/administration requirements and be in a position to comply^{7,25}
 - Tracking, confirming and managing patient receipt of product³
 - Plan for any interaction with telemedicine, virtual visits or home health providers³
- ▶ **Barriers/challenges**
 - Some investigational products can't be administered at home.^{1,7,9}
 - Inadequate data demonstrating impact and acceptance of direct to participant shipping by patients and sites³
 - Limited understanding of cost/benefit relationship and maturation effect (e.g., expense due to heavy administration, overages, distribution budget)³
 - Lack of processes/standard operating procedures (SOPs) that are flexible and scalable for DTP shipping optionality in a hybrid model³
 - Difficulty finding couriers qualified to manage refrigeration requirements and monitoring¹
 - Geographic differences drive site receptiveness⁴¹
 - Ensuring participant compliance if they're not physically at the investigation site¹⁵
 - Injection/infusion must be blinded but preparation could require unblinding. How to ensure blinding is maintained?^{15,25}
 - Devices shipped direct to patient must be traceable at all times⁴¹
 - Need for specialized couriers
 - Duration of time required for kit creation / labelling when sites ship to patients³
- ▶ **Legal/regulatory**
 - Varied landscape globally (and even within the U.S.) for shipping^{1,3}
 - Patient data protection and privacy laws, e.g. patient's address in the sponsor system⁷
 - Regulatory and sponsor drug accountability issues
 - Pharmacy requirements

E. Safety monitoring

- ▶ **Examples of the impact of decentralized solutions on safety monitoring**
 - Examples of remote safety data generation in use: blood tests conducted by local healthcare providers, sample collection kits returned from participant to central research labs, home health visits, telehealth assessments, and reporting via portals or applications.⁴

- Adverse events may be participant reported online, via phone or video calls and/or obtained through clinical care, hospitalization and mortality data or electronic health record query. The later may be used to verify the former.⁴
- In an April 2020 global survey of 100 pharma/biotech companies, 79% of respondents felt decentralized trials can have the same or higher level of data quality and quantity¹³

► Protocol design

- Sponsors must evaluate whether remote methods of conducting safety assessments are sufficient to ensure participant safety or whether in-person visits necessary.⁶⁰
- Source data, data elements and source documents as well as data flow should be well defined and documented for all decentralized solution employed.⁴³
- “Collect only data sufficient to satisfy the needs of safety, science, and regulation”⁴
- Study participants and vendors should be included in decision-making on how to handle responses to safety signals and adverse events identified during home health visits or other remote assessments.⁴³
- Effective participant training can optimize participant adherence to data collection requirements and subsequently optimize data quality.⁴⁵
- Feasibility studies and pilot testing of decentralized solutions and associated data collection can identify unanticipated issues and help optimize data quality.⁴⁵
- Ensure all stakeholders receive clear patient instructions for reporting adverse events and communicate them as frequently as is appropriate.^{3,42,43}
- Consider how investigators will maintain oversight for source documents generated outside of their direct control.⁷

► Operationalizing

- “All data collection, transfer, storage, and handling processes must satisfy local applicable legislation, e.g. General Data Protection Regulation (GDPR) in the European Union (EU) or the Health Insurance Portability and Accountability Act (HIPAA) in the U.S.”⁴
- When utilizing home health professionals or local healthcare providers, clearly define what is source data and how it will get into the study database.^{2,7}
- If any study documents are to be stored in a secondary location, this should be documented in the study trial master file and vendor contracts, as appropriate.⁷
- Document all relevant processes for data collection, storage and access and include safety and personal privacy/data protection safeguards being employed.^{7,25}

- Communication and transparency with participants regarding safety monitoring and action to be taken in the case of an adverse event is critical^{3,25,42,43}
- SOPs for responding to atypical data should consider all decentralized solutions/remote sources for any given trial.⁴⁴
- ▶ **Barriers/challenges**
 - Ensuring significant adverse events are not missed despite infrequent study visits⁵⁰
 - Less frequent or the absence of study visits may necessitate more frequent and/or automated communication with participants⁵⁰
 - Need process for reviewing live data in a timely manner^{1,44}
 - New processes and procedures are required to monitor safety data generated remotely¹
 - Sponsors need to consider how investigators will maintain oversight for source documents generated outside of their direct control.⁷
 - Many patient monitoring tools rely on participants having reliable internet. In the U.S. for example, ~13% of the population does not have reliable internet. In rural parts of the U.S., roughly 1 out of every 3 people doesn't have broadband access, according to a 2019 Pew Research Center survey.²⁶

F. Remote monitoring

- ▶ **Definition**
 - “Monitoring activities as defined either within process documents or in the monitoring plan (MP) that occur away from the study site location... allows monitors to conduct source data review (SDR) (assessing how the data were collected and evaluating whether procedures were conducted per protocol) and can enable source data verification (SDV) of critical data to ensure it was reported accurately in the case report form (CRF).”¹
- ▶ **Examples of how remote monitoring is being planned and conducted**
 - Risk assessments drive mitigation plans, and site location and local regulations determine what is allowed.¹⁸
 - Example of a remote monitoring process in the U.S.:⁴¹
 - Site uses HIPAA compliant tools to provide access to source materials
 - Monitor is provided specific access to only the source materials needed
 - Monitor is notified when materials are ready for review
 - A limited timeframe is established for when materials will be available
 - Remote access promptly removed and source materials deleted if appropriate following review

- Remote access can be provided using secure video and/or secure document/data exchange platforms^{1,18,60}
 - Sites upload certified copies of source records to a sponsor-controlled system or cloud-based repository with appropriate security.⁶⁰
 - Alternatives when on-site monitoring is not possible: “enhanced central monitoring, telephone contact with the sites to review study procedures, trial participant status and study progress, or remote monitoring of individual enrolled trial participants”⁶⁰
 - Statistical analysis is used to determine validity of remote data, especially when remote SDV is not feasible.^{18,41}
- ▶ **Protocol design/operationalizing**
- Determine the best balance between and use of on-site vs remote verification for SDR/SDV⁵⁰
 - Use risk-based monitoring principles to focus central and remote monitoring on the critical data and processes^{1,60}
 - “Automated collection of electronic health record (EHR) data can eliminate the need for transcription of data to the CRF (Case Report Form) and so eliminates the need for some SDV”¹
 - EDC systems can be used to facilitate remote monitoring; sites upload documents which are automatically redacted.¹⁸
 - Protect source documents containing unblinded information from review by blinded study monitors⁶⁰
 - Factors to consider when prioritizing sites for remote monitoring: “centralized monitoring or other information available about site performance (e.g., frequency and severity of protocol deviations previously identified during monitoring visits or currently identified by centralized monitoring, number of randomized active trial participants, experience of site staff, known history of prior major audit or inspection findings)”⁶⁰
 - On-site monitoring should be documented in the same level of detail as on-site monitoring⁶⁰
- ▶ **Barriers/challenges**
- New procedures enabling remote monitoring can put additional burden on site personnel^{1,2}
- ▶ **Legal/regulatory**
- Local and institutional participant privacy policies and regulations may restrict what site master file information a monitor can be given access to¹
 - Health authorities may require some data be monitored on-site^{1,2}
 - The regulatory landscape regarding data privacy and SDR/SDV in particular differs by location and is subject to change post-pandemic²

G. Protocol design

- ▶ **Evidence for the acceptance of and ongoing use of DCT solutions**
 - In a 2020 CTTI member survey exploring lessons learned from the COVID-19 pandemic, 60% of respondents expressed that changes implemented will continued to be implemented in trials going forward. Also ~60% of those implementing changes going forward are evaluating the changes they are implementing.⁴¹
- ▶ **Considerations for determining what decentralized elements are appropriate for a given trial**
 - Trials@Home outlined considerations and criteria for identifying whether a hybrid or decentralized approach might fit a given trial, looking at each study phase in turn.⁵
 - An intervention with an adverse event profile which can be assessed entirely by laboratory data (e.g., elevated liver function tests) would better suited to decentralization than an intervention that could result in clinical signs and symptoms requiring a physical examination (e.g., shortness of breath or palpitations)²²
 - Early phase studies, invasive interventions, and studies for an investigational product that doesn't have a well-established safety profile and/or requires greater oversight may not be well suited to decentralized implementation.^{6,22,25}
- ▶ **Protocol design considerations**
 - Sites
 - Consider site capabilities in feasibility assessments. Define what options sites will be given and what support may be required and can be made available, e.g. may sites use their own vendors if they have them and what support can the sponsor provide to help sites operationalize new solutions for the first time?^{1,7,50}
 - Inform sites of flexibility they will be allowed, e.g. use of community-based resources already in their network or using registered nurses (RNs) vs nurse practitioners (NPs)⁵⁰
 - Inform sites of key, need-to-know information including how data will be captured, how payment will be handled, minimum requirements for local providers and what is considered source⁵⁰
 - Determine training and technical support requirements to successfully operationalize decentralized elements. Include set-up and training for new staff.^{1,4}
 - Develop functional plans and study documents with the detail needed to successfully operationalize DCT solutions^{1,7}
 - Plan in more flexible windows for tests and assessments being conducted remotely.⁹

- Participants
 - Include patients in the trial planning process as early as possible to ensure their input can be incorporated into study plans.^{4,7,40}
 - Determine the participant point of contact for all things study related. Is the role performed by the site or centrally? Who provides what support?⁵⁰
 - “Pediatric patients and their caregivers endorse the critical role of a steady point of contact, such as a study concierge, in the direct-to-family research model. Investigators should consider key family-facing personnel who can play this role outside of a research site or clinic.”²²
 - Offer participants options for interacting with study personnel including email, telephone, video call, etc.⁴
 - Offer participants options for remote or on-site visits and assessments.^{1,50}
 - Determine training, technical support and instructional documentation needed to optimize participant enrollment, compliance, satisfaction and retention¹
 - Ensure participant privacy through all aspects of the trial¹
 - Provide user-friendly interfaces and reduce the number of different apps participants are required to use to improve participant satisfaction.¹³
- Regulators
 - Understand requirements of and consult with relevant regulatory authorities in all planned study locations.^{4,7}
 - Engage with regulatory authorities early in the planning process.^{6,7,40}
- Vendors
 - Use vendors with clinical trial experience or conduct thorough feasibility testing.^{4,40}
 - When contracting with vendors, ensure systems and escalation procedures are in place and satisfy GCP.⁴
 - Consider contingency plans for vendor withdrawal or quality issues.⁴
- Data
 - Trials employing decentralized elements have a greater reliance on data security²⁵
 - Data integrity, flow, ownership and security need to be addressed early in the planning process.^{1,7}
- Other
 - Consider impact of decentralized solutions on insurance and indemnity²⁵

► **Barriers/challenges**

- How to encourage study designers to consider DCT options early in the process and promote internal change management for adopting decentralized solutions within organizations.^{1,7,50}
- Sponsors need help weighing the potential added cost and complexity of using DCT solutions against the potential for long-term improvements in efficiency, participation and/or compliance.^{3,7,50}
- Determining what DCT solutions should be considered for a given study.⁵⁰
- How does participant communication change as decentralized elements are incorporated into clinical trials?⁵⁰
- What is the role of the site in decentralized and hybrid trials?⁵⁰
- Increased sharing of experience and expertise among practitioners would benefit the clinical trials enterprise. Sponsors and investigators are encouraged to publish protocols, methods papers, methods evaluation and trial results as early as possible.^{3,4, 50}

III. Sources

1	TransCelerate, White Paper, 2020
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41	CTTI member survey
42	CTTI Optimizing Mobile Clinical Trials by Engaging Patients and Sites Recommendations
43	CTTI Advancing the Use of Mobile Tech for Data Capture & Improved CT Recommendations
44	CTTI Framework of Approaches for Safety Monitoring and Managing Safety Signals Table
45	CTTI Recommended Strategies for Optimizing Data Quality Table
50	DCT update project team
60	FDA Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency