July 2021

QbD Manual for Decentralized Clinical Trials:

The Quick Reference Guide

ACRO Decentralized Clinical Trials Working Party

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

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Foreword: About ACRO

ACRO represents the world's leading clinical research and technology organizations, which provide specialized services that are integral to the development of drugs, biologics and medical devices. ACRO and its members advocate on a global basis for safe, ethical, high-quality medical research so patients can benefit from the development of new treatments and therapies. This document is a quick reference guide to decentralized clinical trials (DCT). For further details and considerations on preparing for and conducting DCTs, please see the full Quality by Design Manual[1].

Mother, Father, Brother, Sister, Friend, Community, World

This document is dedicated to patients and trial participants and researchers all over the world who are looking for treatments or are on clinical trials with the aim of advancing science and healthcare for everyone. Decentralized clinical trials are a step in the journey to enable greater diversity and operational excellence in clinical trials and to develop safe and efficacious medicines and medical devices faster and more efficiently. Thank you to everyone who has contributed to this paper.

[1] https://www.acrohealth.org/dct/

Introduction to Decentralized Clinical Trials

The ACRO DCT Working Party defines a Decentralized Clinical Trial (DCT) as a trial 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."

There are a variety of approaches to DCTs, ranging from fully decentralized clinical trials to traditional clinical trials that use some aspects or technological strategies of a decentralized trial and are known as hybrid clinical trials. Decisions related to whether a trial is fully or partially decentralized (hybrid) may be driven by factors such as trial population, geography, indication, study phase and investigational product (IP).

There are many well documented benefits of decentralizing clinical trials to all stakeholders from participants, monitors, investigators and sponsors. The expectation is that by combining local healthcare providers and digital health technologies, medicinal product development will be accelerated through enhanced recruitment and retention during DCTs. In addition, more advanced analytical capabilities should result in faster study completion times, increasing the speed of delivery of therapies to participants and creating efficiencies across clinical research processes.

COVID-19 and the Use of DCT Processes

The COVID-19 pandemic revealed the urgency for clinical trials to have the ability to allow participation remotely, with the closure of research sites, while retaining all of the expectations of GCP and other relevant regulations and laws. Regulatory authorities acted quickly in response to the pandemic and published updated guidance for the pandemic period to support management of clinical trials. The updates generally address guidance for decision making around continuing or halting a trial, remote and on-site visits, centralised or remote monitoring and direct to participant shipment of IP. COVID-19 essentially forcing a paradigm shift towards a world where participants can participate in studies from the comfort of their homes and monitors and investigators can have access to tools to engage and interact with participants and their data in real time and remotely.

Participant Centricity of a DCT Approach

One of the primary benefits of decentralized clinical trials is their potential to be a participant-friendly model for clinical trials. DCT processes facilitate the "Participant Centricity by Design (PCbD) approach, which will increase the value and benefits of these clinical trials by ensuring that the participant perspective is baked into all aspects of a DCT from the beginning of the design and software development through to initiation and execution of the trial, rather than as an afterthought.

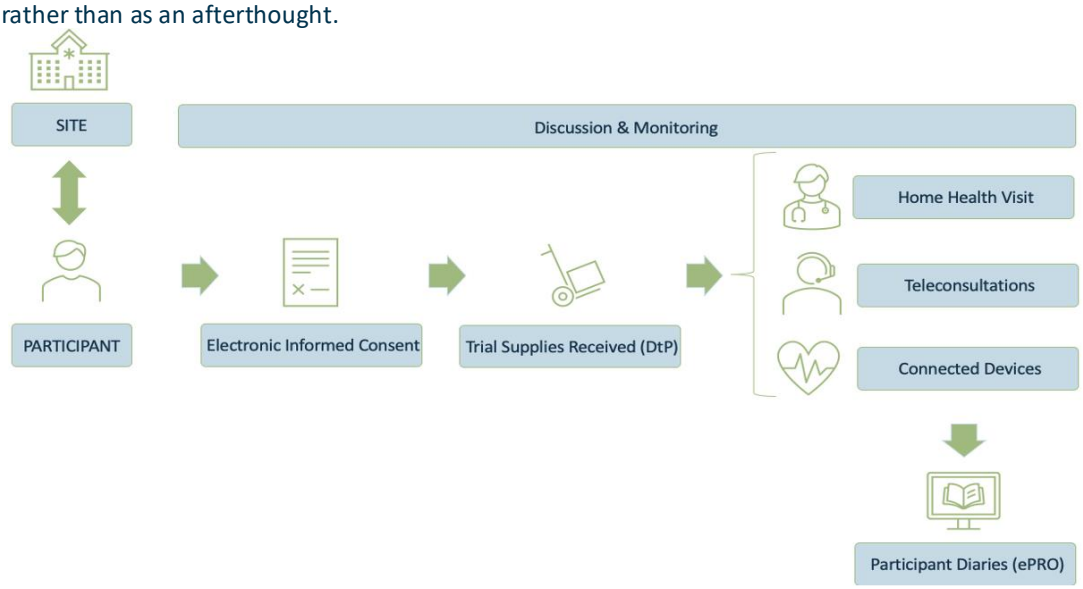

Diagram 1 – The Participant DCT Experience Summary

As consumer expectations evolve, trial participants are demanding a more participant-friendly clinical trial experience. The convenience of a decentralized approach makes this much more attractive and less burdensome. DCTs have shown to give an improved recruitment and participation in clinical trials, ultimately benefiting participants, drug developers and future participants in the longer term. Importantly, the ability to access online medical information means that participants are becoming more informed and involved in their conditions and treatments prior to and during clinical trials and a higher level of interest in the results of clinical development.

Investigators, regulators, and pharmaceutical organisations are increasingly interested in outcomes as measured from the participant's perspective as an improvement in the trial participant and general participant wellness or quality of life, and not just reversal of disease or extension of longevity. Some of the key benefits of DCTs to the participant include reduced participant burden, improved retention, greater control and improved overall experience throughout the trial

Regulatory Overview

All clinical trials regardless of whether a conventional or a DCT must be in accordance with the guidelines, regulations, compliant with ICH GCP, directives, and local laws pertinent to the region and country of where the trial is being executed. Regardless of the approach conventional or DCT, the investigator and sponsor responsibilities do not change[2].

The End-to-End DCT Process

The following diagram shows the end-to-end process of a typical clinical trial, with a DCT outlook, as the green route stops show the processes which may have DCT associated considerations.

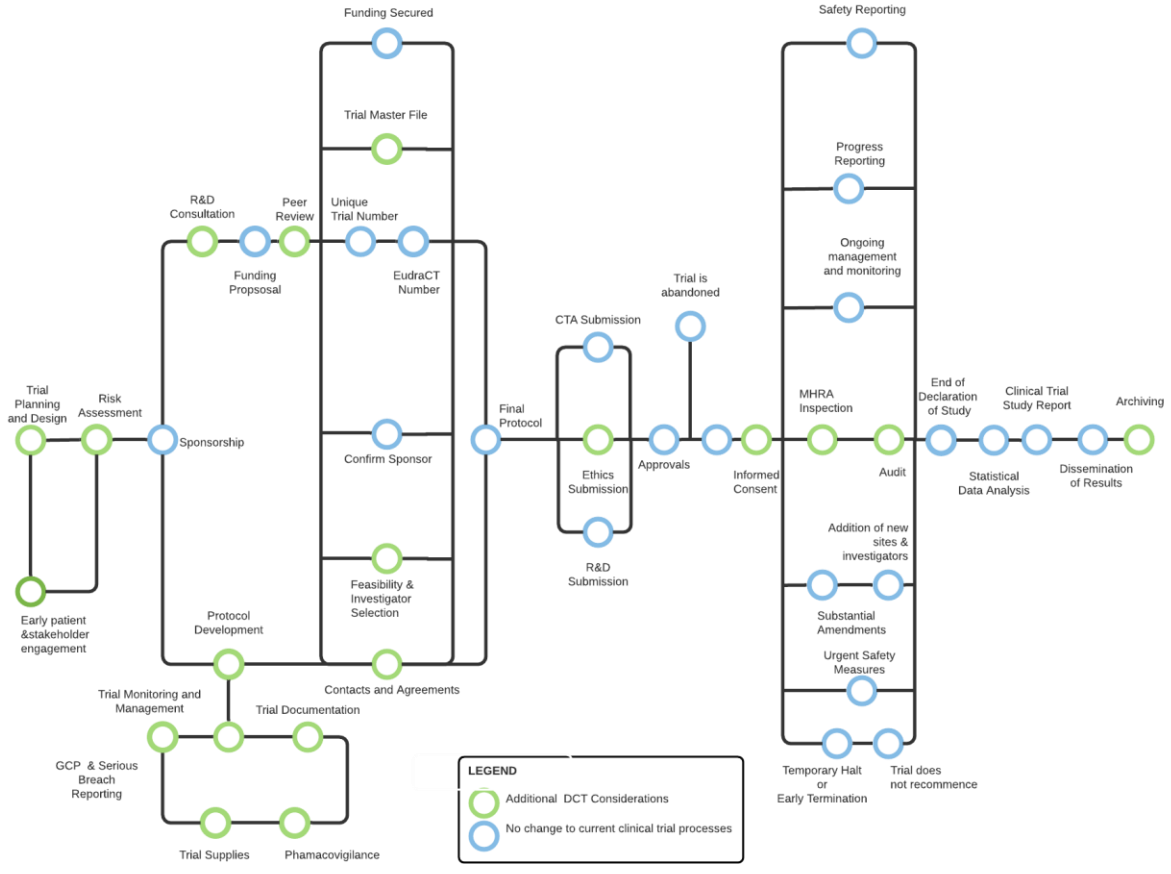

Diagram 2 - This DCT map has been modelled and adapted from the NIHR Clinical Trials Toolkit route map[3].

[2] Clinical Trials Transformation Initiative (CTTI) Decentralized Clinical Trials Project
https://www.ctti-clinicaltrials.org/projects/decentralized-clinical-trials

[3] National Institute for Health Research (NIHR) Clinical Trials Toolkit "Routemap"
http://www.ct-toolkit.ac.uk/routemap/

Data Strategy, Collection, Handling, and Management Processes and Procedures

A common underlying theme with clinical trials is unlocking the power of data and the execution of best-in-class data management procedures. This is multi-faceted, revolving around use of standards to drive consistency and quality, and the alignment and aggregation of quality data sets coupled with data analytics to drive insights. This is challenging with siloed data sources and disparate systems. DCT platforms may include unifying collaborative infrastructures with capabilities to provide faster insights and confidence through greater intelligence for decision making.

As part of a DCT, data collection will occur more via electronic means than compared to a traditional trial. There is guidance around data collection and management outlined by both the MHRA and FDA below[4]:

Sponsors/CROs should have:

- Robust and well-defined data collection, handling, and management procedures
- Detailed understanding of the data flow: A data flow diagram that includes from whom and to whom the data are transferred or transmitted, including all third-party vendors contracted for data collection, data handling, data management and/or data processing

The protocol and/or investigator plan should describe the:

- Data flow
- All electronics systems used in the study
- Source data that are transcribed or manually entered in the EDC System
- Source data that are transferred via an automated system-to-system level exchange
- External data that are transferred to the EDC system (and process for transferring the external data)
- Handling of external medical records.

Pre-trial considerations

Common DCT Consideration Themes

The below diagram describes the themes that were common to all processes impacting a DCT trial, including IT Solutions, Contracts, Training and Regulatory aspects.

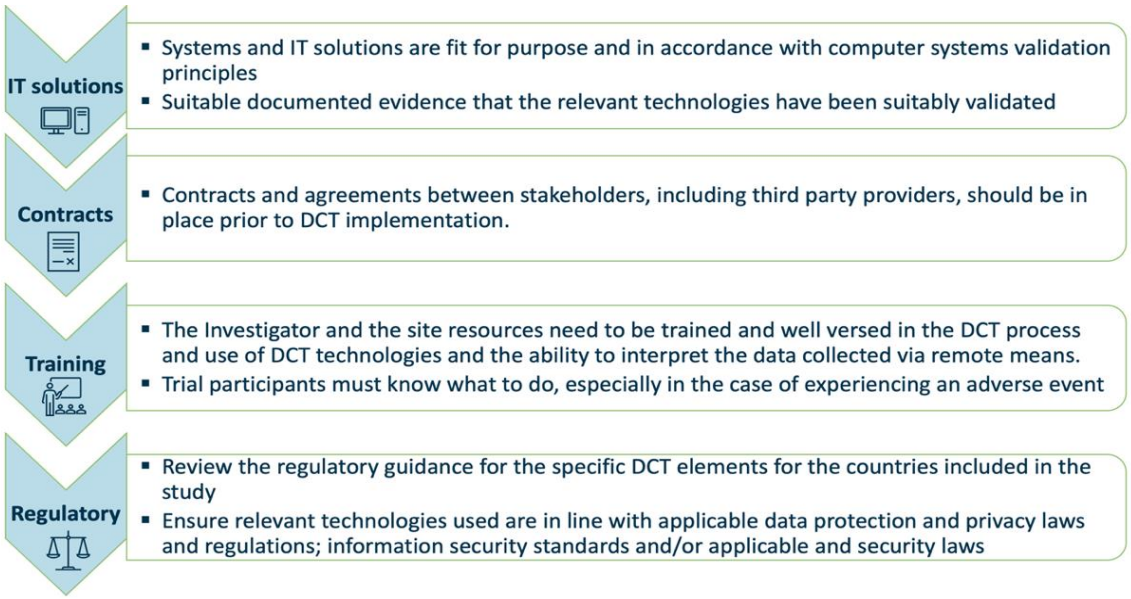

Diagram 3 –Summary of the Common DCT Considerations

General IT and System Considerations

DCTs require an IT system infrastructure that allows for traditional site-based data input by study teams as well as allowing participants to review content and contribute data remotely. As DCTs may collect Identifiable Data

[4] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf - Considerations for the Design and Conduct of Decentralized Clinical Trials: Regulatory Perspectives on DCTs' GCP Symposium Presentation by FDA and MHRA

Concerning Health, these systems may be subject to data protection and privacy laws and regulation regulating those types of data[5,6,7].

Potential Considerations in General IT and System Considerations of DCTs
Consider connectivity and robust infrastructure of the DCT network, ensuring: 1. Role based access levels for sponsor, monitor, site staff, participant is enabled. 2. The integrity and security of electronic records during data collection, transport and while at rest, consider a document (or a data management plan) outlining the data flow (including the data, format, origin and destination, accessibility rights, transfer timing and any review, validation, reconciliation, and verification)[8], and data collection for a DCT. 3. The accuracy and precision of remote sensor measurements. 4. Business continuity and back up plans, as well as testing procedures are documented and followed. 5. Storage, archival, and retrieval of source documents and electronic information 6. A process in place for the scenario in case the device fails, outlining how the participant gets a replacement or has an equivalency in accessing the systems.

Trial Planning and Design

The trial design should be considered before developing the protocol and relevant stakeholders should be consulted in these discussions. This will help ensure that all necessary practical requirements are identified early so that the subsequent protocol design is both scientifically robust and operationally feasible for those who are involved in its execution, either as clinical trial participants, investigators, or vendors.

Potential Considerations in DCT Planning and Design
1. The expected goal, objective and benefits to the different stakeholders should be outlined, including trial participants, relevant third parties etc. 2. Early engagement of the sponsor with all stakeholders and regulators, Ethics Committees, and IRBs 3. Critically question whether there are benefits to running a DCT in comparison to a traditional model 4. Consider any additional safety risks that may be brought with a DCT 5. Analyse the study phase, participant population and demographics and site requirements 6. A specific data management plan/diagram and privacy impact assessment for DCTs to show: a. How the data is normalized, stored, routed and tracked b. Consideration for data ownership/ responsibility and monitoring c. Compliance with country-specific regulations d. Technology meeting participant impairments (colour-blind, blind, deaf, etc) and any impact on data collection e. Configure access to the data for review (DM, Participant, Site, CRA, PM, Investigator, etc). f. Plan any data clarification routes with a direct device collection 7. Determine in the protocol/participant information sheet which elements of the trial can be decentralized and who will have access to the data collected (also in the informed consent form). Design communication models and scenarios, such as participant interfaces with investigators and health care professionals, call centre models, video, telephone and telemedicine interactions.

Protocol Development/ Approval

Protocols should include all additional aspects of a DCT, or hybrid trial described from the end-to-end perspective. Special considerations need to be made to ensure that no additional risks to participants occur by applying DCT methods to the protocol. This should be addressed in the risk benefit section of the protocol along with risk mitigation measures. There should be a high degree of stakeholder engagement during the trial design

[5] EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf

[6] EMA Notice to sponsors on validation and qualification of computerised systems used in clinical trials https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf

[7] Recent updates to EMA GCP Q&As, 'GCP Matters' numbers 8 and 9 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

[8] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf - Considerations for the Design and Conduct of Decentralized Clinical Trials: Regulatory Perspectives on DCTs' GCP Symposium Presentation by FDA and MHRA

which will result in specific callouts in the protocol development to ensure participant safety and accurate collection of any digital endpoints.

Potential Considerations for Protocol Development/ Approval of DCT
1. Prior to designing a trial, a triage process is recommended to assess the suitability of a DCT approach. Those include participant burden, participant safety, integrity of data as well as IMP requirements which also results in a positive impact on participant recruitment/retention and/or compliance. 2. Describe the early engagement mechanisms with stakeholders involved in designing the trial and building in feedback early on. 3. Description of Process and Procedures: a. Outline the different scenarios and trial specific procedures for the DCT including the activities occurring at the investigative site versus what is occurring remotely b. Outline the role of additional resources that will be now supporting the DCT, for example the role of the mobile and Local Health Care Provider (LHCP) in the DCT in conducting study-related activities and evaluating adverse events. 4. Define process/ guidance on what triggers an interaction between HCP, homecare nurses and participant. 5. Outline clearly the accountability of the stakeholders or reference the contractual obligations. 6. Outline the process for informing LHCP of the participant's participation in the research, including upfront confirmation that the LHCP is available and understands that the participant will be in a research study. 7. Outline the process/procedure for communicating information to and from LCHP and the clinical investigator 8. Technological and data considerations including: a. A detailed overview of the technology used in the DCT (all electronics systems and technologies to be used in the study to be described. Outline the types of technology solutions and mobile solutions to be used across the end-to-end DCT) b. Map the data flow, data collection and data storage considerations with a DCT (outline which systems/solution are being used such as mobile technologies, telemedicine, and other ensure that it is made clear how the data flows, is captured and stored). c. Describe how data will be captured, frequency of data collection, the impact on the participant is critical to evaluate and address in the protocol as part of its development. d. Source data that are transcribed or manually entered in the EDC System. e. Source data that are transferred via an automated system to system level exchange. f. External data that are transferred to the EDC system (and process for transferring the external data). g. Handling of external medical records and recording of home care nursing notes and diaries. h. Validation, UAT, back-up, licensing of applications used for monitoring activities. i. Describe the device provisioning to the trial participant and investigational sites. 9. Describe additional risks there may be regarding DCTs in the risk benefit section of the protocol along with risk mitigation measures.

Trial Processes

Informed Consent

The HRA and MHRA have published a Joint Statement on Seeking Consent by Electronic Methods (September 2018) [9] which outline the expectations for conducting both site based as well as remote Electronic Informed Consent (EIC) which should be the basis for eConsent in DCTs.

[9] Joint statement on seeking consent by electronic methods September 2018 https://www.hra.nhs.uk/documents/1588/hra-mhra-econsent-statement-sept-18.pdf

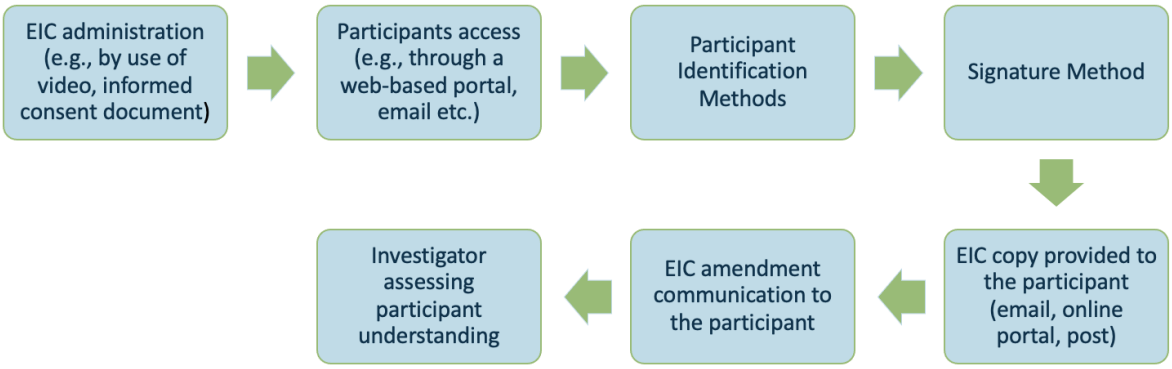

Diagram 4: Potential Considerations for Informed Consent to a DCT

Clinical Trial Supplies

Appropriate procedures and controls need to be in place for Direct-to-Participant (DTP) and Direct-from-Participant trial delivery/dispatch. This includes clinical trial supplies (e.g. IP/device, Non-IMP/auxiliary medicinal products (AxMP) and other ancillary products such as lab sample collection kits, mobile or wearable devices, and bio-sample dispatch. DCTs can make use of Direct-to-Participant shipments to reduce the need for participants to visit sites for the collection, monitor accountability and return of IP supplies and, with combined involvement of Home Healthcare Providers, may also facilitate the administration of IP.

Potential Considerations for DCT Supplies
1. Consider whether the IP is appropriate for home administration /storage: a. For IP that is generally administered in a healthcare setting (e.g. infusions), Sponsors should consider the risk of home administration (e.g. is self- administration a possibility, use of home nursing staff who are trained but not study personnel). b. Certain products may not be suitable for DTP shipment, for example if it is a controlled substance, or requires specific light or temperature storage conditions. 2. Consider if the planned DTP/DFP deliveries are appropriate for use by the participant population, development stage, and trial design. Clearly describe the supply and dispatch procedures either in the protocol and/or a study document for the investigator, participant (including IP training for the participant if required), home nurse, including temperature monitoring during transportation, recording of temperature excursions and actions required if these occur; as well as any specific storage / administration requirements for the IMP for the participant. 3. Obtain necessary EC / CA approvals for IP shipment process and any written information provided to participant to support handling of the IP. 4. Evaluate any specific safety concerns associated with the use of the supplies and describe how these have been identified and managed in prior investigational or marketing experience. 5. Assess if DTP shipment is compliant with applicable data protection and privacy laws and regulations in all considered countries. Ensure participant's consent is obtained. 6. Assess contracting and logistical requirements where depot is in use. 7. Evaluate the national legal and regulatory compliance of planned supply chains. 8. Consider using specialist vendors for DTP shipments to ensure IP stability is maintained and confirmation is obtained of delivery only to clinical trial participant. 9. Arrange for compliance and drug accountability reporting from the participant's location.

Monitoring & Management

The sponsor is responsible for ensuring that robust trial management systems are put in place. A DCT design leverages available technology to facilitate clinical trial oversight, thus allowing for data-driven decisions in real time. For a DCT, monitoring can take the form of a hybrid or remote approach to facilitate monitor access to source documents required for review. Existing electronic source data can be reviewed by the monitor through access to EHR (electronic health records), electronic file sharing system, electronic investigational site file or videoconferencing applications.

Potential Considerations for Monitoring & Management of DCTs
1. Technological and data considerations 2. Outline responsibilities for 21CFR part 11, EMA and UK compliance regarding validation, UAT, back-up, licensing of applications used for the participant, sites, and operations. 3. Determine strategy and training for BOYD, provisioned device scenarios and wearables 4. Evaluate the data flow to efficiently access participant's data. 5. Outline key data requiring monitoring and how technology will support oversight. Determine data access and impact of roles defined within the technology. 6. Description of process and procedures a. Determine monitoring activities required onsite verses the ability to use technology for central monitoring. b. Ability to monitor participant compliance and notifications to allow for timely follow up. c. Define the investigator access to data to ensure oversight/ control/ access is appropriately maintained. d. Define process for recording of home care nursing notes. e. Define triggers for key interaction and information sharing between site, homecare nurses and participant. f. Outline communication mechanisms to ensure the obligations of all parties are being met. g. Roles and responsibilities are defined to ensure individuals are appropriately qualified and competent to perform necessary functions for a DCT. h. Define monitoring oversight and governance required for a DCT due to varies technology being utilized for the study. 7. Investigators retaining responsibility for the management and oversight of source documents generated outside their direct control and what procedures they have in place for their maintenance and retention e.g., from local medical doctors and other local health care providers or generated and collected at home visits by the study participants, clinical investigator, study personnel, or third-party contractors such as homecare nurses.

Ethics Submission

Potential Considerations for Ethics Submission of a DCT
1. The submission process itself will not change with DCTs. However, it is important that the submission package (protocol, ICF, scripts, storyboards, and views of software applications) clearly outline the way in which the trial will be conducted - I.e., use of telemedicine, wearable technologies, use of e-consent, ePRO/eCOA forms, participant portals, remote access to EHRs etc. 2. Make sure the process is transparent about what is being done remotely, and who is involved. 3. Provide screen shots, videos or other evidentiary materials which outline any content or materials with which the participant will be presented. 4. Make sure that all relevant parties are involved in the submission and all aspects of the DCT are made available to the ethics committee ensuring the process is well described and understandable. 5. Where applicable, provide attestation documentation to explain the differences that may exist between electronic versions of a paper process or document. 6. Be able to provide assurances and evidence of data collection, storage, and access documentation to demonstrate participant safety, compliance with applicable data protection and privacy laws/ regulations and implemented technical and organizational protection measures, such as for participant identification and protection of participant identity during remote data collection. 7. Provide a sample of the final product of approved materials once the system in ready to go live, including copies of the informed consent video, as well as a recorded demo of the data collection tools.

Inspection & Audit

European legislation (and SI 2004/1031) requires Member States to inspect organizations that hold clinical trials authorisations or conduct activities on behalf of the clinical trial sponsor, this will not change with the introduction of more decentralized clinical design. GCP inspections, and their conduct, will continue to evolve due to increasing complexity in contractual relationships, trial design, and technology solutions, but core elements such as inspection phases, types and locations are unlikely to change. With more data being collected at the home or workplace of the participant, outside the traditional clinical setting, audit and inspection approaches may differ to evaluate tools and processes employed.

Potential Considerations for DCT Inspections & Audits
1. Provide appropriate system access for the inspection, ensuring complete and direct access. 2. Availability of Critical data definition and identification, with documentation in place to show data flows and data ownership. For 'new' technologies, consider specific data management plans/diagrams (flow between Sponsor, Participant, Vendors, Site Staff, CRO (Data Management, Monitors etc.) a. Data Lineage from source to report – outlining all the data locations, including the data, date, and executioner of handling. b. How was the source data validated before collection? c. Access to the data for inspection. d. How is the data protected at rest and in transit? e. Who owns the data and devices and what data did the participant get back? f. How were participants trained or ensured that they are using any technologies correctly? g. How are technology updates communicated to users? h. How were any SAE or Safety events managed from technologies? i. How were the participants supported for use of technologies? 3. Describe how new technologies are assessed as fit for purpose and validated in line with computer systems validation principles including implications for areas such as compliance with applicable data protection and privacy laws and regulations as well as implemented technical and organizational protection measures, especially if the trial involves social media. 4. Equipment/Materials – ensure availability at site/office of tools (and records of calibration, training etc.) used to perform remote activities (e.g. equipment used by Mobile Nurses). 5. Relevant responsible individuals (i.e., the investigator and DCT study personnel) should be available on site or by phone to answer any questions that may arise. Inspections may need to take place at other locations (e.g., local clinics and pharmacies) of trial-related activities, according to prior arrangements between the investigator and these facilities and ensuring that these other locations' documentation is also available at the site.