Bringing decentralised clinical trial protocols to life

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Abstract

Decentralised clinical trials (DCT) use technology, processes, and services to reduce or eliminate the need for onsite visits. Use of DCT components within clinical trials is becoming widespread and protocols are pivoting from using DCT components as rescue tools during the COVID-19 pandemic to including them as integrated decentralised research methods. To date, there is no consolidated guidance for what DCT component content should be included in the protocol. To enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components, this article outlines a simple scoping process for information gathering and summarises some common considerations around frequently used components. The objective of this article is to provide protocol authors with tools, resources, and guidance to better support the development of clinical trial protocols that include DCT components.

Introduction

E ffective clinical trial protocols are clear, precise, practical, and consistent in communicating the trial purpose and activities to all stakeholders. Recent evidence has shown that protocol design is correlated with trial performance and protocol features can be relatively robust predictors of operational efficiency.[1,2] The more complex a protocol becomes, not only is the trial less likely to run well but there are also likely to be more amendments, longer trial times, and poorer recruitment and retention rates.[3,4]

There is a growing demand for adopting clinical trial approaches that reduce the burden on participants and increase recruitment and retention of a more equitable participant population.[5] Although decentralised clinical trials (DCTs) are not new (Pfizer's REMOTE trial started 12 years ago), it was during the COVID-19 pandemic that trial teams used DCT components as rescue tools to continue trial activities offsite when onsite visits were impractical. Given the nature of the public health emergency, regulatory agencies supported this approach; for example, the United Kingdom's Medicines & Healthcare products Regulatory Agency (MHRA) stated "It is entirely feasible and acceptable to prepare a protocol that incorporates appropriate descriptions of both the procedures for regulatory decision-making and flexibility in how clinical visits, monitoring of trial participants, follow-ups, etc. are implemented. Use of 'decentralised' and digital/virtual elements in a study should be considered".[6]

In the wake of the pandemic, research has shown that compared to traditional trial designs, trials using DCT components recovered faster from the impact of COVID-19.[7] Additionally, analysis has shown that DCT component use provides substantial cost savings and enhances participation.[8–11] This demonstrated trial resilience, combined with participant and economic benefit, will accelerate the transition of DCT components being used as pandemic "rescue tools" to integrated decentralised research methods. The protocol development process must be updated to enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components.[12]

In this article, a simple scoping process is outlined alongside considerations for some frequently used DCT components. The objective of this is to provide protocol authors with tools, resources, and guidance to better support the development of clinical trial protocols incorporating DCT components.

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What are decentralised clinical trials?

The most widely used definition of a DCT comes from the US FDA that defines a DCT as a trial in which some or all of the activities are conducted offsite. A more recent – and potentially more specific – definition comes from the Decentralized Trials & Research Alliance (DTRA) glossary that expands on the FDA definition to clarify that DCTs use technology, processes, and services to reduce or eliminate the need for onsite visits (Table 1).[13,14]

It should be noted that although certain activities or devices are considered to be DCT components, such as wearable or connected devices, a traditional trial with onsite visits does not automatically become a DCT just because it includes such a device – i.e. the DCT components need to materially reduce or eliminate the need to have onsite visits, not just provide an additional opportunity to collect data.

Subclassification of DCTs broadly separates DCTs into "full" or "hybrid" trials. Full DCTs are distinguished from hybrid trials by not requiring participants to go to trial sites at all – all trial-related activities are done at the participant's home or in another local setting.[15] By contrast, a hybrid DCT uses a blended form of onsite and offsite activities; thus, hybrid DCTs can cover a range of configurations.[14]

Scoping a DCT component

One of the most challenging aspects of protocol development is to understand the scope for each trial activity and how they relate and interact with each other – DCT components are no exception. The Association of Clinical Research Organization's (ACRO's) decentralised trials toolkit includes a map of common methods that can help visualise what is available and which methods work together.[16] Additional resources include the ACRO DCT Quality by Design (QbD) manual and the Digital Medicine Society (DiMe) playbooks for digital clinical measures and digital healthcare.[17,18]

These resources can aid discussion and further the trial team's understanding of the

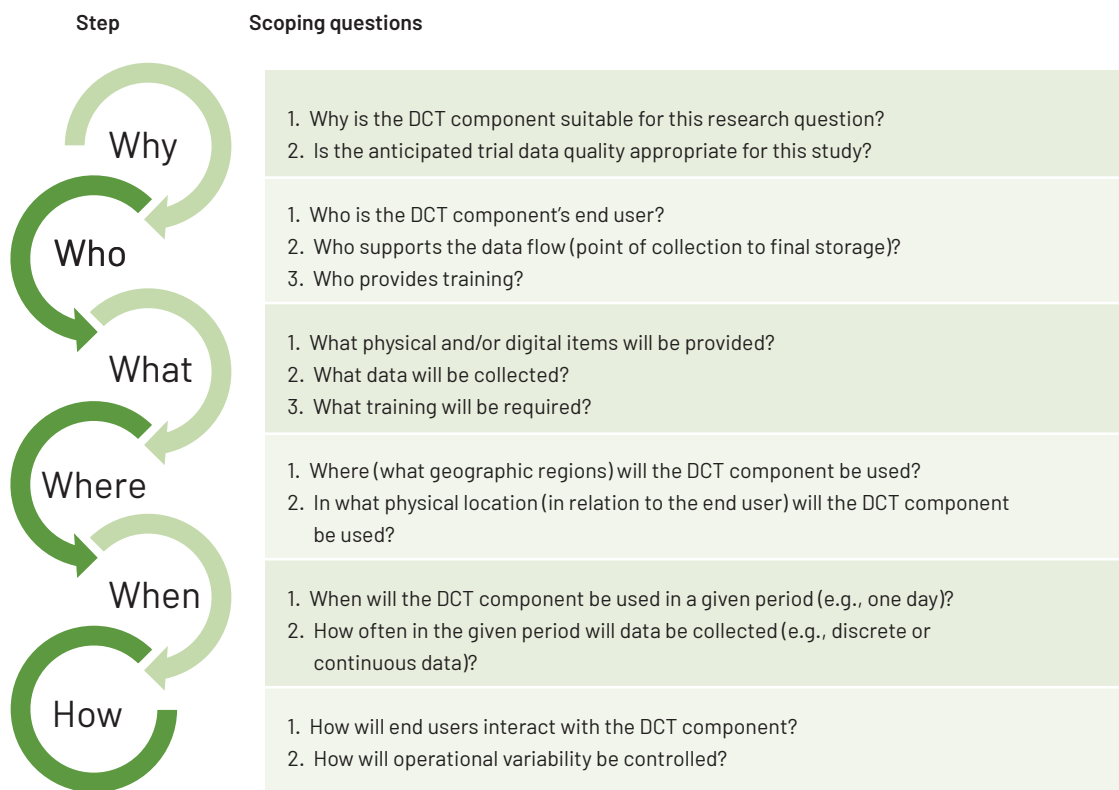| Step	Scoping questions
Why	1. Why is the DCT component suitable for this research question? 2. Is the anticipated trial data quality appropriate for this study?
Who	1. Who is the DCT component's end user? 2. Who supports the data flow (point of collection to final storage)? 3. Who provides training?
What	1. What physical and/or digital items will be provided? 2. What data will be collected? 3. What training will be required?
Where	1. Where (what geographic regions) will the DCT component be used? 2. In what physical location (in relation to the end user) will the DCT component be used?
When	1. When will the DCT component be used in a given period (e.g., one day)? 2. How often in the given period will data be collected (e.g., discrete or continuous data)?
How	1. How will end users interact with the DCT component? 2. How will operational variability be controlled?

Figure 1. Scoping steps and key scoping questions for successful information gathering

prerequisites for DCT component use. Once understood, the DCT component information needs to be successfully incorporated into the protocol. The simple scoping exercise for each DCT component is shown in Figure 1; this approach is broadly aligned with the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials) and the template for intervention description and replication (TIDieR) checklist and guide.[19,20] Although TIDieR is targeted towards enhancing the description of interventions in publications, the objective of improving reporting completeness and enhancing replicability is comparable to the objective here, so it serves as a suitable foundation to identify content required to adequately scope the DCT components.

It is important to note that the information collected as part of the scoping exercise may not be incorporated in the protocol in its entirety since there may be circumstances that would require some details to be omitted. For example, the name of a wearable or connected device may not be included if the trial is multiregional and local variability in the device is anticipated. In such circumstances, cross-referencing a supplementary document besides the protocol is preferable.

Why?

The why is the first – and most important – point to address in establishing DCT component scope. A recent qualitative analysis has highlighted two key questions (this was reinforced in ACRO's recent Q&A resource).[12,21]

1. **Why is the DCT component suitable for this research question?**
   - Clear justification for why DCT components are being used in the trial.
2. **Is the anticipated trial data quality appropriate for this trial?** Consider:
   - Results generalisability (e.g. is a technologically literate population representative of the wider target population)
   - Participant preference (variability in data outcomes dependent on DCT component flexibility and participant familiarity with the component)
   - Big data (challenging datasets and unnecessary participant burden from continuous data collection)
   - Data completeness (missing data).

Both questions form the foundation for each DCT component's risk-benefit assessment. To aid this assessment, ACRO released a DCT risk assessment considerations template as part of their DCT toolkit.[17] This requirement is reinforced by the EMA's guideline on computerised systems and electronic data in clinical trials that states that the approach used to reduce risks (e.g., adoption of DCT components to reduce dropout risk) should be incorporated in protocol design.[22]

Who?

The who in this context refers to the end user and any individuals supporting the end user, data flow, or training. For electronic devices or questionnaires, the end user is likely to be the participant but could also be a caregiver, family member, or other individual. By contrast, end users for home healthcare or electronic clinical outcome assessments are likely to be investigators, nurses, or other healthcare professionals. Regarding individuals supporting the end user, data flow, or training – summary details may be required to demonstrate that a robust process will be in place for the trial. For example, for a wearable or connected device with the participant as the end user, training may need to be provided by site staff during enrolment or by virtual means, and data flow from the device may be managed by the device vendor or the sponsor.

What?

What refers to what physical and/or digital items are provided, what data will be collected, and what training may be necessary. For example, physical items may include material and training documentation provided to the end user or supporting individuals, whereas digital items may include apps, data flow, and troubleshooting support processes. If the information is extensive or likely to differ across geographies, then cross-referencing a supplementary document besides the protocol may be preferrable.

Where?

Addressing the where involves answering two questions:

1. **Where (what geographic regions) will the DCT component be used?** For example, the trial may be multiregional or conducted in a single country where individual states may have a degree of autonomy (e.g. in the USA).
2. **In what physical location (in relation to the end user) will the DCT component be used?** For example, a participant may be using a wearable or connected device for their whole waking period whereas a nurse conducting home healthcare visits may be conducting them at the participant's home or another agreed location.

Regarding the first question: Over the last year or so, regulatory agencies have begun to release dedicated DCT guidance or guidance that addresses certain DCT components – including agencies in Denmark,[23] USA[13] India,[24] and Switzerland.[25] As the adoption of DCT components increases, it's likely countries will release or update guidance on what components can be used and under what conditions they can be used in a trial.

In relation to the second question, the physical location should be understood to describe the intended use and any risk mitigation strategies. For example, if home assessments are required once in the morning and once at night, then the risk mitigation may include setting up reminders and strategies if the participant is away from home for a prolonged period of time such as for work or for vacation.

When?

When relates to when and how often a DCT component will be used – i.e. what timeframe (such as number of times used in a day) and how frequently will the data be collected (such as all the time or occasionally). Data collection can be discrete, where it is collected at a single point of time (e.g. an assessment that is conducted once a day), or continuous, where it is collected continuously (e.g. a wearable or connected device that monitors heart rate for the entire time the participant is instructed to wear it).

How?

The how refers to how the end user will engage with the DCT component and how operational variability will be controlled. The trial team must

> The *why* is the first and most important point in establishing DCT component scope: it consists of addressing the component's suitability for the research question and the appropriateness of the anticipated data quality.

have a clear understanding of how end users are expected to engage with the DCT components under ideal settings and – to a limited degree – control variability in its real-world operation (e.g. what happens if someone doesn't complete a critical assessment upon awakening? Will they get a reminder?). The more critical the DCT component is to the trial (i.e. the *why*) the more important this consideration.

What makes a DCT component?
Categorisation of DCT components remains fluid and different organisations may classify components and approaches differently depending on business or logistic needs. Below are some of the most common categories; their definitions can be found in Table 1.

Telemedicine
Telemedicine in the context of a clinical trial refers to the use of telecommunication technology between investigators and participants to conduct remote clinical assessments (e.g. functional tests such as physical or neurological examinations, collection of clinical data such as participant assessment of intervention benefit, or discussion of remote data collection in conjunction with digital health technologies).

Data collected from telemedicine visits often support key endpoints and as such, the more critical the data the more important the description in the protocol. Key points to consider are whether there is flexibility for onsite, telemedicine visits, or remote visits. In addition, the more critical the data the more likely risk mitigation strategies need to be described in the protocol, e.g. for telemedicine visits at critical time points, the site may use multiple reminders or additional phone calls to ensure scheduled telemedicine visits are not missed.

Applications (apps) and technology
Although no formal definition exists for participant apps and technology, communication and data transfer between participants and investigators or other trial staff may employ commercial or custom-made apps. These apps may be installed on a smartphone, tablet, or laptop for use with telemedicine visits, wearable or connected devices, electronic clinical outcome assessments (eCOAs), home healthcare, or other trial requirements. These electronic devices may be provided by the sponsor as a *provisioned device* for the duration of the trial or the apps may be installed on the participant's preferred device: *bring your own device* (BYOD) option.

The detail required in the protocol for apps and technology does not need to be substantial but sufficient to provide a clear understanding of what is being provided. For example, if the trial includes telemedicine visits, wearable or connected devices and eCOAs – will all data collection be performed through the same interface (e.g. smartphone app) or via several interfaces? Regarding technology, will provisioned devices or BYOD be required, or will this be per participant preference? If BYOD is preferred, what happens if an eligible participant does not have a compatible device? From a regulatory perspective, the risk-benefit for provisioned device versus BYOD is complex and requires careful consideration.[26,27]

Wearable or connected device
Wearable or connected devices include static or wearable devices that can support remote data collection directly from the participant (e.g. wearables like actigraphs that monitor activity levels) or their environment (e.g. air quality). Data collected can be stored locally or centrally and the process from point of collection to point of final storage is part of the *data flow*. According to the EMA's recent Q&A on GCP "a detailed diagram and description of the transmission of

Table 1. Definitions

Name	Definition	Source
Classification and subclassification		
DCT	A clinical investigation where some or all of the trial-related activities occur at a location separate from the investigator's location	FDA 2021
	A clinical trial utilising technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site	DTRA Glossary of Industry Terms 2022
Full DCT	Trials executed through telemedicine, mobile/local HCPs and/or mobile technologies – and are thus not bound by the geographic limitations that affect traditional trials	Apostolaros et al 2020
Hybrid DCT	A suitably flexible scenario that partially eliminates the requirements for participants to visit a physical trial site to perform a protocol-required event that may have traditionally taken place onsite	DTRA Glossary of Industry Terms 2022
DCT Components		
Telemedicine	The use of electronic information and telecommunications technologies to support and promote long-distance clinical healthcare, patient and professional health-related education, public health, and health administration. Technologies include videoconferencing, the internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications	DTRA Glossary of Industry Terms 2022
Applications and technology	Communication or data entry point or both between the site and participant that can be through a smartphone or tablet or laptop device provided by the Sponsor for the duration of the trial (provisioned device), or software can be installed on the participant's preferred device (BYOD)	None
Wearable or connected devices	Electronic devices that can be worn or carried on the body to allow personal data of the user to be monitored and measured through smart sensors that are embedded in the device	DTRA Glossary of Industry Terms 2022
eConsent	Electronic form that may include multimedia components such as images, audio, videos, diagrams, and a digital signature to aid the collection of the informed consent of a participant. Also, documents that the patient has been given the appropriate, and not coercive, written information to support their ability to give fully informed consent. Other examples of consent forms are assent forms.	DTRA Glossary of Industry Terms 2022
eCOA	Electronic capture of a measure that describes or reflects how a participant feels, functions, or survives during a clinical trial. Types of eCOAs include eClinRO measures, ePRO measures, eObsRO measures, and ePerfO measures	DTRA Glossary of Industry Terms 2022
Home healthcare	Home healthcare encompasses a wide range of healthcare services that are given to a patient in their home. A variety of providers may be involved, including but not limited to home health nurses, phlebotomists, doctors, among others. This care is typically provided during home health visits.	DTRA Glossary of Industry Terms 2022
Direct-to-patient shipping	Direct shipment of clinical supplies and investigational medicinal products to the participant's residence or other agreed upon location (e.g. participant's work)	DTRA Glossary of Industry Terms 2022

Abbreviations: BYOD, bring your own device; DCT, decentralised clinical trial; DTRA, Decentralized Trials & Research Alliance; eClinRO, electronic clinician-reported outcome; eCOA, electronic clinical outcome assessment; eConsent, electronic consent; eObsRO, electronic observer-reported outcome; ePerfO, electronic performance outcome; ePRO, electronic patient-reported outcome; HCP, healthcare provider.

electronic data should be provided in the protocol"; this recommendation is also supported by the ACRO QbD manual.[17,28] Additional points of caution include:

- Describing any flexibility related to how end users engage with the device to accommodate a range in technology capabilities and visibility or mobility
- Data collection and validation capabilities
- Handling missing or invalid data.[21,29,30]

Electronic Consent (eConsent)

eConsent is an electronic method for seeking, confirming, and documenting informed consent. DCTs that are fully remote are likely to require eConsent to be provided remotely via an app, whereas hybrid trials may require eConsent provision remotely or at the trial site. Although the consent process does not feature heavily in the protocol, the difference and variability in the eConsent process compared to the traditional paper consent does warrant careful evaluation during protocol development.

Electronic clinical outcome assessment (eCOA)

Much like conventional paper clinical outcome assessments (COAs), each eCOA will require summary details to be included in the protocol and consideration for how it will be accessed and by whom. For patient-reported outcomes (PROs), details for complete PRO reporting are described in the SPIRIT-PRO extension.[31] Additional complexities when describing eCOAs (including ePROs) is that they may be accessed from different apps by different end users – this will multiply the data flow considerations that are recommended to be included in the protocol.[17] Similarly, training requirements may be variable depending on the number of eCOAs and where the users are located, trained or both.

Home healthcare

Home healthcare by nurses, phlebotomists, physicians, or other healthcare professionals can relieve some of the trial participation burden by reducing or eliminating the need for onsite visits. The challenges in incorporating these into the protocol fall into two categories:

1. **Flexibility around who will be able to receive home healthcare.** For example, is home healthcare mandatory or optional in one or all geographies? Alternatively, can home healthcare be a flexible alternative to onsite visits per participant preference? Lastly,

are all participants eligible for home healthcare? – e.g. will all participants in a subgroup that has more assessments be eligible for home healthcare?

2. **Flexibility around where *home* visits take place.** Although home healthcare is often considered to take place at the participant's home, logistically it may not always be feasible. For example, a participant may not feel comfortable with a healthcare provider in their home or may be spending a large part of their day or week away from their home. Other, prespecified safe locations or local clinics may be feasible alternatives.

Direct-to-patient shipping

Direct-to-patient shipping involves providing trial materials or trial interventions (or both) directly to the patient via some home delivery mechanism. Early engagement with clinical trial supply chain stakeholders is essential to allow the time needed to provide logistic and cost estimates as well as establishing the process for protecting personal data. Within the protocol, the preparation, handling, storage, and accountability of medication and samples needs to be clearly stated – as well as for who this applies to (e.g. there may be geographic restrictions on where this DCT component can be used).

Concluding remarks

As DCT component adoption becomes more popular and accepted in clinical trials, the protocol development process needs to keep pace if protocols are to maintain their effectiveness. The proposed scoping process and resources highlighted in this article may serve as tools and guidance to help protocol authors enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components.

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The author declares no conflicts of interest.

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