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Ethical Considerations in Decentralized Clinical Trials

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Abstract As a consequence of the COVID-19 pandemic, the number of decentralized clinical trials, trials conducted in whole or in part at locations other than traditional clinical trial sites, significantly increased. While these trials have the potential advantage of access, participant centricity, convenience, lower costs, and efficiency, they also raise a number of important ethical and practical concerns. Here we focus on a number of those concerns, including participant safety, privacy and confidentiality, remote consent, digital access and proficiency, and trial oversight. Awareness of these ethical complexities will help foster the development of processes and cooperative solutions to promote safe, ethical trials going forward, optimized to decrease burden and increase access for all participants.

Keywords Decentralized clinical trials · Hybrid trials · Remote trials · Bioethics · Electronic Consent · Digital trials

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Introduction

Clinical trials are necessary to provide evidence to demonstrate the safety and efficacy of healthcare interventions and for the development of novel therapeutic products. These trials are typically conducted under standardized, well-controlled conditions that do not necessarily mimic real-world circumstances. Traditionally, clinical trials are conducted at clinical trial sites and with an investigator team, with participants traveling to the site, for all trial study procedures. This traditional approach was disrupted by the COVID-19 pandemic, in part because quarantine, isolation, and social distancing—necessary to decrease the rate of infectivity and protect public health—foreclosed the option of elective research visits to the clinical trial site, and in part because clinical resources were often redeployed in the service of providing patient care. At the onset of the pandemic, many ongoing trials (Ledford 2020), from oncology trials (AlSaleh 2021), to inflammatory bowel disease (Noor et al. 2020), were terminated, suspended, or withdrawn, limiting the acquisition of valuable data in the service of care or research specifically to address the COVID-19 pandemic. International regulatory agencies responded quickly to provide guidance on the conduct of clinical trials during the pandemic, emphasizing the ability to engage, enroll, and retain participants at a distance using remote technologies, telemedicine, local healthcare and imaging facilities, and visits and drug delivery to the home (U.S Food and Drug Administration

2020a, 2020b; European Commission 2022; The Commonwealth Department of Health 2020). Pharmaceutical and device companies, contract research organizations, academic centers, universities, and hospitals quickly re-tooled to adapt to remote activities, coordinating with ethics committees and trial sites (Loucks, et al. 2021; Doroshow, et al. 2021). As a result, decentralized clinical trials (DCTs, also termed tele-trials, virtual trials, remote, and digital trials), once rare and seemingly experimental, increased in number, range, and popularity. Not only did DCTs address the challenge of social distancing but other benefits—and challenges—were appreciated. Here we address ethical and practical considerations in the decision to deploy and in the conduct of DCTs.

DCTs have been defined as "a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites" (U.S. Food and Drug Administration, 2023). In general, DCTs are executed in whole (fully decentralized trials) or in part (sometimes termed hybrid trials) through mobile technologies and/or local healthcare providers with a decreased reliance on research facilities and/or intermediaries for data collection. They vary in location, methods, and procedures from traditional trials, but many of the ethical issues are similar and depend upon the specifics of the DCT element(s), the study population, and the study question, research procedures, and conduct of the trial (U.S. Food and Drug Administration, 2023). In the past, many—or even most—site-based trials have involved one or more DCT elements, such as local blood draws, but the COVID-19 pandemic increased acceptance of DCT elements and even fully decentralized trials. DCTs make use of electronic consent (eConsent), digital health technologies (DHTs), and devices for data collection (e.g., wearables, smartphones, digital communications), telemedicine, home health visits, local pharmacies, and imaging facilities. They involve remote monitoring, and reliance on local healthcare practitioners (HCPs) and can include the shipment of an investigational product to the home. While DCTs differ in important ways from traditional trials, some of the ethical considerations of elements of DCTs are not substantively different. It is important not to hold DCTs to a different standard than traditional clinical trials but rather focus ethical analysis on those aspects of DCTs that involve new or different ethical concerns. Each element of a DCT should be evaluated independently and then collectively: consideration of the benefits, risks, and alternatives of each element informs the risk-benefit assessment of a clinical trial structured as a DCT.

Benefits of DCTs

Adoption of DCTs occurred rapidly as a result of the COVID-19 pandemic, and the apparent advantages of DCTs were quickly popularized. The benefits of DCTs—and the comparison to traditional trials—have not been empirically or rigorously investigated and further research is needed. That said, participant access, recruitment, and retention, even when study eligibility would permit enrollment, have been challenging in traditional clinical trials. When considering volunteering to participate in a trial, eligible participants weigh the potential benefits and risks of the intervention with the burden of participation: they consider transportation and access to the site, interruption of work and home responsibilities, childcare and eldercare needs, food, lodging, the number of required visits, and the costs of participation (e.g., transportation, lost wages, potential costs of associated care that may not be covered by other means) (Desai 2020). People who are not traditionally seen at a research site (e.g., academic medical center in an urban setting) may not even be identified as eligible or offered access to a trial. This is especially true of people who have been historically underrepresented in research, vulnerable populations, rural populations, and those of lower socio-economic status (Nicholson 2011). A cross-sectional survey of cancer patients demonstrated that reducing patient time and travel burden through remote technologies and other DCT elements would increase the likelihood that respondents would consent to participation; that likelihood varied with income and age (Adams, Long, and Fleury 2022). The burden of travel and trial out-of-pocket expenses have shown a differential impact on the participation of lower-income compared with higher-income populations (Nipp, et al. 2015; Borno, et al. 2018; Hauck, et al. 2021). When asked, however, at least in the United States, racial and ethnic minority populations are as willing as non-Hispanic whites to participate in health research (Wendler, et al. 2006). Thus, access to health research appears

to be a critical factor for diversified participant populations, and DCTs appear, at least in part, to address access challenges.

In addition to travel inconvenience and expense, there are other apparent advantages for participants, including the ability to optimize their own schedule and maintain their responsibilities to work, home, child- and eldercare. Some participants already have a trusting relationship with a local HCP, and the ability to see that local HCP may provide continuity and a sense of security. Optimally, of course, participants should be able to choose whether they prefer their research visit to occur at home, a local facility, or the clinical research site, but "choice" entails consideration of other issues (e.g., data comparability and integrity) as discussed below.

While there are apparent advantages to participants, there are also potential benefits to clinical trial sponsors and investigators. By eliminating logistical barriers to participation, DCTs provide the opportunity to reach more diverse and representative populations who have often been excluded from clinical trials, including people living in rural communities and minoritized populations. There are also presumed efficiencies in the conduct of DCTs, real-time access to participants, and potentially decreased cost. But while DCTs offer the opportunity for diverse participation, efficiencies, and patient-centricity, there are also ethical issues that require consideration and review. It is to these ethical challenges that we now turn.

Participant Safety

Perhaps one of the most important reasons to require participants to be seen in a research facility rather than locally is for safety considerations: the ability to directly observe the consequences of the intervention, the availability of licensed personnel, and the access to emergency equipment. In addition, adverse events can be recorded accurately and completely when witnessed. In DCTs, special provisions need to be made in the event of an adverse consequence, including training the participant on what to observe, how to respond, and when to report. Additionally, research personnel, HCPs, and home healthcare workers need to be adequately trained to identify and report adverse events consistently via a digital platform. Therefore, what is already known about an intervention will impact the DCT decision: a first-in-human trial of an intravenous product is less likely to be amenable to home or local administration than a registration trial of an ointment or cream (e.g., a treatment for eczema). Similarly, the eighth infusion of a medicine is less likely to result in an immediate reaction than the first. Patients with multiple, severe comorbidities are likely to be at higher risk than normal volunteers or people with a single, well-defined disorder. Each of these considerations and others (e.g., age of the participant, availability of and distance to home health or local providers, approaches to mitigate risk, etc.) will bear upon the overall assessment of DCT acceptability. Sponsors, investigators—and ethics committees—must weigh each of these elements in rendering an informed, case-by-case, decision about ethical acceptability.

If the intervention is judged to be able to be given at home or locally, the product must be shipped to the location. Practical issues such as (1) chemical characteristics (e.g., physical stability, sensitivity to light, requirements for temperature-controlled shipment), (2) shipment details, such as packaging and tracking, who will receive the shipment and the documentation thereof, (3) administration procedures, including training the participant, home health nurse or local provider, (4) oversight of and documenting the administration, and (5) product accounting, use, storage, and disposal or return, must be considered not only for safety but feasibility (Flaherty, et al. 2021; Malone, et al. 2022). Additionally, considerations such as the ability to maintain a "blinded" trial, location of a nearby acute care facility, availability of social supports to assist, potential for abuse or diversion, and others will factor into both the decision as to the appropriateness of a DCT and whether a given participant is able to leverage a local option.

While participant convenience may be increased by not having to travel, the burden of product administration is largely shifted either to the participant if they are receiving it at home or to the HCP if at a local clinical site. Participants (and HCPs)[1] may or may not be comfortable with

[1] While not an ethical concern, remuneration to the HCPs for their research time and work must also be arranged, as they cannot bill these services to payers. Some national health insurance plans include clinical research in allowable provider activities.

the responsibility and may prefer to receive the intervention at the research site. Further, some participants have ongoing relationships with their providers who are part of the research team; they may prefer to be seen at the research site, particularly if they need to be seen for other reasons. For some non-interventional trials and some other research studies, of course, including survey research, observational studies, pragmatic trials, and trials conducted at the point of care, these issues are not relevant.

Provisions for adverse event reporting differ in DCTs than in traditional clinical trials. Traditionally, the participant is seen periodically and predictably and asked about any adverse events. The research team would be able to ask questions and document the adverse event, judging its severity and relatedness, and educate the participant to be alert for intercurrent potential adverse events that may occur between visits. In DCTs, it is the participant who first must recognize that the "event" should be reported and then know how and to whom to report. For obvious symptoms such as a rash at the site of application of an ointment, identification of a reportable event is obvious. But other symptoms, particularly common symptoms such as headache or fatigue may be less obvious to the participant as possibly related to the trial intervention. There must be a heightened awareness by the participant as to the potentiality of an adverse event, particularly since they may not be seen at regular intervals. In addition, a third-party provider should be identified, an HCP who could see the participant and make the assessment of severity and relatedness and be trained so that their assessment is consistent with that of the study investigators. The participant should know who to contact and where to go to be evaluated if a serious adverse event occurs, independent of its relatedness to the study. When, how, and to whom to report must be clear, and the study team must provide for a responding clinician and process, with attention to the fact that adverse events may be reported at any hour. Ensuring that the participant understands that reporting symptoms or concerns is not only anticipated but welcome is an important message to ensure safety.

Privacy and Confidentiality

In most DCTs, some or all of the data are collected, transferred, stored, analysed, and shared electronically. In addition to data collected as part of the trial, participants are often made aware of trials through social media or electronic communications (e.g., patient portals associated with a healthcare facility), the informed consent process may be virtual, and documentation of informed consent may be electronic (eConsent). While DCTs, in theory, increase research access, each of these methods carries risks to participant privacy and confidentiality that should be considered.

DCTs often make use of digital health technologies (DHT, e.g., wearables, smartphones, tablets) for the collection and transfer of data. The interposition of technology between the participant and the investigator, and the fact that participants may be entering data that contains private information that they would not have otherwise shared on technology platforms, introduces additional layers of risk. First, some of these platforms may not be secure. Second, some may share data with third parties (e.g., the software developer) unbeknownst to the participant (or embedded so deeply in the terms of service that no one might notice or understand the implications). Third, the software deployed for the research may be able to access other information on or collected through the device (e.g., contacts, geolocation) that present new risks to the participant. Fourth, use of the DHT assumes that only the participant has access to—and secure access to—the technology, but certainly that is not always true. Some family units, for instance, share one smartphone or one computer. Fifth, there is always concern of a security breach.

An important component of the evaluation of risks is the development of a comprehensive data management plan as a component of protocol development itself. Knowing what data are requested and how they will be collected, transferred, processed, stored, shared, and validated will likely expose areas of vulnerability. Further, data mapping, transformation, and integration are often necessary, involving third-party vendors, including the vendor(s) for technology, software, cloud storage, and analysis.

These concerns all share the common feature of risks to privacy and confidentiality. The sponsor,

investigator team, and ethics committee, each have a responsibility to evaluate that risk and introduce mitigation strategies (e.g., equivalent alternatives, data minimization, data encryption, increased security provisions, access controls over data sharing and re-use) wherever possible. The risk evaluation will also vary with the nature and sensitivity of the information being collected and shared: response to a topical cream to treat eczema differs from information about drug use or suicidality. After risks have been minimized, stakeholders must weigh the risks against the element(s) of the DCT considered for use and against the benefits of the research itself.

Individual participant considerations will also impact privacy and confidentiality. Some participants may not have spaces or time in their homes where privacy can be guaranteed. Multi-generational housing, children and others at home, and shared devices all compromise participant privacy and may impact their comfort and ability to disclose certain private information. At the time of participant enrollment, the investigator and their study team should respectfully inquire about the participant's life setting and circumstances, their living situation, access to and comfort with digital technologies, including whether any technology is shared. Only by asking about the actualities of the participant's situation can practical concerns be addressed, and risks mitigated.

Communications from the research team must not disclose the nature of the research or the condition. Notifications that specify the medication to take or the HCP to call may indirectly indicate the underlying condition. Reminders such as, "This is an automated reminder to take your Harvoni® now," wherein the only indication for Harvoni® is to treat hepatitis C, immediately alert the reader to the diagnosis. In addition to participant risks, there are third-party risks to other individuals in the vicinity of the participant as well, in that their information (e.g., geolocation, voice recognition) may be captured during data collection unbeknownst to them.

With the knowledge of the participant's living conditions, the investigator and research teams should address concerns about privacy during the informed consent process. It is important for these risks to be transparent to the participant, and whether alternative methods for participation are available and allowable so that they can make an informed decision about the research.

Remote Consent

Voluntary informed consent is a foundational necessity in human participant research. In DCTs, remote electronic consent (eConsent) is often utilized (U.S. Food and Drug Administration 2016). eConsents offer rapid sharing and communication, the ability to readily update the form after ethics committee approval, convenience, social distancing, and participation of people with limited mobility or access to a facility. They also offer the ability to embed video demonstrations or other ancillary information about the research itself that is a "click" away. Imagine the enhanced understanding of an MRI if one could click on the word and view a 15-second video or even include an image so that participants have a visual image of the machine. The potential participant can choose which resources and information they wish to view, and in a language and format that they prefer.

While there are robust technology platforms to support eConsent processes, ethical concerns arise. First, the participant's identity must be verified and signature procedures compliant with the legal provisions of the jurisdiction in which the participant resides; these requirements can themselves be challenging particularly if the potential participant is unknown to the study team. Second, the study team must be certain that the prospective participant fully understands the research and that all questions have been answered. Simply sending a consent form for an interventional clinical trial to the participant is inadequate; a face-to-face discussion is generally necessary, even if that discussion is held virtually (e.g., videoconferencing). Third, the participant should have time to review the materials and know who to contact for further information, and the document should be in the preferred (plain) language of the participant. Verifying understanding is challenging in all circumstances and is particularly salient when the conversation is remote. Finally, the investigator and their study team should spend the time to establish a relationship and rapport with the potential participant, often challenging in a remote setting.

It is important to consider whether and when remote consent—and remote visits—may not be appropriate and when an in-person visit is necessary. There are medical reasons to require an in-person interaction, such as when the performance status of a potential participant may have changed and must

be reassessed or when capacity to consent requires additional interventions for evaluation. There are also social and personal reasons to encourage or require an in-person visit, particularly when the study is complicated, prolonged, or will depend on the relationship itself (e.g., behavioral interventions that can be performed remotely but may differ from an in-person interaction). The development of trust, comfort, and understanding cannot be underestimated.

Digital Access and Proficiency

An underlying requirement of many elements of DCTs is the participant's ability to deploy digital health technologies paired with the comfort of seeking assistance when needed. Many people today own or have access to digital technologies, but not all, and access to the internet (and therefore access to digitally-enabled research) is uneven. Digital access varies by location (urban > rural, high-income settings > low-income settings), age (younger > older), gender (men > women), and other factors. As of 2022, fully one-third of the world's population did not have access to the internet and approximately one-half failed to have access to high-speed connectivity (Signé 2023a, b). Even in the United States, a high-income country, 10 per cent of the population lack access to broadband, 40 per cent of rural areas experience slower connectivity compared with 4 per cent of urban areas (West and Karsten 2016), and 63 per cent of those living on Tribal lands or in U.S. territories lack access to twenty-five Mbps/three Mbps broadband (Federal Trade Commission, 2015). While improving, these discrepancies and inequities in research access persist. It is therefore important to provide whatever devices are needed for the trial—and not depend upon the participant providing their own software—and assistance with the use of digital technologies (e.g., technical helpdesk) as part of a DCT plan, and to provide financial remuneration for the cost of data plans and internet access if the participant incurs these incremental costs.

The unequal access to digital technologies foreshadows a different ethical consequence of DCTs: that DCTs will not advance the sustained effort to address diverse representation in clinical trials. In relying on remote technologies, a new class of underrepresented populations in clinical trials, rural communities, elderly participants, people for whom the national language is not their preferred language, and others, often underrepresented in the past, will continue to be underrepresented in DCTs. The promise that DCTs will address the lack of diversity in clinical trials lends itself to empirical evaluation.

Trial Oversight and Responsibilities

In a traditional clinical trial, the investigator sees and evaluates every participant, knows the capabilities of their research team, selects sub-investigators with whom they are or become familiar, and has well-established monitoring processes. Even in large multi-site traditional trials, while the investigator may not personally know the site investigators or their institutions, there are individuals at or around the research site should the necessity arise. In DCTs, however, the principal investigator, while responsible for the conduct of a trial, shares responsibility with the sponsor, third-party vendors, HCPs, local laboratories, and healthcare facilities, many of which may not be known to the investigator at the start of the trial. Investigators may or may not have visibility into the contracts between the sponsor and their selected vendors and may not have the authority to challenge the vendor selection or the actions of individual actors. Further, remote monitoring at the scale required of DCTs is evolving, and its sufficiency difficult to assess.

Each of these concerns presents challenges with ethical, legal, and practical concerns. The investigator bears responsibility and accountability without necessarily having the appropriate authority. Legally, the investigator and their institution are the first respondents to regulatory compliance reviews and malpractice claims. Practically, DCTs introduce new practices and methodologies, including those necessary for recruitment, retention, participant safety, data collection, and monitoring; change often portends resistance. Better elucidation of the issues and clarity of the roles and responsibilities of each stakeholder will

help to ease, but not eliminate, concern. Regulatory authorities could assuage concerns by clarifying the responsibility matrix, in other words, that the investigator is accountable only for those elements which they have the authority to change. Experience will be helpful in this regard.

Conclusions

Most clinical trials have used elements of DCTs for years, such as allowing local blood draws or imaging, and electronic patient diaries, among others. The COVID-19 pandemic, however, heralded the increased deployment of digital technologies and increased engagement of local HCPs and healthcare, imaging, and laboratory facilities. These are welcome additions to the methods of conducting clinical trials and provide flexibility, choice, and convenience for participants. To maintain the advantages of DCTs and grow their acceptability, multiple ethical concerns and uncertainties must be addressed. It is the responsibility of all stakeholders in the clinical trial ecosystem to develop and share processes that ensure participant safety, privacy and confidentiality, data quality, and oversight, grounded in the ethical conduct of research.

Declarations

Competing interest There are no competing interests to disclose.

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