VIEWPOINT

Ensuring Virtual Vigilance in Decentralized Clinical Trials

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Clinical trials require a range of procedures from screening to consent and from assignment to an intervention—often in a randomized fashion—to the measurement of outcomes. Historically, participants traveled to the controlled environment of a clinical trial site for these activities, often with inconveniences of loss of time, money, or both. In a decentralized clinical trial (DCT), some or all trial-related activities take place at locations other than the trial site, such as the home, a local pharmacy, community centers, local clinicians' offices, or mobile units. The use of DCTs and the technology that enables them is growing considerably,[1,2] spurred in part by the COVID-19 pandemic, in which site closures, risk of infections, travel restrictions, and supply chain interruptions prompted a need to pivot from a site-centric model to a participant-centric model.[3] DCTs are emerging to be highly heterogeneous, using an array of different technologies and research service solutions, with some being fully decentralized and others taking hybrid approaches. As just 1 example, the ACTIV-6 DCT has enrolled more than 10 000 outpatients with COVID-19 using a platform that enables fully remote participation or fully in-person participation.[4] Participants enroll online using an electronic consent process, upload documentation of their illness, have their study medications mailed to them, and then complete regular surveys to assess symptoms and hospitalizations. Such approaches have the promise of making more clinical trials available to more people more quickly.

Technologies such as wearables and smartphones, telehealth platforms, patient portals, and secure applications are being widely deployed, with the intention of reaching historically underserved populations.[1,2,5,6] While continued innovations will be needed to overcome barriers associated with lack of quality internet connectivity, limited data plans, lower literacy and digital literacy, and lack of devices in rural and underserved populations, DCTs create other meaningful efficiencies such as decreases in travel, time, and burden for patients. DCTs are especially important for research on rare diseases and diseases affecting populations with limited mobility.[7] National initiatives are being launched with the goal of bringing clinical trials to everyone, everywhere. For example, the new effort by the National Institutes of Health, Communities Advancing Research Equity for Health (CARE for Health), aims to implement innovative study designs that extend research into the frontlines of clinical care in primary care settings—reaching broad communities including people in rural settings; people across racial, ethnic, and gender groups; and older adults. Incorporating DCT applications will be essential to success.

As clinical trials increasingly incorporate decentralized features, there are meaningful threats to the validity of their results. Our experience with the web of technologies and research services needed to operate a DCT has unearthed challenges not addressed by traditional monitoring and oversight practices. Based on the lessons learned from dozens of trials conducted at our institute using decentralized approaches, we suggest a practical approach to applying the US Food and Drug Administration (FDA) guidance on DCTs.

Major high-risk activities of DCTs are verifying participant identity, delivering the investigational product to the participant, and minimizing lags between participants' data entry and identification of the need for action to ensure safety and study compliance, including adherence to treatment and outcome measurements. With these risks to integrity forefront, and consistent with the principles of using decentralized elements and risk-proportionate monitoring, we propose that DCTs frame their monitoring and oversight to ensure that the *right patient* receives the *right intervention*, contributes the *right data*, and that the *right response* occurs for adverse events or nonadherence.

Right Patient

When conducting a trial remotely, care must be taken to ensure that it is the enrolled participant providing information through whatever data portal is used and that falsified or fabricated information is not entered. Participants and staff may never interact face to face; thus, participant identity must be reconfirmed at each interaction—for example, via internet protocol address tracking, facial recognition, or fingerprint scans, along with 2-factor authentication. Technologies such as internet protocol address tracking fail when 2 participants in the same study share the same device, and security measures can introduce privacy concerns, exacerbating health inequities. Regarding consent, FDA guidance makes clear that electronic consent (e-consent) is acceptable and notes the potential for multimodal and longitudinal engagement with participants.

Right Intervention

Some DCTs involve mailing the investigational product. For example, the PROACT Xa trial involved mailing a study drug (apixaban or warfarin) to patients with a mechanical aortic valve.[8] When the product is mailed directly to a patient, ensuring chain of custody of an interventional product poses challenges, as shipments may go missing en route, couriers may refuse to deliver directly to participant addresses in extremely rural or extremely urban environments, and participants may refuse product delivery or return the intervention. Reliance on post office boxes may also complicate delivery, and ambiguity in current regulatory guidelines may limit prescribing investigational agents across state lines.[9] Consequently, investigators should consider the process by which materials get to participants as high risk and monitor accordingly. Investigators need a means of confirmation that participants can and do receive the product and adhere to trial protocols.

Right Data

While many patient-reported outcomes can be assessed by remote communication, care must be taken that data are not unknowingly provided by a surrogate. Tools such as wearables and at-home specimen collection kits offer another avenue for collecting data and measuring safety and outcomes requiring similar care.

Biometrics, video technology, and telehealth can be used to confirm the participant's identity and to directly observe a task or activity. Measuring outcomes completely is critical for a clinical trial and should be monitored in real time given the challenges of remote follow-up and the heterogeneity of encounters with varied health care systems or clinicians that can occur in a DCT. Metadata can be a useful tool for understanding data provenance, understanding where and how participants are interacting with data collection systems, and identifying unintended activity.

Trial data systems are often considered repositories, secured in accordance with appropriate state, local, and federal regulations. For a DCT, the data system needs to meet the same regulations, and data integrity and protection must be ensured at the source and during transmission. There are also logistical, regulatory, and security challenges to obtaining the right data and linking disparate data systems. When electronic health records are used, multiple Health Insurance Portability and Accountability Act authorizations may be needed for health systems with which the investigators have no association, and utility of real-world data is limited by access. Such challenges must be overcome to achieve complete and accurate data collection.

Right Response

To ensure patient safety, data entered remotely must be monitored by investigators in real time and acted on appropriately, not simply added to a database. For example, trials that include a questionnaire that could signal patient distress or suicidal ideation should have a plan for how to respond to such signals and mitigate risk of harm.[10] That plan can be especially complicated when safety and outcomes data are collected remotely and participants do not have a relationship with a site. There may be unknown risks to health and safety, and these must be managed in a timely manner. Clarifying the roles and responsibilities of researchers, clinicians, and sites in mitigating these risks before the trial begins is a critical step toward safeguarding participants, providing a blueprint for institutional review boards and ethics committees to review risks associated with DCTs. A good example is the Australian model, Teletrials, which uses telehealth technology to communicate between a primary site and satellite site to extend reach.[2] In this model, a detailed plan defines responsibilities across the sites, in addition to specifying the "right" response.[2]

Because trial data systems may be the only mechanism by which participants engage with the study, we recommend these systems be bidirectional with the participant, much like patient portals provide a mechanism for patients to communicate securely and in a timely way with their clinicians. Using the electronic data capture system as a bidirectional communication system can also provide a hub to help with participant management and ensure that a participant has the opportunity to ask questions and report worrisome issues and events the sites need to know about, while simultaneously providing the opportunity for sites to react to nonadherence with the intervention or challenges with data collection.

Conclusions

As DCTs mature, trial sponsors and designers are advised to start developing and applying monitoring and oversight of practices modernized to the decentralized trial framework. Decoupling trials from sites may offer opportunities for direct data from participants, broader reach, and greater access, but this cannot be allowed to undermine integrity of the data. Monitoring should ensure the right participants and right data requirements so that as clinical trial deserts are eliminated, health inequities are not undermined by lack of research rigor.

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