Editorial

Despite negative perceptions of clinical trial conduct during the coronavirus disease 2019 (COVID-19) pandemic, are decentralized clinical trial methods here to stay?

Lisa Cooper^, Nadina Jose

Department of Health Informatics, School of Health Professions, Rutgers, The State University of New Jersey, Newark, NJ, USA

Correspondence to: Lisa Cooper, PhD. Stanley S. Bergen Building, Suite 136, Rutgers, The State University of New Jersey, 65 Bergen Street, Newark, NJ 07101-1709, USA. Email: lisa.cooper@rutgers.edu.

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Introduction

The execution of clinical studies at the site level was drastically modified during the coronavirus disease 2019 (COVID-19) pandemic in order to minimize interruption of treatment and risk to study participants, retain quality of study data, and achieve development milestones. With the support of health authority guidance documents (1-3), procedural changes that were implemented include, but are not limited to, subject visits being conducted via telephone or video, informed consent being obtained electronically, investigational drug being delivered directly to subjects' homes, and remote entry and monitoring of study data. Zhu *et al.* (4), conducted a survey of clinical research staff across China to assess perceptions on how procedural changes resulting from the COVID-19 pandemic impacted four core areas: subject enrollment, patient care, study supplies and data management, and research milestones and quality management. The results of the survey support findings from several other studies (5-11); yet, decentralized clinical trials are becoming more prevalent post-pandemic.

Overall perceptions

In general, survey respondents expressed negative perceptions in all core areas apart from research milestones and quality management. It is not surprising that subject enrollment and patient care scored least favorably, as most studies were forced to stop or delay enrollment of new subjects and ongoing studies with active treatment had to implement new provisions for patient visits such utilizing telemedicine technologies (12,13). Study supplies and data management questions also received mostly negative responses; however, those regarding the number of and time to evaluation of (missed) safety reports, as well as the need to perform unscheduled unblinding of ongoing trials, were all assessed as positively impacted by the pandemic. The positive views of safety reporting are explained by the authors as possibly being attributed to the application of telemedicine and the direct transmission of patient health records to the investigator. However, the quick assessment of safety events and follow-up treatment decisions as a result of telemedicine was clearly not realized as an improvement in patient care overall. In fact, responders acknowledged that subjects would prefer to have local assessments performed. The need for interpersonal interaction to build a positive doctor-patient relationship has been identified as a continued struggle in China. Telemedicine may further compound negative patient care perceptions if both the site staff and patients lack proper training and education on its

^ ORCID: 0000-0002-2403-8105.

use (14). However, in a study of patient online reviews from three Chinese hospitals, it was found that fewer complaints were made against doctors and facilities during the pandemic, a possible result of patient empathy towards the hardships endured by medical personnel and appreciation for their continued services (15).

In an age where electronic medical records, case report forms, and patient diaries are routinely utilized, one might expect that data entry, at worst, would have remained neutral, yet it was assessed negatively. If telemedicine improves safety reporting due to quick accessibility to patient data, presumably all patient data is as easily accessible. Reasons for delayed data may therefore be due to other reasons such as diverting staff efforts to other areas like caring for COVID-19 patients, establishing new processes, or even being unable to work due to pandemic safety protocols. Most quality management and research milestone questions were surprisingly assessed as positive. The two questions which received negative views were on-site monitoring and delays in milestones such as ethics approvals and study meetings.

Decentralized clinical trials

The first decentralized clinical trial was conducted in 2011 by Pfizer, which assessed the safety and efficacy of Detrol LA (tolterodine tartrate), a treatment for overactive bladder (OAB) (16). The study was part of the Food and Drug Administration's Clinical Trials Transformation Initiative (CTTI) (17). Since then, hundreds of decentralized trials have been performed, many of them using a hybrid model in which some aspects of the study are performed at the site while others are done remotely (18). Conceptually, decentralized clinical trials have the potential to reduce research time, resources, and overall cost while increasing access to a wider pool of patients, thereby improving enrollment diversity, generalizability of results, and improving patient care through broader access to treatment (19). During the COVID-19 pandemic, implementation of decentralized clinical trial methodologies and technologies were expedited. Many organization infrastructures did not have the applicable processes in place to support the necessary changes and the speed in which the numerous changes were instituted, which likely contributed to the negative perceptions observed for clinical trial conduct during the pandemic. As indicated by the survey results obtained by Zhu *et al.* (4), the biggest challenge for site clinical research staff during the shift of ongoing studies to decentralized processes was patient care. Even though some decentralized clinical trial methodologies had been implemented pre-pandemic in the form of electronic medical records and other digital systems to gather data at the point of care, it was only during the pandemic that the need to expand the use of such systems was heightened, shifting into environments where subject access to and knowledge around electronic applications may be limited, and as a result, subjects' frustrations can bleed into other areas of study conduct such as protocol deviations. Additionally, the lack of or limited in-person evaluations can contribute to inadequate investigator subject oversight overall (20-22).

Improving perceptions

The technologies used to support decentralized clinical trials are continuously growing in number and improving. Compliance with national and local laws for such technology can be burdensome to clinical trial sites as well as costly and should be evaluated when deciding to implement them. It is also important to consider the design of the study protocol when implementing decentralized modalities (23). Study design should align with the methodologies proactively, rather than forcing such systems to comply with a study ill designed to utilize such functions. Further review of what has been used in studies conducted during the pandemic compared to those conducted pre-pandemic could provide insight for individuals who are responsible for study design, data collection, and clinical operations.

Additionally, these technologies will require new or updated procedures and processes for which research staff training should be prioritized in advance of the need to utilize the system in a study. This will allow staff to become familiar with the systems, which may lead to quicker data input and fewer errors. More importantly, study sponsors and investigational sites should implement mechanisms for reducing subject burden as it pertains to accessing and using technology. Ensuring subjects have appropriate internet access and equipment to attend remote visits, as well as user friendly training, may improve study compliance (20-22). Unfortunately, during the pandemic, these efforts, which took time to develop and perform, were not always practical, leaving staff and subjects learning as they went or in some cases, feeling frustrated enough to discontinue participation.

Future of clinical trials

Are decentralized methodologies here to stay? While change is hard, change is inevitable. The more time one has to adapt to changes, the better one's perception of the change will be. In some respects, clinical trial conduct methodologies have started to revert to pre-pandemic standards, but for the most part, more decentralized methodologies are being incorporated into clinical trial protocols. As social distancing restrictions lift, more in-person visits are being conducted, in-person site monitoring is able to resume, and drug distribution at the site rather than directly to subjects has been reestablished by some sites. Yet not all activities implemented during the COVID-19 pandemic will disappear. Decentralized clinical trials, when given the opportunity to be properly planned for and executed, can be positively perceived in all core areas. Time and experience play a major role in such perceptions. What is clear is that hybrid decentralized clinical trials have been around for a lot longer than the COVID-19 pandemic and will continue to drive the future of clinical trials.

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