Virtual clinical trials

Priya Ranganathan, Rakesh Aggarwal[1], C. S. Pramesh[2]

Department of Anaesthesiology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, [1]Director, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, Tamil Nadu, [2]Director, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Abstract

Virtual clinical trials refer to clinical trials that take advantage of digital technologies, including computer and mobile device apps, web-based tools, and remote monitoring devices, for one or more of the trial processes, such as participant recruitment, counseling, informed consent, measurement of endpoints, and/or adverse event monitoring, to obviate or reduce the need for participant visits to the trial site. The advantages of such trials may include higher recruitment rates, better compliance, lower dropout rates, reduction in time for trial completion, and lower costs. The use of such trials increased manifold during the COVID-19 pandemic and is likely to continue in the future.

Keywords: COVID-19, decentralized clinical trials, digital technology, Internet, remote clinical trials, wearable devices

Address for correspondence: Prof. Priya Ranganathan, Department of Anaesthesiology, Tata Memorial Centre, Homi Bhabha National Institute, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: drpriyaranganathan@gmail.com
Received: 27-08-22, **Accepted:** 05-09-22, **Published:** 08-03-23.

INTRODUCTION

Virtual clinical trials, also known as remote, digital, decentralized, or siteless trials, involve the use of digital technologies to facilitate trial-related processes.[1-3] Sometimes, in-person and digital techniques may be combined, creating "hybrid" trials. Virtual clinical trials were introduced several years ago; however, in recent years, the challenges posed by the COVID-19 pandemic have resulted in an exponential increase in their popularity and conduct.

CHALLENGES WITH TRADITIONAL CLINICAL TRIALS

Conventional clinical trials are centered around the trial site(s) and require patients to visit the site to complete trial-related processes. The trial protocols tend to be complex, and regulatory and safety requirements mandate frequent site visits at all stages of the trial, namely screening, counseling, consenting, administration of interventions, outcome assessment, and follow-up. Further, for performing these processes, the site needs infrastructure and staffing, both of which consume resources. Thus, such research sites are typically set up in larger medical institutions, which may be located far from the participants' place of residence. The need for repeated visits to such institutions means that certain types of participants – the elderly, those with disabilities or mobility issues, and those living in remote areas – are disadvantaged and less likely to participate. In addition, site monitoring of the trial by the sponsor results in additional resource expenditure.

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.picr_184_22

How to cite this article: Ranganathan P, Aggarwal R, Pramesh CS. Virtual clinical trials. Perspect Clin Res 2023;14:203-6.

VIRTUAL CLINICAL TRIALS

Virtual clinical trials aim to decentralize the conduct of a clinical trial, bringing some or all of the procedures closer to the participants' place of residence, thus making it more convenient for the participants (participant-centric approach). Experience shows that most aspects of a clinical trial are amenable to be conducted digitally.

Ethical and regulatory approval

An initial step in a clinical trial is the submission of documents to obtain ethics committee approval. Many ethics committees now permit and have facilities for the digital submission of documents. Members of the ethics committee may meet virtually rather than in person, to discuss and issue research approvals. The Indian Council of Medical Research guidelines for research during the COVID-19 pandemic permit the use of digital modalities for such meetings.[4] It is also possible to have centralized ethics committees and obtain a single ethics approval for multicentric projects; this is particularly useful for sites that do not have their own ethics committees or whose ethics committees are unable to convene meetings within a short time for any reason. Similarly, the process for obtaining regulatory approval from licensing authorities is also possible through a web-based application.

Screening and recruitment of participants

Accruing adequate numbers of participants is a major challenge in clinical trials. Artificial intelligence tools (including but not limited to natural language processing) can be used to search through electronic medical records to identify potential participants for clinical trials and match them to appropriate trials. This is particularly helpful in the identification of participants for trials in rare disease conditions. Screening of participants is important to ensure that trial eligibility criteria are fulfilled, and to guarantee the safety of participants and validity of trial data. Screening may be done virtually, by accessing participant data through digital tools.

Consenting and enrollment of participants

Consenting subjects for participation in a clinical trial is an important and complex process. This involves providing the participants information about the trial, allowing them enough time to understand this information, answering any questions or doubts they may have, and finally documenting the voluntary informed consent. Conventionally, this could involve multiple site visits, which may be a deterrent to participation. In a virtual clinical trial, technology is used to aid the consenting process. For example, participant information sheets may be e-mailed to the subject or made available on a digital platform; discussions happen through a tele-or videoconference and finally, the participant either electronically signs the consent form or signs a physical copy at home and mails it back to the investigator.

Administration of study interventions

Participants visit research sites to receive study interventions. Depending on the frequency of administration and complexity of the intervention, this could take a significant amount of the participant's time. In a virtual trial, various techniques could be used to obviate the need for site visits. For oral medications, the drugs may be directly delivered to the participant by research staff, a courier or mail, or picked up by the participant from a location near their residence. For parenteral medications, participants could visit medical centers close to their house, or have research nurses visiting them at home.

Care of study participants

Trial participants need periodic assessments and continued medical care to ensure compliance to the trial protocol and allow early identification of any toxicity. In a virtual trial, the care of participants is outsourced to medical facilities located close to the participants. The researcher obtains information from these local centers through access to electronic records. In addition, the research team can employ other methods such as home visits by research nurses or the use of tele-or video consultations to keep track of participants. The choice between these modes of assessment depends on the nature of the intervention in the trial as well as the data to be collected, for example., whether these can be recorded by the participant herself or need measurement by another person.

Similarly, several modalities are available to monitor adherence to trial medication(s).

Assessment of efficacy and safety outcomes

Timely and reliable assessment of both efficacy and safety outcomes is one of the most important aspects of a research study. Virtual trials use various ways to allow study outcomes to be assessed without site visits. Clinical outcomes can be assessed periodically either at local centers or during home visits by a clinical team. Study outcomes can also be planned such that participants can self-report their data – for example, home glucose testing by finger prick method or urine sampling for proteinuria. Several modern devices such as fitness bands and sleep trackers provide continuous real-time data on physiological parameters, and can be programmed to directly relay information to the research team. Outcomes involving questionnaires can be administered through e-mail, telephone, or video consult by

a member of the research team. Laboratory and radiological parameters can be assessed at facilities located close to the participant. From these facilities, test results can either be reported using standard formats, or the samples/images can be sent to a central facility for reporting by a study investigator (to ensure uniform assessment).

Study monitoring

Monitoring of clinical trials is critical to ensure compliance with the study protocol, prevent harm to participants, and ensure that data are reliably captured. Methods of remote monitoring include accessing trial documents through e-mail or videoconferencing tools, or allowing monitors to access electronic medical records remotely. Risk-based monitoring is another adaptation which allows monitors to move away from 100% source data verification and reduce the intensity and volume of monitoring by focusing on areas at high risk for errors.[5]

ADVANTAGES OF VIRTUAL CLINICAL TRIALS

Virtual clinical trials offer several benefits. They decrease the need for site infrastructure and staffing, thereby reducing trial costs. They broaden the spectrum of participants who can participate in the trial. This serves to increase the generalizability of the trial results through the inclusion of more diverse participants as well as improve trial accrual. By obviating repeated site visits, participant compliance and retention are enhanced and the timeliness of measurements may improve. The need for decentralized trial operations provides real-world data on the efficacy of interventions. Innovative methods of data collection also provide continuous real-time data rather than data at specific time points and allow earlier identification of adverse events.

CHALLENGES IN CONDUCTING VIRTUAL CLINICAL TRIALS

Virtual trials are heavily dependent on the availability of technology such as access to the Internet and familiarity with web-based applications. This may itself, counterintuitively, lead to the exclusion of certain groups of participants. Virtual trials may not be suitable for all types of clinical trials – for example, early phase trials and trials investigating complex or potentially-toxic interventions, which may require specialist care, are best carried out as site-centric studies. The dependence on digital methods for processes such as consenting, data transfer, and data storage (e.g. in the cloud) raises issues of participant confidentiality and data privacy. The remote delivery of study interventions is dependent on supply chain logistics, and drug efficacy may be affected by storage and handling conditions. Similarly, quality control is essential when relying on local laboratories or imaging centers for study assessments.

EXAMPLES OF VIRTUAL CLINICAL TRIALS

Orri *et al*. describe a virtual clinical trial investigating the efficacy and safety of extended-release tolterodine in participants with overactive bladder (the REMOTE trial).[6]

The research team recruited participants through the Internet, screened them for eligibility using web-based questionnaires, performed laboratory testing at community facilities, and maintained initial run-in data using electronic diaries. Physical examinations were performed by local physicians. An interactive web-based method was used to obtain informed consent countersignature by the physician. Study medications were shipped directly to the study participants.

The VERKKO trial was a Phase IV clinical trial in persons with diabetes that assessed the use of a patient-centric online clinical trial platform integrated with a wireless blood glucose meter in a virtual clinical trial setting.[7] The study involved no site visit at all. The participants were invited through advertisements on social media to self-register their interest in an online system, and their applications were reviewed online by the study team. Selected participants reviewed electronically provided patient information before digitally signing the informed consent form, and had 3G-capable, wireless glucose meters directly delivered to them. Glucose measurements were automatically transmitted from the device into a digital application for real-time review by the participants and the study site. Performance indicators from this study were compared with those of a similar protocol which was carried out as a traditional site-centric study. The virtual trial showed better participant recruitment, the ability to include elderly participants, improved compliance, and excellent participant satisfaction. Furthermore, the study site reported having spent less time on the study coordination activities. Thus, both the participants as well as the researchers found this virtual trial to be useful.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kadakia KT, Asaad M, Adlakha E, Overman MJ, Checka CM, Offodile AC 2nd. Virtual clinical trials in oncology-overview, challenges, policy considerations, and future directions. JCO Clin Cancer Inform

2021;5:421-5.
2. Loucks TL, Tyson C, Dorr D, Garovic VD, Hill J, McSwain SD, *et al*. Clinical research during the COVID-19 pandemic: The role of virtual visits and digital approaches. J Clin Transl Sci 2021;5:e102.
3. McDermott MM, Newman AB. Remote research and clinical trial integrity during and after the coronavirus pandemic. JAMA 2021;325:1935-6.
4. National Guidelines for Ethics Committees Reviewing Biomedical and Health Research during COVID-19 Pandemic. Indian Council of Medical Research; April, 2020. Available from: https://t.co/5P3ckgUE59. [Last accessed on 2022 Aug 27].
5. Jaguste VS. Risk-based monitoring: Review of the current perceptions and toward effective implementation. Perspect Clin Res 2019;10:57-61.
6. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. Contemp Clin Trials 2014;38:190-7.
7. eClinicalHealth Announces Successful Results for an Entirely Remote Online Clinical Trial. Available from: http://www.businesswire.com/news/home/20160621005604/en/eClinicalHealth-Announces-Successful-Results-Remote-Online-Clinical. [Last accessed on 2022 Aug 26].