

Digital clinical trial: A new norm in clinical research

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Abstract

The advent of digital technologies has been well blended with every aspect of human lives. Despite not being a new concept, the adoption of digital health technologies in clinical research, i.e., digital clinical trial has not been utilized extensively. However, with the prevailing COVID-19 pandemics, such transformation in clinical trial seems imminent. Few components of a trial such as consent, remote site monitoring, recruitment process which can be modified through digital technologies, are further specified by the regulatory authorities such as FDA and EMA. However, such novel method cannot be implemented without facing any limitations. All stakeholders pertinent to virtual clinical trial including the provider of digital technologies should align themselves with the patient-centric approach to propagate this concept. It is expected that such a transition is well accomplished and adopted by the sponsors without any compromise in scientific as well as ethical standard.

Keywords: Clinical trial, digital technology, remote consultation

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INTRODUCTION

A clinical trial includes a systematic study of any new advancements in health care, experimented on human participants; representative of the target population. A wise simulation of trial setting to clinical practice should be ascertained to facilitate sound clinical decision-making. The success of any such trial is attributed to the complex scientific methodology involving sophisticated steps conducted over the years. From an ethical perspective, the basic aim of such clinical trial involves overall benefit to patients (Beneficence) while averting any kind of harm (nonmaleficence). Despite some of the instances of setbacks encountered, adherence to such scientific standard as well as ethical integrity remains a priority for all the stakeholders involved, i.e., regulatory bodies, sponsor, investigators, and contract research organization (CRO).

Advancement in digital technology has transformed the traditional concept of the clinical trial to a newer and underutilized method such as virtual/decentralized clinical trial. The site-based model of a clinical trial includes steps such as on-site patient visit, recruitment, interventions, or any diagnostic workups by investigators team at a specified time interval. Given the current COVID 19 pandemic crisis, such a conventional approach can be jeopardized due to restriction in travel, social distancing, and less physical contact. In any virtual clinical trial, such steps can be executed through novel technologies involving telemedicine, e consenting, or remote site monitoring methods such as apps or electronic devices. Therefore, the adoption of such digital health technologies would foster the transformation of a conventional design aided by necessary investment along with regulatory support.

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BASIS AND THE UNMET NEED

Most of the stakeholders including regulatory bodies are comfortable with the traditional model of any clinical trial. However, the complexity incorporated in any such model would culminate into some of the undesirable consequences. Patient recruitment is one of the key problems in the execution of a conventional trial resulting in scarce participation of the eligible individual. A population-based analysis, as well as an online survey carried out by various organization, reflected such gap in recruitment (<10% of the targeted population).^[1,2] Inadequate enrolment is faced by almost 80% of the trials, hence early termination in phase 3 studies (~30%) ensue.^[3] Concomitantly, such limitation can pose quality compromised health decision attributed to the paucity in scientific evidence generation as well as a loss of revenue for the pharmaceutical industry.

Such aforementioned issues can be abated by the implementation of voluntary counseling and testing (VCT), which is well-aligned with participants need. Some of the consumer-friendly technologies, i.e., smartphones can allow any participants to take part in any trial from their comfort zone, i.e., own residence, workplace. Moreover, wearable or in-home sensor devices can provide objective data (i.e., any vital signs, parameters like continuous glucose monitoring); supplemented with subjective data (i.e., patient-reported outcome). Hence, such integration would simulate real-world evidence in the absence of potential bias attributed to data collection or human error. Digitization in the trial will also obliterate geographical limitation to hasten patient recruitment. Very few numbers of study site are involved to conduct trial digitally, hence less requirement in workforce and resource is ensured. Moreover, procedures such as a home visit by nursing and community staff, microsampling, and any mobile health-care facilities pertinent to the trial procedure including shipping of trial medication can complement digital tools and technologies used in VCT.^[4] The salient difference of VCT with a conventional clinical trial is depicted in Table 1.

EXAMPLES OF VIRTUAL CLINICAL TRIALS

The model, although not being practiced extensively, is not a new concept either. In 2001, a randomized study by Eli Lilly for assessing safety and efficacy of tadalafil in erectile dysfunction was the very first trial to include a digital component. A better trial experience was stated by most of the participants who previously were participants of a conventional clinical trial. Components such as informed consent, data collection, and storage of such data in a safe web-based repository were adequately adjudged.^[5]

Subsequently, REMOTE trial was conducted by Pfizer in 2011–2012 to assess efficacy and safety profile of extended-release tolterodine applied in patients of overactive bladder. Tools like online screening through web-based questionnaire, online informed consent, and e-diaries were used. Study result concluded similar safety and effectiveness compared to that of conventional trial executed by the same methodology. Some of the unique characteristics of virtual design, i.e., shipping of study medication to their residence, continuous online physician (i.e., investigator) availability and sharing of trial data for any kind of use by patients in future, ascertained better trial experience among participants.^[6] Subsequently, Sanofi completed a remote phase 4 diabetes management trial (2014-2015) VERKKO trial, in Finland using a wireless glucometer. Relevant data such as blood glucose profiling by glucometer were automatically linked to an online database system for review by patients as well as investigators. The study was deemed better as it was better accepted in study participants prompting timely completion in the study (faster glucose profiling by patients and less time in study coordination) in comparison to the traditional model.^[7] Moreover, a justified sample size was achieved with fewer dropouts than the conventional design.

MODIFICATION OF CONVENTIONAL DESIGN: REGULATORY PERSPECTIVE

Due to the ongoing COVID-19 pandemics, there have been extensive reports of termination as well as delays in ongoing trials globally. Most of the impedance was attributed to postponement of enrolment followed by slow enrolment and delay in initiation.^[8] Paucity in the availability of research sites paved the way for slow enrolment due to the overwhelming presence of COVID-19 patients in many of the health-care facilities. As a consequence, COVID-19 drug intervention or repurposing trial take precedence for most of the investigators, prompting deficit in their numbers for other trials.^[8]

The predominance of such issues in the context of maintaining patient safety has been acknowledged by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).^[9,10] The issue has been further aggravated by paucity in resource attributed to the strain over the supply chain and incapability of sponsors to conduct study visits. Digitization of trial could well be utilized to counteract the aforementioned situation. Therefore, three critical steps of any trial have been specified by the FDA and EMA that can be predisposed to the virtual modification.

Table 1: Salient differences in between conventional and virtual clinical trial

Key features	Conventional	Virtual
Available study participants	Local to study site	No limit
Screening	Telephone call or study site visit	Online questionnaire
Informed consent	On-site	Online, i.e., eConsent
Physical examination	On-site	Teleconsultation
Laboratory testing	On-site	Microsampling, home-kit, mobile facilities
Dispensing medication	On-site	By shipping or mobile health care facilities
Data collection	On-site by study team	Mobile device or automated sensor
Trial monitoring	Multiple sites	One or two remote coordinating center
Expected participation and retention	Lower	Higher
Participant safety in pandemic like situation	Less	More
Time	More	Less
Cost	Cost-effective	Costly

Patient consultation

As protocol-specified study visits being not feasible, on-site subject consultation should be substituted with any alternatives deemed appropriate by the sponsors. These approaches can be teleconsultation through a virtual platform, arrangements of at-home visits by a local physician or mobile research nurses to conduct protocol-specified procedure, i.e., collection of specimens, monitoring vitals or any procedures leading to proper data capture, shipping of study equipment directly to the patient.

Patient consent

Obtaining and documentation of an appropriate informed consent are deemed as a critical step in any trial from an ethical perspective. Conventionally, it is done on a study site by investigators i.e., ink-on-paper signature. However, eConsent can be incorporated by the sponsors if permitted by the local country regulation and/or the site ethics committee. Online questionnaire can be applied before acquiring consent to check for compatibility as well as an understanding of trial procedures and objective among study subjects. Alternatively, participants can be allowed to ask questions as well as provide their feedback simultaneously to simulate a real-world two-way communication interface.^[11] For example, the utilization of audiovisual consenting procedure might help in India to facilitate such communication.

Site monitoring

The responsibility of sponsors is to keep monitoring various study sites to assure the quality and operational standards being maintained accordingly. However, such study visits can be restricted in future. Various remote study coordination center can replace such activities where remote access to all relevant documents can be accessed by stakeholders including sponsors, Institutional Review Board, and CRO.

LIMITATION

Despite some of the promises put forth, there are definite challenges that need to be addressed precisely.

Patient compliance

The compliance issue of the participants with digital tools needs to be considered throughout the ongoing trial. For the elderly population, recruitment and further formalities may be an arduous task as they are more adapted to human interaction and interpersonal relationship.^[11] Moreover, some of the digital platforms are not extensively used by them, unlike the younger generation. However, few of the trials were completed involving older participants specifying that innovative technologies used in virtual trials can be aligned to the need of participants who are not digitally adapted a priori. For example, the average age of participants in VERKKO trial was above 50 with several participants being older than 70 years.^[7]

Multistep and time-consuming verification procedure can lead to very less sample size due to the compromise in patient acceptability.^[6] Therefore, the screening procedure before study enrolment should also be simplified and user friendly.

Regulatory perspective to maintain subject confidentiality

Acceptability to any conventional clinical trial is based on inherent trust built in between physician and patients, which is further governed by strong ethical principles. However, there is paucity in legal documents or regulation in case of commercial providers of digital tools or health-related technologies. This can prompt such authorities to share confidential data without any consent of the participants.^[12] Many of the defensive strategies like storage of anonymized data secured by user id and password, secure webmails by a trusted provider can be adopted. Therefore, keeping the privacy of any confidential data is a priority without any compromise in the accuracy and reliability of the collected data required for clinical research. Regulatory guidance similar to that of HIPAA in the USA or GDPR in the EU can be promulgated to ensure the confidentiality of private data used in health care.^[11] Regulatory guidance, currently in a very nascent stage, needs to be more sophisticated to

approve VCT for development in any novel pharmaceutical compounds.

Prioritization of independent research organization

As previously discussed, the key components such as patient recruitment, consultation, and follow-ups can be taken care of by many CRO deployed by sponsors. Any innovative solution for such aforementioned activities, provided by CRO, can well be incorporated by sponsors into pertinent trial activities. For example, reaching out to participants living in a remote area or any resource compromised surroundings by providing innovative approaches pertinent to the trial objective.^[12]

VCT is not applicable in some of the clinical research setting or scenario. It cannot be utilized in phase I trial where close safety monitoring is done over the clock. Virtual tools cannot be used in case of requirement of a sophisticated set up like trial done in an intensive care unit for life-threatening disease. It can also be not ideal in a situation where imaging examination or physical examination cannot be carried out by allocating remote health staff for home-visits.

Perspective and challenges in India

The development of any novel therapeutics for a range of disease condition is well justified in India harboring nearly 1.3 billion population with diversity in various aspects. Subsequently, with the adoption of newer technologies, the clinical trial market size is expected to attain a share of USD 3.5 billion by 2025.^[13] As digital progress in healthcare technology is well poised to spurt, certain issues need to be addressed during implementation.

Most of the physicians including investigators in a trial are well comfortable with the conventional site-based method of consultation. However, during the recent ongoing pandemic, practice in teleconsultation has been prevalent in the country, prompted by telemedicine guideline put forth by MoHFW in March 2020.^[14] Despite physician, other key stakeholders including sponsors, ethics committee, regulatory bodies should well be properly acquainted with any digital transformation related to their activities. Formal training program including webinars or workshops must be conducted at regular intervals to serve such purpose. Similarly, education and awareness of the target population of any such trial must also be a priority to enable them well compliant with the procedures. For example, the demonstration of any tools or wearables by community health staff or ASHA workers, video conference, or distribution of leaflets about how to use any specific digital tools. This procedure should be a long-term

activity concomitant with acquiring proper feedback from the target population. Technological advancement, another key issue, should be strengthened simultaneously. For example, the establishment of smooth internet access in remote areas of the country. Larger IT companies should jointly collaborate with various government agencies to figure out scrupulous execution of such a plan in upcoming days.

So far, the regulatory authority of our country has been trying to up to par require standards. There have been instances of extensive engagements on the use of such technologies with various agencies, which have been discussed by DCGI in many scientific forums. A guideline proposed by ICMR in April 2020 encouraged the use of technology for study participants like information of study related activities through webcast or video conference; obtaining eConsent by digital signature.^[15] It has also encouraged the submission of electronic document for EC review as well as a potential replacement of on-site EC meeting by video conferencing.^[15] However, unlike FDA and EMA, there is paucity in information or guideline related to other pertinent activities such as patient recruitment, study visits, or data collection.

However, the digitization of health care in the country is expected to thrive, prompted by the launch of national digital health mission.^[16] The existent fragment data will be streamlined through unique health ID for every citizen in the country. It will pave the way for a larger and diverse data pool, i.e., electronic health record that can be utilized by any sponsors for conducting any R&D activities. It will further enthruse collaborative and scientific exchange of any such data in between different sectors for the sake of innovation. However, adequate security and privacy of such data pool must be ascertained. The government should introduce any data privacy law (like HIPAA as previously discussed) or guideline to utilize such data in productive ways.^[16]

COMMENTS

Digital health technologies, despite being underutilized, are poised to be an acceptable solution to transform the conventional clinical trial. However, various limitations need to be addressed properly for successful implementation in the impending future. A complete re-innovation of infrastructure, as well as stronger resolution for change among all stakeholders, must be ensured. Rather than research site, paradigm shift into better participant centric clinical trial experience should be adopted to ascertain better propagation of such design.

The recruitment and trial intervention will enable participants to be treated at home. Therefore, it will be replicative of true treatment experience in a real-world setting. As previously discussed, various patient-reported outcomes (i.e., quality of life parameters) will be captured which is not otherwise done in the conventional setting. Moreover, digital recruitment will attract a diverse and larger patient pool unlike the homogeneous pool recruited in a conventional clinical trial. All these factors will advocate enriched evidence generation, drifting toward generating real-world effectiveness experience rather than a sole efficacy and safety data in a sophisticated and controlled setting. The former effectiveness data are generally captured through diverse postmarketing studies conducted for a longer time. Hence, the virtual trial will supplement such studies earlier in the development stage as well as align any such studies to be done in a timely and convenient way in the future. With the prevailing crisis of COVID-19 pandemics, VCT can be a crucial alternative, acceptable to most of the clinical researchers or sponsors globally.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Anderson A, Borfritz D, Getz K. Global public attitudes about clinical research and patient experiences with clinical trials. *JAMA Netw Open* 2018;1:e182969.
- Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *JAMA* 2004;291:2720-6.
- Carlisle B, Kimmelman J, Ramsay T, MacKinnon N. Unsuccessful trial accrual and human subjects protections: An empirical analysis of recently closed trials. *Clin Trials* 2015;12:77-83.
- von Niederhäusern B, Saccilotto R, Schädelin S, Ziesenitz V, Benkert P, Decker ML, *et al.* Validity of mobile electronic data capture in clinical studies: A pilot study in a pediatric population. *BMC Med Res Methodol* 2017;17:163.
- Eilenberg KL, Hoover AM, Rutherford ML. From informed consent through database lock: An interactive clinical trial conducted using the internet. *Ther Innov Regul Sci* 2004;38:239-51.
- 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.
- National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation; Shore C, Khandekar E, Alper J, editors. *Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop*. Washington, DC: National Academies Press (US); 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548975/>. [Last accessed on 2020 Jul 26].
- Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER, *et al.* Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal J Epidemiol* 2020;10:878-87.
- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. US Food and Drug Administration; 2020. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>. [Last accessed on 2020 Jul 20].
- Guidance on the Management of Clinical Trials during the Covid-19 (coronavirus) Pandemic. European Medicines Agency; 2020. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. [Last accessed on 2020 Jul 20].
- Ali Z, Zibert JR, Thomsen SF. Virtual clinical trials: Perspectives in dermatology. *Dermatology* 2020;236:375-82.
- Steinhubl SR, Wolff-Hughes DL, Nilsen W, Iturriaga E, Califf RM. Digital clinical trials: Creating a vision for the future. *NPJ Digit Med* 2019;2:126.
- Indian Clinical Trials Market Analysis Report by Indication (Oncology, Autoimmune), By Phase (I/II/III/IV), by Study Design (Interventional, Observational), Vendor Landscape, and Segment Forecasts, 2018–2025. Grand View Research; 2018. Available from: <https://www.grandviewresearch.com/industry-analysis/india-clinical-trials-market>. [Last accessed on 2020 Sep 04].
- Telemedicine Practice Guidelines. Board of Governors in Supersession of the Medical Council of India; 2020. Available from: <https://www.mohfw.gov.in/pdf/Telemedicine.pdf>. [Last accessed on 2020 Sep 04].
- National Guidelines for Ethics Committees Reviewing Biomedical & Health Research during COVIDs-19 Pandemics. Indian Council of Medical Research; 2020. Available from: https://ethics.ncdirindia.org//asset/pdf/EC_Guidance_COVID19.pdf. [Last accessed on 2020 Sep 04].
- Ozair FF, Jamshed N, Sharma A, Aggarwal P. Ethical issues in electronic health records: A general overview. *Perspect Clin Res* 2015;6:73-6.