



A Review on Virtual Clinical Trials: The Future

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ABSTRACT

A clinical trial is a study designed to demonstrate the efficacy and safety of a drug, procedure, medical device, or diagnostic test. Since clinical trials involve research in humans, they must be carefully designed and must comply strictly with a set of ethical conditions. Logistical disadvantages, ethical constraints, costs and high execution times could have a negative impact on the execution of the clinical trial. Rapid innovation in health and health care technologies, interventions, and products require the proliferation of rigorous clinical trials to evaluate their efficacy and effectiveness. To meet these needs, the field has been slowly moving toward increasing adoption of virtual clinical trials. VCTs use tech devices and social engagement platforms to conduct trials from a patient's home. These electronic processes offer new opportunities for a patient-centric approach to clinical research. So that the participant does not require travel to a clinical research site. The subject can participate from home using mobile device or a wearable gadget (maybe a phone, watch, or even glasses) is linked to the clinical research study. These wearable sensors record data such as body temperature and blood glucose levels, Spo2, Heart rate, Sleep cycle which are sent automatically to the study electronic data capture (EDC) record. The subjects are recruited through notifications instead of newspapers or doctors clinic, informed consent (Eligible participants are selected through screening followed by e-consent which is a set of Presentations followed by questionnaires to the participants), patient counseling, through to measuring clinical endpoints and adverse reactions (ADRs are reported to Adverse event reporting system). To conclude, until now VCTs have been used in Phase II-IV trials. Results from these trials have shown promising results. Besides, it has also been able to meet the goal of the pharma industry (low risk and high return) when conducting clinical trials.

Keywords: Virtual Clinical Trials, Decentralised trials, Patient centric trials.

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INTRODUCTION

A clinical trial is a study designed to demonstrate the efficacy and safety of a drug, procedure, medical device, or diagnostic test. Since clinical trials involve research in humans, they must be carefully designed and must comply strictly with a set of ethical conditions. Logistical disadvantages, ethical constraints, costs and high execution times could have a negative impact on the execution of the clinical trial. ¹Rapid innovation in health and health care technologies, interventions, and products require the proliferation of rigorous clinical trials to evaluate their efficacy and effectiveness. To meet these needs, the field has been slowly moving toward increasing adoption of virtual clinical trials (VCTs). These generally involve evaluating the effect of a clinical intervention (often a pharmaceutical product) within research participants' own settings, as opposed to a clinical trial site. Virtual trials are defined as clinical trials in which all or part of the study incorporates digital health technologies and

enables remote participation outside of the traditional brick-and-mortar study sites. These are also known as "decentralized," "remote," "site agnostic," "direct-to-participant," "location flexible," "mobile," "flexible,". VCTs models can reduce costs, shorten trial timelines, increase protocol adherence, and boost recruitment numbers and participant diversity, while simultaneously allowing for continuous real-world data collection in the context of real-life settings and events. ²⁻³

Clinical drug development is a time-consuming and complex process that takes around 6–15 years. ⁴ The cost of developing a new drug, from research and development to marketing approval, is approximately USD 2.6 billion. ⁵ Approximately 85% of therapies fail through early clinical development, and only half of those reaching phase 3 are approved. ⁶ Patient recruitment is the single biggest cause of clinical trial delays, and 30% of phase 3 study terminations are due to enrollment difficulty. Approximately 80% of trials fail to meet the initial enrollment target and timeline. ⁷ These delays can result in up to USD 8 million per day in lost revenue for pharmaceutical companies. Additionally, nearly USD 6 billion annually is spent on patient recruitment. Moreover, less number of the eligible population in the world participate in clinical trials, and those who do participate attend an average of 11 visits at the trial site in 6 months. ⁸



Virtual clinical trials are a relatively new and underutilized method of conducting clinical research using technologies (apps, electronically monitoring devices, etc.) and online social engagement platforms. VCT are not a new or separate type of clinical trial but a modification of clinical trials that makes trials cost-effective, timesaving, and easier for the participants.⁹ With the use of digital health technologies, VCT manage to recruit faster, improve retention, and increase participant diversity and representation.¹⁰⁻¹¹ In conventional clinical trials participants are recruited through hospital visits, medical clinics, or using media such as newspaper/radio/television ads. Moreover, the target populations are often limited by their geography. In VCT recruitment is targeted directly to the patient by web-based platforms (e.g., Google search engine), without geographical limitation, reaching potential eligible patients worldwide. Patients can sign up, add additional information, and answer questionnaires about demographics, disease history, and geographical location on specific websites. To fulfil the inclusion criteria and to confirm the diagnosis some online recruitment platforms require image upload of target lesions, i.e., photos of body parts affected, for example, by acne, atopic dermatitis, or psoriasis. This kind of recruitment initiative is very appealing as 80% of internet users are seeking healthcare information.

Furthermore, running online campaigns compared to newspaper/radio/television ads, allows: flexibility as one can turn a campaign on or off at a moment's notice, proper tracking in place can specifically target actual leads (i.e., atopic dermatitis searches only), and it may be cost efficient with a lower cost per patient than traditional media. Informed consent is given remotely if allowed by the national/ state ethical review board.¹² An online questionnaire can test the participants' understanding of the informed consent. In addition to the online information the participants have the opportunity to ask questions and discuss relevant topics with the investigator through a phone or online video call before giving the consent.¹³⁻¹⁴ Furthermore, a limited number of study sites are involved in VCT, led by principal investigators whose team review all the data as they are reported in real time to monitor the health and safety of the participants. Studies are managed centrally by a remote study coordination center facilitating all research activities. This is different from conventional clinical trials with many study sites and study teams which contribute to the increased expense.¹⁵

Methodology

Virtual clinical trials use tech devices and social engagement platforms to conduct trials from a patient's home. These electronic processes offer new opportunities for a patient-centric approach to clinical research. So that the participant does not require travel to a clinical research site. The subject can participate from home using mobile device or a wearable gadget (maybe a phone, watch, or even glasses) is linked to the clinical research study. These

wearable sensors record data such as body temperature and blood glucose levels, Spo2, Heart rate, Sleep cycle which are sent automatically to the study electronic data capture (EDC) record. In some VCT, the investigator visits the subject home for drug administration and follow-up. When a visit is approaching, the mobile device provides automated reminders to the participants, allowing the participant to reschedule the appointment within a time frame permitted by the study protocol. And that's just the beginning of what the future is likely to hold for so-called virtual clinical trials. Virtual clinical trials represent a relatively new method of collecting safety and efficacy data from clinical trial participants from their own location. These trials take full advantage of technologies (apps, monitoring devices, etc.) and online social engagement platforms to conduct each stage of the clinical trial from the comfort of the patients home--including recruitment (The subjects are recruited through notifications instead of newspapers or doctors clinic, informed consent (Eligible participants are selected through screening followed by e-consent which is a set of Presentations followed by questionnaires to the participants), patient counseling, through to measuring clinical endpoints and adverse reactions(ADRs are reported to Adverse event reporting system). By relying on electronic processes, many argue that virtually conducted clinical trials offer opportunities for a more patient-centered or a centric approach.

Previous and Ongoing VCT:

- The first study to have a virtual element was a randomized study of the efficacy and safety of tadalafil for the treatment of erectile dysfunction by Eli Lilly in 2001. In addition to traditional study visits to the clinical sites, the participants were invited to fill out an online questionnaire. In a post-study survey, 77% of patients with traditional clinical trial experience indicated that the VCT was better than a traditional trial.
- In 2011, Pfizer pioneered the virtual clinical trial model with its Research On Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial. The REMOTE trial was the first randomized clinical trial using web- and smartphone-based patient recruitment, enrollment and collection of study data without requiring patients to visit a physical study site. One of the main goals was to compare the virtual approach to a conventional Phase IV clinical study in order to determine if the virtual trial design would be a feasible way to conduct future trials.
- The REMOTE trial was a randomized, phase 4 trials to test a novel web-based trial design for evaluating the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder.¹⁶ The physical examination was carried out by a local physician. To verify participant identification and minimize fraud, secure and confidential third-party (IDology, GA, USA) online identity verification was used. The informed consent process consisted of an online automated slide



presentation following a multiple-choice test. Participants were subsequently contacted by the investigator's study staff for a telephone discussion about the trial and review of the informed consent details. Nevertheless, the results indicated that the study was just as safe and effective as a traditional clinical trial.¹⁷

- Sanofi conducted a virtual diabetes trial (VERKKO) to be conducted remotely in Europe. This virtual clinical trial has one key difference compared to Pfizer's REMOTE study in that no drug is being tested. Instead, Sanofi has teamed up with three other organizations to test a 3G-capable, wireless glucose meter. This trial represents significant advancement in the clinical trial community, as it is the first clinical trial using an electronic informed consent approved by European regulatory agencies.¹⁸
- The VERKKO trial was conducted with a "sister protocol" in which a second trial was conducted in a traditional manner with in-person visits and training at the trial site. This allowed a direct comparison of traditional trial with the VCT. Seventy-four participants were recruited online, of whom 60 were enrolled in the

study. The average age of the participants was 56 years. All age groups reported a consistently positive experience. Besides the high patient satisfaction rates the study also reported reduced study coordination activities, faster study completion, and increased patient retention rates. The entire study was managed primarily between a single investigator and a study nurse, and the study site estimated having spent 66% less time engaged in study coordination activities. The VERKKO trial showed that patient compliance improved 18%, the study site spent 66% less time engaged in study coordination activities, and the online recruitment was completed 56% faster compared to the traditionally conducted trial.¹⁹⁻²⁰

- VCT are also used to get better data directly from real life, allowing for more effective development of medicines. GlaxoSmithKline conducted the Patient Rheumatoid Arthritis Data from the Real World (PARADE) study in 2016.²¹ The study was conducted using a downloadable iPhone application to collect and track common symptoms of rheumatoid arthritis through iPhone sensors for 300 patients over a 3-month period.

Table 1: Previous/on-going clinical trials:²²

Sponsor	Year	Phase	VCT/Hybrid	Details	Subjects enrolled
Duke University	2016–2020 (estimated)	NA	VCT	Compare the effectiveness of two doses of aspirin to identify the optimal dose for secondary prevention in patients with atherosclerotic cardiovascular disease	15,000
Hoffmann-La Roche and Genentech	2015–2019 (estimated)	Phase 3	Hybrid	Evaluate the efficacy and safety of rituximab compared with mycophenolate mofetil in participants with pemphigus vulgaris	135
Eli Lilly	2017–2018	Phase 4	Hybrid	Estimate missed bolus insulin doses in diabetics	79
AOBiome	2017	Phase 2b	Hybrid	Topical Probiotic spray for mild to moderate Acne	372
PellePharm	2016-2017	Phase 2	Hybrid	Topical patidegib for basal cell carcinomas (Gorlin syndrome)	36
Sanofi	2014-2015	Phase 4	VCT	Remote system to diabetes management	60
Pfizer	2011-2012	Phase 4	VCT	Efficacy and safety of Tolterodine ER 4mg in patients with Overactive Bladder	18

ADVANTAGES OF VIRTUAL TRIALS:

- Virtual clinical trials have many advantages over the traditional model, which uses multiple study sites and requires multiple patient visits to the site in order to conduct the study protocol. The main advantage is that the virtual trial design maximizes patient availability and enrollment in the study. Because patient recruitment and enrollment is often the longest stage

of a clinical trial with almost 80% of trials failing to meet initial targets. Unlike site-based clinical trials, which require frequent visits to a research facility, remote clinical trials are based from the patient's home so those with mobility issues, such as the elderly or patients who live in rural areas--are also able to participate in the trial.



- The convenience of a virtual methodology will increase numbers of patients willing and able to enroll. Also, electronic health records can help identify increasingly targeted trial subjects and online patient support networks which could be used more to raise awareness of trials and directly recruit subjects. Another advantage to virtual trials is their potential to keep subjects engaged with the study. As many as 40% of Phase III trial subjects become disengaged and drop out of the study. Some of the causes of this attrition are related to convenience--due to issues like the inconvenience of traveling to study sites, or the complexity of the trial design and data collection.
- Virtual clinical trials could remove the need for frequent travel to study sites and automate data collection, increasing patient engagement and retention.
- Virtual trials also offer the ability to reduce risk in the drug development process. Data from remote monitoring devices could be accessed by trial investigators in real time.
- Remote monitoring capabilities could thus facilitate an adaptive clinical trial approach, allowing improvements in trial design based on the accumulating data. Decisions to terminate a drug's development could also be made faster, improving patient safety and reducing expenditure on failed trials that have unfortunately become the norm in the drug discovery process. Potentially leading to better data quality and shorter timelines.

Contrast between Traditional Research and Virtual Trials:

In traditional research approaches, data are collected via direct assessment of study subjects at study sites, while virtual approaches eschew direct observation in favour of remote data capture via connected devices wherever patients happen to be. Patient identification can be facilitated by geo-targeted digital recruitment, such as pop-up ads on social media outlets and internet search engines. Patient eligibility can be ascertained by including electronic medical records access in the consenting process, thereby permitting the study team to contact the patient's healthcare provider to confirm diagnosis, medical history, medication use. And smartphone apps can be programmed with reminders as well as gamification elements to ensure that patients continue to transmit data and stay engaged throughout the study duration. (See Table: 2)

REGULATORY ACCEPTANCE:

The pandemic has forced researchers to think of alternatives and shift to virtual trials. In March 2020 FDA issued its guidance on ways to conduct trials during the pandemic. In this statement FDA encouraged sponsors to start assessing alternative methods for keep going on the track within the existing limitations of COVID-19. This paved the way for Virtual Clinical trials in the Clinical trial Arena.²³ A VCT is as new to the regulatory body as it is to a sponsor.

Thus in terms of novelty, it imposes equal challenges to regulatory authorities as it does to a pharma company. In this respect, the USFDA is looking for inputs for the following issues: how to encourage the adoption of technological tools in clinical trials; what are the barriers to a VCT; how a VCT will influence patients, and eventually the regulatory requirements.²⁴

Table 2: Difference between Conventional clinical trials and virtual clinical trials

	Conventional clinical trials	Virtual clinical trials
Recruitment method	Hospital, medical clinics, newspaper	Web based, e.g., social media
Available patient population	Local (near the study site)	No limits (worldwide)
Pre-screening	Telephone calls	Electronic questionnaire
Study sites	Many	Few (site-less)
Patient visits	Many (in person)	Less frequent (home-based patient)
Informed consent	In person	E-consent
Trial activities, e.g., education, information		Videoconference, telehealth
In person at study site		
Physical examination	At study site	By photos, remote visits, in-home nurse visits
Laboratory testing	At study site	Micro sampling, home-kit, mobile phlebotomist, clinic local to patient
Medical imaging	Study site	Clinic local to patient
Data collection	Collected by study team	Mobile device, e.g., phone, apps, watch, electronic patient reported outcomes, e-diaries, interactive response technology
Dispensing of medications	At study site	Shipping drugs to home
Outcomes	Collected via study team	Electronic clinical outcome assessment collected through connected digital tools, e.g., digital biomarkers



LIMITATIONS OF VCT

However, inspite of all these advantages there are some limitations:

- There is a potential concern about patient data. Privacy and data protection steps have to be taken or data should be stored in the server in encrypted format.
- Elderly patients are not familiar with usage of technology is a major concern that greatly impacts the trial and data that it generates.
- The lack of human interaction in the recruitment process can be a barrier, predominantly in patients with high age that need a personal relationship to get involved in a trial. However, Sanofi's trial was successful in recruiting participants using the same strategy and the average age of the recruited patients was 60 years, indicating that modern technology used in VCT does not exclude participation of the elderly.¹⁹
- The self-enroll concept can lead to recruitment of a convenience sample of the population that may differ from the general population in terms of certain demographic or disease-related characteristics, making the results less generalizable. However, combining different methods of recruitment can improve the generalizability of the results.
- Concerns over transferring large amounts of sensitive health data over the internet can be a challenge, but proper implementation of technologies and defense strategies like storing anonymized data on external web servers secured by ID and password, using secure web mails, and web servers hosted by trusted providers will minimize this risk to an acceptable level.²⁵ The privacy of the recruited participants must be guaranteed.
- On the other hand, integrity, accuracy, and reliability of the collected data from electronic health records, mobile devices, and wearable sensors are necessary. Some companies use two way digital health technologies where they reach out to participants to confirm reading accuracy of, e.g., data collection from a smartphone app or a mobile device that gathers data without manual input from the participant. The participant has the opportunity to review the collected data for error.
- The study coordination center requires a sophisticated information technology platform for implementation and operational efficiency. In addition, the regulatory framework for approving VCT for pharmaceutical development is still in its early phase, making the guidance in this field unclear.
- Some areas of clinical research are not ready for remote monitoring, and the virtual approach is not advanced enough to attempt in phase 1 studies where patients need to be closely observed and located near a clinical site in case there is a reaction. Nor is it suitable

for certain diseases that require sophisticated or in-hospital monitoring. Acute life-threatening diseases (e.g., strokes) are possibly not appropriate for a full VCT.

CONCLUSION

Digital technologies can help reimagine clinical trials, to overcome the common challenges of on-time patient recruitment, retention, adherence, and stringent clinical trial execution Timelines faced by life sciences companies. The Digital forces like Computing, cloud, Big Data, Artificial Intelligence and robotics, and social media offer opportunities to reimagine clinical trial processes. Virtual studies will augment rather than replace traditional study practices and workflows. On-site monitoring is still a mainstay of the study, for example, but much of the data is monitored remotely, as appropriate. Some Pharmaceutical companies are conducting virtual trials in-addition to on-site traditional trials in phase iii & phase IV for additional data from diverse patient population across the world. Perhaps virtual clinical trials are used in rescue studies, where traditional models have failed (e.g. for geographically dispersed groups or rare disease populations). The primary purpose of a clinical trial is to identify drug efficacy and safety parameters in humans. The timely completion of a trial depends on numerous factors, including site performance, timely recruitment of patients, dropout rate, patient adherence and compliance to the treatment, and the ability to take related decisions faster. As patient-specific factors can lead to delays during trials, a strong digital connect presents an opportunity to build trust with patients. Moreover, with the advent of technology, there are newer avenues to analyse trial information differently and generate more evidence. These trials typically provide participant access to research teams through Web-based portals, sometimes provide home visits, and collect data through networked wearable's and medical devices, surveys, and other means. Although there are certainly complexities related to the massive amount of data generated, safety concerns, and other considerations, this approach holds great potential for growth. To conclude, until now VCTs have been used in Phase II-IV trials. Results from these trials have shown promising results. Besides, it has also been able to meet the goal of the pharma industry (low risk and high return) when conducting clinical trials.

The global COVID-19 pandemic caused by the coronavirus has led to lockdown and thereby impacted several businesses worldwide. There has been an increasing demand for the development of medicines and vaccines to curb the outbreak. This has led to an increase in digital/virtual clinical trials as these can be conducted via a digital platform. The VCTs minimize the travel burden on both the staff and the participants and reduce the risk of infection. Such advantages have further fueled the digital clinical trials market growth. Moreover, technological advancements in healthcare infrastructure and alliances between biotechnology, pharmaceutical & clinical research



organization are anticipated to boost the virtual clinical trials market growth in the near future.

A report from the Tufts Center for the Study of Drug Development (CSDD) deduces that the cost of developing a prescription drug that gains market approval is US \$2.6 billion.²⁶ Companies are increasingly integrating R&D information for quicker and improved decision-making and leveraging computational methods and predictive analytics techniques to improve clinical trial productivity and success rates. As the healthcare ecosystem matures, there are tremendous opportunities to examine and fine-tune emerging patient-centric strategies in trials.

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