Virtual Clinical Trials: Perspectives in Dermatology

Zarqa Ali\textsuperscript{a}  John Robert Zibert\textsuperscript{b}  Simon Francis Thomsen\textsuperscript{a,c}

\textsuperscript{a}Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark; \textsuperscript{b}LEO Innovation Lab, Copenhagen, Denmark; \textsuperscript{c}Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

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\textbf{Abstract}

\textbf{Background:} The cost of developing a new drug is approximately USD 2.6 billion, and over two-thirds of the total cost is embedded in the clinical-testing phase. Patient recruitment is the single biggest cause of clinical trial delays, and these delays can result in up to USD 8 million per day in lost revenue for pharmaceutical companies. Further, clinical trials struggle to keep participants engaged in the study and as many as 40\% drop out. To overcome these challenges pharmaceutical companies and research institutions (e.g., universities) increasingly use an emerging concept: virtual clinical trials (VCT) based on a remote approach. \textbf{Summary:} VCT (site-less) are a relatively new method of conducting a clinical trial, taking full advantage of technology (apps, monitoring devices, etc.) and inclusion of web platforms (recruitment, informed consent, counselling, measurement of endpoints, and any adverse reactions) to allow the patient to be home-based at every stage of the clinical trial. Studies have shown that VCT are not only operationally feasible, but also successful. They have higher recruitment rates, better compliance, lower drop-out rates, and are conducted faster than traditional clinical trials. The visual nature of dermatological conditions, the relative ease in evaluating skin diseases virtually, and the fact that skin diseases often are not life-threatening and rarely require complex examinations make VCT very attractive for dermatological research. Further, making correct diagnoses based on photographs and patient symptomatology has always been part of the dermatologist’s routine. Thus, VCT are in many ways made for dermatology. Herein we describe VCT and their implications in dermatological research.

\textbf{Introduction}

Clinical drug development is a time-consuming and complex process that takes around 6–15 years \cite{1}. The cost of developing a new drug, from research and development to marketing approval, is approximately USD 2.6 billion \cite{2}. Approximately 85\% of therapies fail through early clinical development, and only half of those reaching phase 3 are approved \cite{3}. Over two-thirds of the total cost, in both money and time, of the discovery and development of a new drug is embedded in the clinical-testing phase \cite{4}. Patient recruitment is the single biggest cause of clinical trial delays, and 30\% of phase 3 study termina-
Virtual clinical trials (VCT) are a relatively new and underutilized method of conducting clinical research using technologies (apps, electronically monitoring devices, etc.) and online social engagement platforms. Making correct diagnoses based on photographs and patient symptomatology has always been part of the dermatologist’s routine. The visual nature of dermatological conditions, the relative ease in evaluating skin diseases virtually, and the fact that skin diseases often are not life-threatening and rarely require complex examinations make VCT very attractive for dermatological research. Thus, VCT are in many ways made for dermatology.

Herein we discuss advantages and challenges of VCT and outline the implications of VCT for dermatological research.

Methods

This narrative review was conducted using PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov. The searches were carried out using the following terms: “virtual clinical trial,” “remote trial,” “web-based trial,” “decentralized,” “hybrid study,” and “hybrid trial.” For the present paper interventional studies including the words “virtual,” “remote,” “hybrid”, or “decentralized” were selected. Studies not including any intervention or virtual/remote element were excluded. Further, telemedicine and teledermatology studies were excluded. Updated information on trials was found in the press release from the pharmaceutical companies sponsoring the trial.

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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 [7]. With the use of digital health technologies, VCT manage to recruit faster, improve retention, and increase participant diversity and representation [8]. Further, VCT overcome the challenges faced in conventional clinical trials like many long appointments during working hours [9].

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) and social media (e.g., Facebook, Instagram), 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 fulfill 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 and within eczema alone there are 4,343,000 searches/month (searches on Google, USA, November 2018). 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 [10]. 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 call before giving the consent [11, 12]. Furthermore, a limited number of study sites are involved in VCT. There is often only a single site, or one site in each country in global studies, led by a principal investigator 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. VCT also allow data collection from multiple sources and reporters, e.g., mobile devices like phone, apps, watch, electronic patient-reported outcomes, and e-diaries [13]. This is in contrast to conventional clinical trials where the data collection is made by the study team. (Table 1).
Previous and Ongoing VCT in Nondermatological Indications

To our knowledge, 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 [14] (Table 2). 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 [14].

A decade later the first trial to enroll and manage study participants entirely remotely with no visits to the investigator site and only using a variety of web-based resources, the REMOTE trial, was conducted by Pfizer Inc., in collaboration with Mytrus Inc. (San Francisco, CA, USA) from 2011 to 2012. The REMOTE trial was a randomized, phase 4 trial to test a novel web-based trial design for evaluating the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder (ClinicalTrials.gov ID: NCT01302938) [15]. At the time, tolterodine ER was already approved and on the market. However, the company wanted to compare the virtual approach to a conventional phase 4 clinical study to determine whether the VCT design would be a feasible way to conduct future trials. Participants were recruited online and screened using web-based questionnaires and laboratory test results.
The physical examination was carried out by a local physician. To verify participant identification and minimize fraud a 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. The goal was to recruit 283 participants. More than 5,000 participants registered on the trial website, of whom 456 passed the initial screening, identification verification, and signed consent. About 200 passed additional medical screening and were countersigned by the investigator. After laboratory testing, 118 entered the placebo run-in; only 18 completed e-diary assessments and were randomized to treatment. The mean age was 46 years (range 31–64) and 48 years (range 28–66) in the placebo and intervention group, respectively. Nevertheless, the results indicated that the study was just as safe and effective as a traditional clinical trial [16].

In 2014–2015, Sanofi in collaboration with Langland and Mendor completed a successful fully remote diabetes management phase 4 clinical trial in Finland, the VERKKO trial, to test a 3G-capable, wireless glucose meter [17]. 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 with the VCT.

Seventy-four participants were recruited online, of whom 60 were enrolled in the study (81% conversion ratio). The average age of the participants was 56 years (range not available). 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 [17, 18].

In an ongoing ADAPTABLE trial, the investigators will compare the effectiveness of low and high dose of aspirin to identify the optimal dose for secondary prevention in patients with atherosclerotic cardiovascular disease (ClinicalTrials.gov ID: NCT02697916) [19]. Informed consent and randomization will occur online, and patient comprehension and patient-reported outcomes will be recorded throughout the study. Further, to estimate missed bolus insulin doses in diabetics Eli Lilly have conducted a phase 4 hybrid study, comprising tra-
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Implications of VCT for Dermatological Research

Pfizer’s REMOTE trial was the first to demonstrate that VCT are operationally feasible. However, VERKKO by SANOFI showed that VCT are not only feasible but...
also successful and can deliver excellent performance and results. VCT have higher recruitment rates, better compliance, lower drop-out rates, and are conducted faster.

The experience from teledermatology is that online healthcare is safe and effective [32]. Many dermatological diseases require frequent check-ups, and with online communication, time consuming visits are not necessary [33].

An additional advantage with VCT is that they are more accessible to participants who otherwise may be excluded from, or reluctant to participate in, a traditional clinical trial.

The elderly, disabled, and those with mobility issues or other traveling difficulties can participate in VCT without discomfort associated with traveling. Even patients who live in rural areas or very remotely from the trial sites can participate in VCT. Young people of working age do not have to take time off from work or spend time travelling. Further, it is valuable when studying rare diseases or rare exposures, where it is critical to maximize enrollment of all eligible patients. As a consequence of this broad recruitment strategy, a more diverse patient population may also be more representative of the real-world than traditional clinical trials.

From an economic point of view there may be achieved savings associated with VCT. The time spent conducting a study is reduced due to shorter enrollment periods and faster data collection. Further, the traditional setup of multiple study sites is also eliminated. The cost of managing a single VCT study site is estimated to be between USD 1,500 and 2,500 per month, so any reduction in the number of operational study sites offers considerable capital savings [34]. In addition, the need to reimburse patients for travel expenses decreases. It is believed that the savings can be achieved, although this approach requires technological support.

Unlike site-based studies, data in VCT are not collected by investigators during site visits, but through the central study coordinating center. Data are submitted electronically, and the clinical outcome assessment is done by a study physician or directly by automated software algorithms.

**Limitations of VCT**

Despite the many benefits, there are some challenges of VCT that should be addressed. The REMOTE trial had many recruitment issues, possibly explained by the fact that the older generation did not use modern technology and social media to the same extent as the youth. Even though social media was a great way to spread awareness of the trial, it did not build enough trust for patients to sign up as the goal of up to 283 recruited participants was not reached. 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.

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 [7, 35]. 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 [7]. Regulatory demands such as HIPAA in the USA and GDPR in the EU is overcoming this challenge though.

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. Further, VCT might not work if imaging examination, a full physical examination, or other types of evaluations cannot be completed by health staff during home visits.

In conclusion, studies to date have demonstrated that VCT are not only operationally feasible, but also successful. VCT show high recruitment rates, have better compliance, lower drop-out rates, and are conducted faster. VCT have been used in phase 2–4 trials showing promising results. VCT meet the goal of the industry in being “low-risk, high-return” trials. We expect to see more of these trials in the future, particularly in dermatology.

**Key Message**

Virtual clinical trials are operationally feasible and may cause the earlier launch of new pharmaceutical products.

**References**


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