Virtual Clinical Trials: Perspectives in Dermatology

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Keywords

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Abstract

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. **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.

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Introduction

Clinical drug development is a time-consuming and complex process that takes around 6–15 years [1]. The cost of developing a new drug, from research and development to marketing approval, is approximately USD 2.6 billion [2]. Approximately 85% of therapies fail through early clinical development, and only half of those reaching phase 3 are approved [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 [4]. Patient recruitment is the single biggest cause of clinical trial delays, and 30% of phase 3 study termina-

tions are due to enrollment difficulty. Approximately 80% of trials fail to meet the initial enrollment target and timeline [5]. These delays can result in up to USD 8 million per day in lost revenue for pharmaceutical companies. Additionally, nearly USD 6 billion annually are spent on patient recruitment. Moreover, only 2% of the eligible population in the USA participate in clinical trials, and those who do participate attend an average of 11 visits at the trial site in 6 months [6].

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.

Virtual Clinical Trials

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 over-

come 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 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 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).

Table 1. Differences 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	Electronic consent
Trial activities, e.g., education, in-person formation	In person at study site	Videoconference, telehealth
Physical examination	At study site	By photos, remote visits, in-home nurse visits
Laboratory testing	At study site	Microsampling, 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, consumer-generated physiological and behavioral measures collected through connected digital tools, e.g., digital biomarkers
Study setup	Many study sites and study teams	Single virtual coordinating center with a virtual principal investigator
Duration	Time-consuming	Timesaving
Cost	Costly	Cost-effective
Patient retention	High drop-out rate	High retention rate
Enrollment	Restricted by access to study site	Maximizes enrolment

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 inves-

tigator 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.

Table 2. Overview of virtual clinical trials (VCT)

Sponsor	Year	Phase	VCT/hybrid	Detail	Enrolled
Duke University [19]	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 (estimated)
Hoffmann-La Roche and Genentech [30]	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 [20]	2017–2018	Phase 4	Hybrid	Estimate missed bolus insulin doses in diabetics	79
AOBiome [25]	2017	Phase 2b	Hybrid	Topical probiotic spray for mild-to-moderate acne	372
PellePharm [26]	2016–2017	Phase 2	Hybrid	Topical patidegib for basal cell carcinomas (Gorlin syndrome)	36
Sanofi [17]	2014–2015	Phase 4	VCT	Remote system to diabetes management	60
Pfizer [15]	2011–2012	Phase 4	VCT	Efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder	18

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 tradition-

al 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-

ditional sites plus VCT, in collaboration with Science37 (ClinicalTrials.gov ID: NCT03368807) [20]. Science 37 Inc. is a mobile technology and clinical trial company that focuses on the development of networked patient-centric models for clinical research to accelerate biomedical discovery, and is one of the leading companies in VCT [21].

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. (ClinicalTrials.gov ID: NCT01197144) [22]. 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.

Finally, other VCT have been conducted using self-directed mobile health research apps such as those based on the ResearchKit platform (Apple, San Francisco, CA, USA). ResearchKit can be used to execute trials remotely without any face-to-face interaction between researchers and study participants. As many as 36 apps have been reported to use ResearchKit to conduct observational studies on general citizens (citizen research) and generate large datasets for secondary research with nearly half of the apps focusing on chronic conditions in adults [23].

VCT in Dermatology

Several VCT have been conducted and are ongoing in dermatology [24]. In 2017 AOBiome's randomized, phase 2b hybrid study evaluated a topical probiotic spray containing beneficial bacteria for mild-to-moderate acne [25]. The 12-week clinical trial recruited volunteers through social media and internet advertisements. More than 8,000 people were screened online to check eligibility. The resulting 372 participants received the drug or a placebo in the mail. They used company-issued iPhones to take selfies of their acne and a phone app to send the photos to physician investigators for evaluation. The study lasted less than 12 months and was much faster than anticipated. Further, AOBiome reported that the online recruitment was relatively fast, dropout rates were lower than expected, compliance was better than expected, and the trial was cheaper to administer than a traditional trial.

From 2016 to 2017, PellePharm included 36 subjects in a double-blinded, dose escalating, randomized, vehicle-controlled, hybrid, phase 2 study (ClinicalTrials.gov ID: NCT02828111) [26]. The study compared the efficacy

and safety of patidegib gel 2.4% applied once or twice daily in comparison with that of vehicle on biopsy-confirmed nodular basal cell carcinomas (BCC) in four sequential cohorts. Within each cohort subjects were randomized in a 2:1 ratio to receive active or vehicle gel. The sequential cohorts were as follows: cohort 1 – patidegib gel 2% or vehicle, once daily; cohort 2 – patidegib gel 4% or vehicle, once daily; cohort 3 – patidegib gel 2% or vehicle, twice daily; and cohort 4 – patidegib gel 4% or vehicle, twice daily. The study showed that use of patidegib gel 2% was significantly more effective in clinical and histologic clearance of BCC after 3 months compared with the topical vehicle gel. Furthermore, patients using topical patidegib gel did not experience any of the significant side effects characteristic of oral hedgehog inhibitors (e.g., hair loss, taste loss, or frequent muscle cramps) [27].

Recently, Naked Biome completed recruitment (10 subjects enrolled) in a phase 1 hybrid study with one virtual site, Science 37, about a topical probiotic for moderate acne (ClinicalTrials.gov ID: NCT03450369) [28, 29]. The investigators hypothesized that eliminating resident disease-associated bacterial strains and replacing them with health-associated strains may improve, mitigate, and prevent acne. The study will evaluate the safety, tolerability, and clinical impact of the application. Further, the investigators will be profiling the change in microbiome over the course of therapy to determine whether exogenously delivered bacteria can populate the skin and cause a shift in the microbiome safely and subsequently impact acne biomarkers that may correlate with clinical disease.

Several VCT are expected in the near future. Genentech in collaboration with Hoffmann-La Roche are conducting a multicenter, randomized, double-blind phase 3 study to evaluate the efficacy and safety of rituximab compared with mycophenolate mofetil in patients with moderately-to-severely active pemphigus vulgaris [30]. The hybrid study will enroll more than 100 patients spread on 60 physical sites around the world where one virtual site was managed by Science37. The virtual site managed by Science37 is so far the quickest recruiter compared to traditional physical sites. Ten subjects were enrolled worldwide at 21 physical sites and in the same amount of time one virtual site enrolled 10 subjects [31].

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.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

J.R. Zibert and S.F. Thomsen conceived the presented idea. Z. Ali carried out the searches and took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research and manuscript.

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