Research Techniques Made Simple: Teledermatology in Clinical Trials

Caroline W. Laggis1, Victoria L. Williams2, Xiaoshi Yang3 and Carrie L. Kovarik4

Teledermatology is well established as a means of providing high-quality healthcare at a distance, particularly to patients in underserved populations. Technologies in teledermatology can be used to complement traditional methodologies of clinical trials, expanding accessibility of trials to people typically unable to participate in research. Tools of communication technology may enhance many aspects of clinical trials in dermatology, from recruitment and retention of participants to collection of real-time data. Clinical trials can be made completely virtual or incorporate aspects of virtual technologies at any stage of research. Virtual clinical trials are considered highly patient-centered, as the ability of participants to engage with research staff from their own home often supplants the need for many or all on-site clinic visits. As technological advances influence every aspect of modern life, clinical trials will also evolve to incorporate these tools, meeting participant expectations and overcoming traditional challenges of conducting research. Virtual clinical trials come with specific issues pertaining to analysis of data, technology, and oversight. As more virtual trials are conducted, advantages and limitations of using such technology in research will become clearer and regulatory guidelines will be more firmly established.

INTRODUCTION

Telemedicine has been in existence for decades as a way to provide healthcare at a distance using communication technologies, and dermatology is well-suited for the delivery of diagnoses using visually based video and photography. Using teledermatology, clinical services can be provided to underserved populations in a reliable and cost-effective manner when compared to more traditional face-to-face modalities (Yang et al., 2018). Systematic reviews (Mounessa et al., 2018; Warshaw et al., 2011) and numerous studies (Armstrong et al., 2018; Balakrishnan et al., 2018) have shown acceptable concordance rates between diagnoses rendered through teledermatology and traditional face-to-face
BRIEF OVERVIEW OF VIRTUAL CLINICAL TRIALS

Virtual technologies have historically been utilized to complement conventional methodologies of drug development. Pfizer was the first to conduct a fully virtual clinical trial in 2011, establishing a framework for workflow and pitfalls. Other notable trials, including those in dermatology, are highlighted in Table 1. The PEMPHIX trial (Hoffman-La, 2018) was the first to recruit and monitor patients virtually in a randomized control trial to compare oral with infused medications. This trial investigated the safety and efficacy of rituximab versus mycophenolate mofetil in the treatment of pemphigus vulgaris, a rare autoimmune blistering disease. Approximately 10% of the participants enrolled virtually. Communications and data input were done almost entirely through mobile applications and teledermatology visits. This study noted an enrollment speed for participants using virtual methods approximately 20 times faster on average than more conventional enrollment techniques at a traditional site (Neuer, 2016), which is significant given the relative rarity of the disease under investigation. Table 1 also lists several ongoing and recently completed telemedicine-based virtual trials.

WHAT IS THE ROLE OF TELEDERMATOLOGY IN CLINICAL TRIALS?

Teledermatology and different modes of communication technology can be used to enhance clinical trials. Clinicians should be aware of the range of tools that can simplify or streamline portions of clinical research, most notably the recruitment of participants, collecting feedback and data from participants and staff, and retention of participants. These tools can be integrated into parts of a trial without the trial becoming entirely virtual. Figure 1 illustrates the patient’s journey through a clinical trial and where aspects of teledermatology can be incorporated along the way.

Recruitment and screening of participants

The recruitment of participants into clinical trials is frequently a major obstacle to the success of a study. With conventional methods, reports show that 10% of studies fail to enroll a single patient, and 25% under-enroll (Lamberti and Getz, 2015). The Clinical Trials Transformation Initiative outlined the actionable recommendations needed to improve patient recruitment (Huang et al., 2018), many of which could be addressed with the use of telemedicine as part of the methodology. Social media outlets are a prime example of widely accessible avenues for advertisement regarding new clinical trials and engagement among participants. One study currently underway (Studer, 2016) focuses on the use of a wireless blood glucose meter in a completely virtual clinical trial setting in which all participants were recruited through Facebook and then self-registered with an application at a separate site. A research coordinator then screened the study materials, and the required materials and equipment were mailed to the selected participants. Additionally, with global use of social media, there is a greater potential to involve more diverse and underrepresented patient populations when compared to traditional methods of recruitment.

Collecting participant feedback and real-world trial data

Completed virtual clinical trials have shown that quality data can be reliably provided directly to coordinators using a web portal or an application downloaded on a smartphone (Table 1). This technology can be utilized to allow patients to enter data on their own time. Customized online surveys provide an easy mechanism to collect data on patients’ experiences, perspectives, and self-reported disease metrics (Maymone et al., 2018). These surveys can be rapidly developed and administered, as well as collected and
Daily virtual clinical trials aim to decrease patient burden, enhance patient-centered models for data collection and monitoring, events and side effects of trial interventions. Disease severity, response to treatment, or potential adverse taken by the participant or trial staff, can be used to monitor developments (Hirsch et al., 2017). With more convenient and implications to scientific, financial, ethical, and policy developments (Hirsch et al., 2017). With more convenient and patient-centered models for data collection and monitoring, virtual clinical trials aim to decrease patient burden, enhance compliance with protocols, and improve retention of participants.

WHAT TECHNOLOGIES ARE AVAILABLE WITHIN THE REALM OF TELDERMATOLOGY?
Table 2 provides examples of the “virtual toolbox” available to investigators. The most applicable to dermatology clinical trials are social media outlets for recruitment, online survey tools for data collection, synchronous and asynchronous study visits using photography or video conferencing, and patient portals for communication with study coordinators and providers.

In other fields, investigators have pioneered real-time sensors, such as blood glucose monitors for patients with diabetes and motion-detector sensors for patients with neurologic conditions. A dermatology trial recently utilized wrist-worn actigraphy sensors to measure nocturnal scratching in patients with atopic dermatitis (Moreau et al.,

### Table 1. Overview of Previous and Ongoing Virtual Clinical Trials

<table>
<thead>
<tr>
<th>Disease/Study (Dates of Study)</th>
<th>Purpose</th>
<th>Telem Medicine Use in Trial</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Overactive bladder, REMOTE trial (2011–12)</td>
<td>New drug study</td>
<td>Telemedicine was used via a patient-facing web portal in order to manage participants from their homes.</td>
<td>Trial ended early, primarily because of complicated online processes at key steps</td>
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<td>Parkinson’s disease (2011–12)</td>
<td>Evaluate the feasibility of providing specialty care to individuals with Parkinsonism via web-based telemedicine in their homes</td>
<td>Video conferencing with participants</td>
<td>Remote clinical assessments were conducted nationally and rapidly from a single site, confirming self-reported diagnosis</td>
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<td>Alzheimer’s disease (2014–15)</td>
<td>Monitor real-world function in home environments of participants</td>
<td>Data gathered from strategically placed sensors were used to assess global cognitive and motor impairment in real time.</td>
<td>Patterns of intra-individual variation detected in each of these areas were used to predict outcomes, such as low mood, loneliness, and cognitive function</td>
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<td>Acne, AOBiome Study (2017)</td>
<td>Determine the efficacy of a new topical ammonia oxidizing bacteria for treatment</td>
<td>Trial was conducted entirely using virtual technologies and utilized photographs patients took of themselves, which were uploaded to an app on iPhones provided by the trial.</td>
<td>The Phase 2b of the study achieved the primary endpoint at week 12 of a statistically significant 2-point reduction in an Investigator’s Global Assessment of acne severity compared to vehicle control (P = 0.03)</td>
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<td>Pemphigus vulgaris, PEMPHIX trial (2014–ongoing)</td>
<td>Compare efficacy of rituximab to mycophenolate mofetil in the treatment of pemphigus vulgaris</td>
<td>Communications with research team took place almost entirely in patients’ homes using a smartphone app, mobile nurses, and study coordinators. This study was a hybrid, with infrequent visits to the clinic over years.</td>
<td>Study is active, but no longer recruiting</td>
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<td>Severe acne (2016–18)</td>
<td>New drug study of a subcutaneous drug</td>
<td>Virtual enrollment, self-photography, and nurse-assisted photography at home, and home lab draws</td>
<td>Phase 2a placebo controlled RCT enrollment completed</td>
</tr>
<tr>
<td>Cluster headache (2016–18)</td>
<td>New drug study of subcutaneous drug</td>
<td>Virtual enrollment and monitoring, home-based injections, and lab draws at home</td>
<td>Phase 2a placebo controlled RCT, enrollment completed; 80% of patients enrolled virtually</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease (2016–ongoing)</td>
<td>New drug study of oral drug</td>
<td>Virtual enrollment and monitoring, home-based assessments, and intermittent imaging at study site</td>
<td>Phase 2a placebo controlled RCT, enrollment completed</td>
</tr>
<tr>
<td>Type II diabetes (2018–19)</td>
<td>Study of recently-approved diabetes drug in underrepresented minority populations</td>
<td>Virtual enrollment and monitoring, home-based assessments, and home-based or local lab</td>
<td>Phase 4 study of marketed drug in new population, recently closed</td>
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</table>

All trials listed, except REMOTE and Alzheimer’s studies, reported using a patient portal with capacity to perform both store-and-forward, as well as video telemedicine.

Abbreviation: RCT, randomized control trial.

1 Hirsch et al., 2017; Jadhav, 2016; Orri et al., 2014
2 Dorsey et al., 2015a; Dorsey et al., 2015b
3 Lyons et al., 2015
4 Jackson, 2017; Singer et al., 2018
5 Hoffman-La, 2018

analyzed, with a lower cost and fewer errors than traditional telephone or mail questionnaires.

Trial data can also be collected virtually using wearable sensors to track compliance with the trial’s design and allow daily “e-journal” entries. Photographs and videos, whether taken by the participant or trial staff, can be used to monitor disease severity, response to treatment, or potential adverse events and side effects of trial interventions.

Retention of participants

Traditional clinical trials have a high drop-out rate, with only 50% average participant retention (Lamberti and Getz, 2015). Poor retention causes significant delays and costs, as well as implications to scientific, financial, ethical, and policy developments (Hirsch et al., 2017). With more convenient and patient-centered models for data collection and monitoring, virtual clinical trials aim to decrease patient burden, enhance
2018). Wearable sensors allow objective outcome measures to be more easily and accurately monitored in the home than a monthly diary of events or reliance on patient reporting.

Certified Clinical Trial Research Pharmacists are specially trained, licensed pharmacists who operate through site-less clinical research organizations to virtually access participant data and interact with participants as needed in their homes (Hirsch et al., 2017). Incorporation of Certified Clinical Trial Research Pharmacists has the potential to improve the safety and satisfaction of clinical trial participants in drug studies.

WHAT ARE THE ADVANTAGES OF USING TELEDERMATOLOGY IN CLINICAL TRIALS?
The primary advantages of using clinically-based telemedicine for healthcare delivery are the decrease of the burden of patients in need of medical care and the improvement of healthcare access for underserved populations, a concept that also applies readily to virtual clinical research. Opening up clinical trials to patients in geographically remote areas or disparate living conditions provides an opportunity to study diverse and previously uninvolved sectors of the population and may lead to study populations that are more representative of the actual population with the disease. Some dermatological diseases are more prevalent in elderly or low-income populations. However, because of significant comorbidities or social issues, these groups may have difficulty committing to frequent on-site appointments required by traditional trial models and may benefit from technological methodologies. Rare diseases in dermatology require wider recruitment areas and multiple facilities, which can be made possible with virtual clinical trials.

In developing countries, the burden of skin disease is high but often inadequately studied because of the lack of healthcare infrastructure and limited research funding. Mobile data collection tools have been used with success in these settings for health surveillance research, epidemiologic data collection, and studies to monitor disease severity and treatment response (Baloyi et al., 2018; Devi et al., 2015; Forsell et al., 2011; Ha et al., 2016; Laytin et al., 2018; Quercia et al., 2018). Communication technology can provide an opportunity for these underserved patient populations to benefit from access to new and potentially more efficacious diagnostic and therapeutic interventions in clinical trials.

Overall, virtual trials are considered more patient-centered by “engaging patients directly in research functions, overcoming geographic obstacles to connect stakeholders, and incorporating patient input into the research process” (Covington and Veley, 2015). The advantages also extend to the study coordinator role, as one study reported 66% less time spent on study coordination activities when compared to traditional methods (Studer, 2016). Easing recruitment and retention of participants enhances the efficiency of conducting clinical trials. New drug trials average 12 years in investment time and billions of dollars to complete (Sertkaya et al., 2014). Transitioning to virtual methodologies may significantly decrease cost and accelerate completion of trials by centralizing collection of data and decreasing the number of sites to maintain. Figure 2 illustrates the advantages and disadvantages of using teledermatology in clinical trials.
WHAT UNIQUE ISSUES ARE INVOLVED WITH THE USE OF TELEDERMATOLOGY IN CLINICAL TRIALS?

Sampling issues
In general, patient participation in medical trials has not reflected the shifting demographics of the population of the United States, especially among minority ethnic populations (Charrow et al., 2017). In comparison, participant populations that are self-recruited via social media often more appropriately reflect population demographics. However, this population may not represent a true random selection and may be viewed as a “convenience sample.” Self-selected participants may also represent a biased population, as they may be more prone to use the Internet or computers. Recruitment techniques are ideally designed to enroll the most representative selection of the population that will ultimately receive the drug, thus they should be multipronged in their approach (Covington and Veley, 2015).

Technology and coordination issues
Given the heavy reliance of virtual clinical trials on smartphones and videoconferencing, technological access and functionality become key concerns. A high-speed signal and access to a smartphone or computer is essential for participants. In 2017, approximately 64% of people around the

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Table 2. Toolbox for Incorporating Aspects of Telemedicine into Clinical Trials

<table>
<thead>
<tr>
<th>Aspect of Clinical Trials</th>
<th>Telemedicine Tools</th>
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<tr>
<td>Recruitment and screening of participants</td>
<td>- Social media outlets provide highly visible avenues for recruitment of participants</td>
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<td></td>
<td>- Online questionnaires and web-based portals for streamlined registration and simplified screening of participants into trials</td>
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<td></td>
<td>- Partnerships and engagement with patient advocacy groups or patient communities</td>
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<td>Gaining informed consent</td>
<td>- Participants can read over study information on their own time, interact with investigators and staff virtually, save documents, and sign informed consents online</td>
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<td>Participant education</td>
<td>- Numerous modalities for patient education can be streamlined on web-based portals, including tutorial videos, informed consent videos, and documents on key points of trial information</td>
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<tr>
<td>Participant feedback and data collection</td>
<td>- Web-based portals allow for participant feedback during their own time, including perspectives, experiences, and questions related to the ongoing trial through online communication systems and message boards</td>
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<td></td>
<td>- Data collection through web-based or app-based portals via online surveys, participant “e-journals,” digital data points from wearable sensors, and weights of medications to ensure proper usage</td>
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<tr>
<td></td>
<td>- Photographs and video conferencing (taken by participants and/or trial staff) can be used to monitor disease severity, response to intervention, and adverse side effects</td>
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<tr>
<td>Adherence and data quality</td>
<td>- Text messages or other push reminders about upcoming visits or for medication adherence can be sent within study apps or directly to participants’ mobile devices</td>
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<td>Retention of participants</td>
<td>- Improved compliance and understanding of trial protocols by shifting the convenience towards the participant</td>
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<td>- Flexible data entry times based on participants schedule and in their own home</td>
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<td></td>
<td>- Decrease or elimination of on-site visits</td>
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<tr>
<td>Monitoring for adverse events and safety</td>
<td>- High accessibility to coordinators via web-based portals for discussion of adverse events at any interval rather than waiting for on-site visit appointments</td>
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<td></td>
<td>- Safety monitoring via patient or staff entered outcomes on a regular basis</td>
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<tr>
<td></td>
<td>- Incorporation of Clinical Trial Research Pharmacists for drug related questions and monitoring</td>
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Figure 2. Advantages and disadvantages of virtual clinical trials.

Major advantages and disadvantages of using technology in clinical trials or conducting an entirely virtual clinical trial.
world had access to the Internet, and 72% owned a smartphone, and these numbers are substantially higher in the United States (Poushter et al., 2018). Conducting trials using smartphones provided by the researchers is one way to expand eligible populations. However, this may exclude certain sectors, such as elderly patients who have limited experience using similar technology or populations in developing countries where unreliable connectivity may pose a problem.

Coordinating multiple parties involved in clinical trials onto a single virtual conference call can be more difficult than simply requiring all parties to be present at the time of a participant visit. Thus, studies that require multiple disciplines and significant coordination of trial resources may not work well with completely virtual methodology. Other potential complications of virtually conducted trials include difficulty in administering trial medications via mail, coordinating infused medications, and ensuring participants are compliant with obtaining necessary lab testing outside of an office visit setting.

When participants are required to use video conferencing or store-and-forward photographs for data collection, there must be clear instructions and quality cameras provided to assure standardized, high-quality images. This is particularly essential in dermatological clinical trials where photographs or video monitoring may be a primary tool for assessment of disease progression and success of interventions. A recently published article about acne (Singer et al., 2018) demonstrates the reliability of assessing standard clinical outcomes from smartphone-based digital photographs compared to in person visits. Because smartphone cameras and the use of them are nearly ubiquitous in the population, reliable and methodical training is the primary limitation to widespread clinical trial usage of these photographic modalities from home.
RESEARCH TECHNIQUES MADE SIMPLE

Regulatory and legal issues
There is not yet a standardized set of guidelines that clinical investigators can follow regarding the implementation of virtual technology into studies. Currently, virtual trials are being conducted on a case-by-case basis and regulatory guidelines vary by region and country. Lack of standard guidelines and regulatory uncertainty may be a reason more groups are not conducting virtual trials.

Other legal considerations include ensuring appropriate licensure is held or acquired among health practitioners in all states where participants in the study reside. Finally, a major benefit of virtual trials is that a single site can recruit patients from multiple states.

CONCLUSION
Development of and access to technology within health care has progressed at a faster rate than the methodologies used to conduct clinical trials. Participants appreciate the convenience offered by clinical trials that provide access to online registration, monitoring, and virtual data collection. Direct access to study coordinators is often expected by clinical research participants, and virtual platforms make this access more feasible. Integrating virtual tools into clinical trials is critical to advancing research methodologies. Standardized regulatory guidelines would enhance the industry’s ability to conduct these trials with confidence.

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CONFLICT OF INTEREST
VV serves as a consultant for Patient Discovery Inc, which has created a web-based educational program for patients on biologic medications and that could be utilized for clinical research. The other authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS
Conceptualization: CWL, CLK; Data Curation: CWL, VLW, XY, CLK; Formal Analysis: CWL, XY, CLK; Investigation: CWL, VLW, CLK; Methodology: CWL, CLK; Project Administration: CWL, CLK; Supervision: CLK; Writing – Original Draft Preparation: CWL; Writing – Review and Editing: CWL, VLW, XY, CLK

SUPPLEMENTARY MATERIAL
Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

REFERENCES
RESEARCH TECHNIQUES MADE SIMPLE


DETAILED ANSWERS

1. Which statement is true regarding previous and ongoing virtual clinical trials?

Answer: C. Use of technology has improved recruitment and retention in a clinical trial concerning pemphigus vulgaris

One main benefit of incorporating technology into virtual clinic trials is the potential to improve recruitment and retention of participants, as shown in the early findings of the PEMPHIX trial. Choice A is wrong because there have been at least two successful virtual clinical trials in the field of dermatology, one related to acne and the other related to pemphigus, and several others that are in progress at the current time. Choice B is wrong because the REMOTE trial did have issues with too many complicated online steps that ultimately led to the trial ending early. Choice D is wrong because it has primarily been neurology and endocrinology that have pioneered trials involving wearable sensors.

2. Which study might be inappropriate to consider conducting completely virtually?

Answer: B. Multistage study with various subpopulations requiring frequent coordination of social work, pharmacy, physical therapy, oncology, and dermatology

The coordination of all disciplines into the same conference call for patient visits may be too cumbersome to be feasible if conducted virtually. However, choices A, B, and D represent examples of studies that would likely benefit from being conducted virtually.

3. Which of the following is false regarding use of social media in recruitment of participants for clinical trials?

Answer: A. Study population can be viewed as a random sample of the general population

Choice A is a false statement because a population drawn from social media alone should be considered a “convenient sample,” rather than a random sample, as participants are relatively self-selected to be involved in studies. Choice D is a

4. Which of the following is not an advantage of incorporating technology into a clinical trial?

Answer: D. No need for training to ensure quality of photos taken by participants for data collection purposes

For data collection purposes in dermatology studies, it would be essential to make sure participants had a standardized guideline for taking photographs of their skin and it would be imperative to provide a device with a camera, such as a smartphone, so that participants had appropriate access to the tools they need to provide data back to the coordinators. Choices A, B, and C all represent advantages of using technology in clinical trials.

5. Which of the following is an important limitation regarding the use of technology in clinical trials?

Answer: A. Storage of online data must comply with rigorous privacy standards

The primary coordination site is responsible for ensuring data is collected and stored in a manner that complies with patient privacy standards, and thus represents a potential limitation. Choice B is wrong because there are currently no set guidelines for researchers to follow in regard to conducting clinical trials and the lack of FDA-approved guidelines is one of the biggest limitations to conducting clinical trials currently. Choices C and D are wrong because the vast majority of the population is comfortable using smartphones and social media in their daily lives, and in many developed and developing countries, the access to high-speed and reliable Internet is no longer a limitation.