



Research Techniques Made Simple: Tele dermatology in Clinical Trials

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Telemedicine is well established as a means of providing high-quality healthcare at a distance, particularly to patients in underserved populations. Technologies in tele dermatology 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.

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Description: This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

Objectives: At the conclusion of this activity, learners should be better able to:

- Recognize the newest techniques in biomedical research.
- Describe how these techniques can be utilized and their limitations.
- Describe the potential impact of these techniques.

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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 tele dermatology, 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 tele dermatology and traditional face-to-face

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SUMMARY POINTS

- Technological advances in telemedicine, mobile devices, and cloud computing have provided numerous tools that can be used to enhance traditional methodologies of clinical research and have paved the way for conducting clinical trials virtually.
- Virtual clinical trials offer many advantages over traditional modalities for certain research scenarios, including diversifying research populations, reaching underserved areas, improving recruitment and retention of participants, gathering patient-driven data, and potentially improving efficiency while decreasing cost.
- When using aspects of virtual clinical trials, it is important to recognize current limitations, such as the lack of regulatory guidelines and the need for standardization of data collection methods, for example, photographs taken by participants for dermatology-based research.

consultations as well as comparable management concordance and patient satisfaction. Although not as well established as the healthcare-based clinical applications, tele dermatology is emerging as a useful methodology for conducting clinical trials.

In dermatology, clinical trials are typically conducted in a medical facility and require regular visits by the research participant. Now, with the use of technology, all or part of a clinical trial can be conducted virtually. The general concept of a virtual clinical trial is that most, if not all, steps take place in participants' homes with the assistance of a coordination center (Hirsch et al., 2017). A single, or a few, facilities are appointed to manage administrative information, real-time data, and safety concerns provided virtually by participants and research staff. Some study designs combine more traditional clinical trial methodologies with new technologies to create a hybrid or augmented site approach. In this paper, we aim to provide an overview of appropriate uses for tele dermatology in clinical trials and discuss potential ways that technology can be leveraged as a tool to accelerate scientific discovery, decrease participant burden, and augment traditional clinical research. Advantages, as well as unique issues and limitations with the use of tele dermatology in clinical trials, are also outlined.

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 telemedicine 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?

Tele dermatology 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 clinic trial and where aspects of tele dermatology 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

Table 1. Overview of Previous and Ongoing Virtual Clinical Trials

Disease/Study (Dates of Study)	Purpose	Telemedicine Use in Trial	Outcome
Overactive bladder, REMOTE trial (2011–12)	New drug study ¹	Telemedicine was used via a patient-facing web portal in order to manage participants from their homes.	Trial ended early, primarily because of complicated online processes at key steps
Parkinson’s disease (2011–12)	Evaluate the feasibility of providing specialty care to individuals with Parkinsonism via web-based telemedicine in their homes ²	Video conferencing with participants	Remote clinical assessments were conducted nationally and rapidly from a single site, confirming self-reported diagnosis
Alzheimer’s disease (2014–15)	Monitor real-world function in home environments of participants ³	Data gathered from strategically placed sensors were used to assess global cognitive and motor impairment in real time.	Patterns of intra-individual variation detected in each of these areas were used to predict outcomes, such as low mood, loneliness, and cognitive function
Acne, AOBiome Study (2017)	Determine the efficacy of a new topical ammonia oxidizing bacteria for treatment ⁴	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.	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 ($P = 0.03$)
Pemphigus vulgaris, PEMPHIX trial (2014–ongoing)	Compare efficacy of rituximab to mycophenolate mofetil in the treatment of pemphigus vulgaris ⁵	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.	Study is active, but no longer recruiting
Severe acne (2016–18)	New drug study of a subcutaneous drug (ClinicalTrials.gov: NCT02998671)	Virtual enrollment, self-photography, and nurse-assisted photography at home, and home lab draws	Phase 2a placebo controlled RCT enrollment completed
Cluster headache (2016–18)	New drug study of subcutaneous drug (ClinicalTrials.gov NCT02619617)	Virtual enrollment and monitoring, home-based injections, and lab draws at home	Phase 2a placebo controlled RCT, enrollment completed; 80% of patients enrolled virtually
Nonalcoholic fatty liver disease (2016–ongoing)	New drug study of oral drug (ClinicalTrials.gov NCT02913105)	Virtual enrollment and monitoring, home-based assessments, and intermittent imaging at study site	Phase 2a placebo controlled RCT, enrollment completed
Type II diabetes (2018–19)	Study of recently-approved diabetes drug in underrepresented minority populations (ClinicalTrials.gov NCT03434119)	Virtual enrollment and monitoring, home-based assessments, and home-based or local labs	Phase 4 study of marketed drug in new population, recently closed

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.

¹Hirsch et al., 2017; Jadhav, 2016; Orri et al., 2014

²Dorsey et al., 2015a; Dorsey et al., 2015b

³Lyons et al., 2015

⁴Jackson, 2017; Singer et al., 2018

⁵Hoffman-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

compliance with protocols, and improve retention of participants.

WHAT TECHNOLOGIES ARE AVAILABLE WITHIN THE REALM OF TELEDERMATOLOGY?

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.

Investigators in other fields 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.,

Patient Journey in Clinical Trial

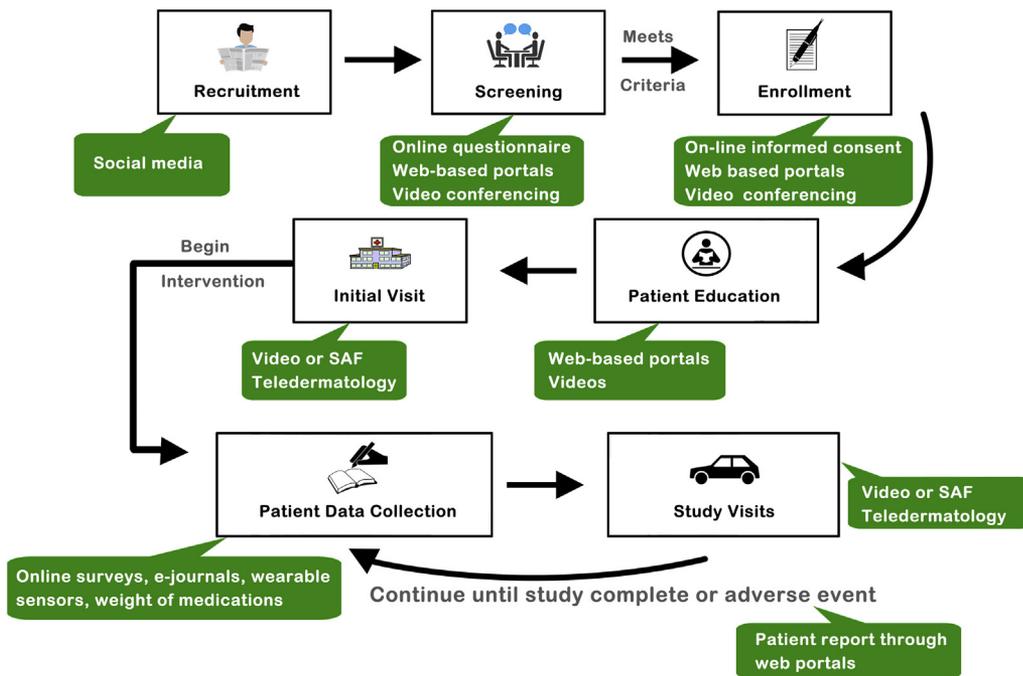


Figure 1. The patient journey in a virtual clinical trial. The patient journey through a clinical trial, with green dialogue boxes indicating points in which tools of telemedicine may be used to improve participant experience, streamline protocol, and provide a more patient-centered approach. SAF, store-and-forward.

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 tele dermatology in clinical trials.

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

Aspect of Clinical Trials	Telemedicine Tools
Recruitment and screening of participants	<ul style="list-style-type: none"> - Social media outlets provide highly visible avenues for recruitment of participants - Online questionnaires and web-based portals for streamlined registration and simplified screening of participants into trials - Partnerships and engagement with patient advocacy groups or patient communities
Gaining informed consent	<ul style="list-style-type: none"> - Participants can read over study information on their own time, interact with investigators and staff virtually, save documents, and sign informed consents online
Participant education	<ul style="list-style-type: none"> - 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
Participant feedback and data collection	<ul style="list-style-type: none"> - 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 - 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 - 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
Adherence and data quality	<ul style="list-style-type: none"> - 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
Retention of participants	<ul style="list-style-type: none"> - Improved compliance and understanding of trial protocols by shifting the convenience towards the participant - Flexible data entry times based on participants schedule and in their own home - Decrease or elimination of on-site visits
Monitoring for adverse events and safety	<ul style="list-style-type: none"> - High accessibility to coordinators via web-based portals for discussion of adverse events at any interval rather than waiting for on-site visit appointments - Safety monitoring via patient or staff entered outcomes on a regular basis - Incorporation of Clinical Trial Research Pharmacists for drug related questions and monitoring

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

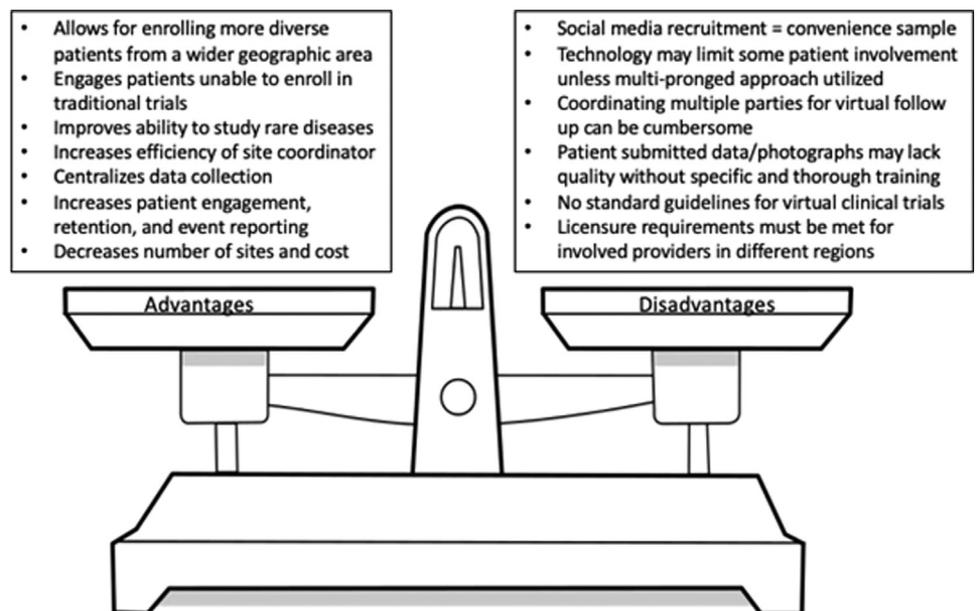
prone to use the Internet or computers. Recruitment techniques are ideally designed to enroll the most representative selection of the population that will ultimately receive the drug, thus they should be multipronged in their approach (Covington and Veley, 2015).

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

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.



MULTIPLE CHOICE QUESTIONS

1. Which statement is true regarding previous and ongoing virtual clinical trials?
 - A. There has never been a successful virtual clinical trial in the field of dermatology
 - B. The first virtual clinical trial had no issues with implementation of online registration for their participants
 - C. Use of technology has improved recruitment and retention in a clinical trial concerning pemphigus vulgaris
 - D. Dermatology has pioneered the use of wearable sensors for data collection in virtual clinical trials
2. Which study might be inappropriate to consider conducting completely virtually?
 - A. Comparing use of two systemic medications for a rare autoimmune disease across several states
 - B. Multistage study with various subpopulations requiring frequent coordination of social work, pharmacy, physical therapy, oncology, and dermatology
 - C. An interventional clinical trial with a new topical drug for rosacea requiring weekly evaluation of clinical progression of disease and patient-reported experiences using the medication
 - D. A trial designed to study the effect of an oral medication for acne on liver enzymes on a monthly basis
3. Which of the following is false regarding the use of social media in recruitment of participants for clinical trials?
 - A. Study population can be viewed as a random sample of the general population
 - B. Social media represents a tool to recruit participants over a wider and more diverse population than traditional methods
 - C. Facebook has been used in previous trials for the recruitment of participants to clinical trials
 - D. A study that recruits participants with social media alone may exclude some populations
4. Which of the following is not an advantage of incorporating technology into a clinical trial?
 - A. Patient-centered data collection allows participants to enter data on their own time rather than attend frequent on-site clinic visits
 - B. Potential for increased communication between study coordinators and research participants

- C. Streamlined online informed consent and study registration
 - D. No need for training to ensure quality of photos taken by participants for data collection purposes
5. Which of the following is an important limitation regarding the use of technology in clinical trials?
 - A. Storage of online data must comply with rigorous privacy standards
 - B. The current guidelines for conducting virtual clinical trials are too restrictive
 - C. The general population is uncomfortable with communication technologies like social media and applications on their phones
 - D. Most potential participants do not have access to reliable Internet

Note: See online version of this article for a detailed explanation of correct answers.

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

VW 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

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SUPPLEMENTARY MATERIAL

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

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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

true statement because if recruitment strategies are not multipronged, some populations, primarily those who choose not to participate in social media, including the very elderly, would be excluded from the study. However, given the widespread availability of social media platforms, the study would likely benefit from an increased diversity of the population, including the underserved who are typically excluded from participating in trials (Choice B). Facebook has been successfully used in several trials to help recruit participants (Choice C).

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.