VIEWPOINT

Remote Research and Clinical Trial Integrity During and After the Coronavirus Pandemic

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Approximately 1 year ago, in March 2020, clinical trials were suddenly and severely disrupted by the COVID-19 pandemic. Pandemic-related restrictions that limited or prevented in-person visits resulted in unprecedented obstacles to clinical trial enrollment, data collection, and intervention delivery for many clinical trials.[1] As of April 21, 2021, ClinicalTrials.gov listed 1773 suspended clinical trials, with many trials identifying the COVID-19 pandemic as the primary reason for suspension. Ongoing trials that were not suspended are likely to be experiencing challenges with enrollment and fidelity to aspects of study protocols that require in-person contact, including interventions and outcome assessment.

Many clinical trial investigators replaced in-person interactions with alternative approaches conducted remotely.[2] A survey of 245 clinical trial investigators reported that the proportion of participant interactions conducted remotely increased from 9% in January 2020 to 57% in May 2020.[2] Remote interactions with participants implemented in response to the pandemic included mailings or drop-off of devices, such as physical activity monitors or pulse oximeters for outcome measurements, and mail delivery or drop-off of pills or devices for trial interventions.[3,4] Additional activities implemented to avoid in-person visits included use of telephone, web-based or video interactions, home visits, or outdoor visits to collect outcomes or administer interventions.[3-5] These remote activities facilitated clinical trial progress during the pandemic.

Embedded trials build data collection for a clinical trial into essential clinical care and represent another alternative to in-person clinical trial interactions. An example is the ongoing Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE) trial (NCT04262206), in which 20 000 participants 75 years or older are randomized to atorvastatin 40 mg daily or placebo and followed up with the electronic health record for outcomes of disability-free survival and cardiovascular events. Medications are mailed to participants' homes. Outcomes that are not part of routine clinical care, including detailed cognitive assessments and physical performance testing, are collected at participants' homes by trained research staff. A visit to a research laboratory is required to collect blood for a biorepository of red blood cells and DNA.

An example of a fully remote trial was a randomized, double-blind, clinical trial conducted in St Louis, Missouri, that evaluated whether fluvoxamine, compared with placebo, improved outcomes in 152 outpatients newly diagnosed with COVID-19.[4] Eligibility screening was conducted by email and telephone and COVID diagnosis was confirmed using electronic health record review. Informed consent was obtained remotely, typically electronically. Participants performed baseline and follow-up self-assessments at home with equipment, including a pulse oximeter, blood pressure monitor, and thermometer, delivered to their doorstep. Self-collected baseline data were reported by telephone to study staff. After randomization, participants were instructed by telephone or email to begin the study drug, delivered to their doorstep. After randomization, participants entered outcome data twice daily via emailed RedCap surveys. Telephone-based data collection was used for individuals without internet access. The primary outcome, consisting of an oxygen saturation of less than 92% while breathing room air combined with dyspnea or hospitalization for dyspnea or pneumonia, occurred in none of 80 participants in the fluvoxamine group and in 6 of 72 (8.3%) in the placebo group (absolute difference, 8.7%; 95% CI, 1.8%-16.4%; $P = .009$). In summary, this preliminary clinical trial was successfully completed without any in-person contact.[4]

After the pandemic, these alternative clinical trial methods could remain, potentially facilitating trial participation for individuals with multiple comorbid health conditions, for whom travel to a medical center is difficult. For example, with increased availability of portable devices, some in-person assessments for trials such as with electrocardiograms (ECGs), carotid ultrasound, spirometry, polysomnography, strength testing, and walking speed could be conducted at home or in a mobile van. Video-administered neuropsychological testing was recently validated.[5] However, participants with cognitive impairment must have a caregiver to assist with testing.[5] Whether other tests that are usually collected in-person could be safely and accurately obtained remotely remains unclear. Could a research participant demonstrate ability to stand from a chair independently and safely, while encouraged using standardized instructions via video? How would the risk of a fall be managed? Could a cognitive test be administered over video while controlling background noise and household member interference? Could someone at home properly self-administer spirometry testing and read results off a small digital screen or transmit data via Bluetooth? Despite a do-it-yourself era of online instructional videos, this type of data collection may not provide rigorous and reproducible results.

Some evidence justifies caution before abandoning or greatly reducing in-person visits for evaluation of clinical trial participants. First, the degree to which medical center visits discourage clinical trial participation is unclear. In a systematic review of 13 studies conducted before the pandemic, that evaluated barriers to clinical trial participation by older adults with cancer,

transportation difficulty represented just 1 of 9 identified barriers to clinical trial participation.[6] Many barriers to participation, including lack of sufficient knowledge about trial participation and concern about treatment toxicity, would not be mitigated by a remotely delivered trial.[6] A study of 2 recruitment methods used for a randomized trial of exercise and nutrition interventions in 121 older adults (≥65 years) from 42 assisted living facilities that had an initial goal of recruiting 5 to 15 participants per facility, concluded that a recruitment method with greater in-person interaction was more efficient, effective, and less costly than alternatives without in-person interactions.[7] Second, some interventions in clinical trials, particularly behavioral interventions, are less potent when delivered remotely.[8,9] Third, outcome measures that require bulky equipment, sterile technique, or special skill to obtain, such as tissue biopsies, computed tomography or magnetic resonance imaging, oxygen consumption, and some blood testing, may be impossible to collect remotely. Yet these outcomes may be critical to understanding the biological targets of an effective therapeutic intervention, which in turn can help identify future novel therapies. Fourth, subjective outcomes, typically amenable to remote collection, are not substitutes for objective testing. Objective and subjective outcomes can yield disparate results and when collected together provide a more thorough understanding of the benefits and harms of interventions.[3,8] The **Table** summarizes potential considerations when conducting clinical trials remotely. When established safety precautions are followed such as social distancing, masking, and administering COVID-19 screening questions prior to visits, attending medical center visits is safe.[10]

Investigators should aim to reduce unnecessary travel by participants to the medical center, which is associated with time, inconvenience, and costs for clinical trial volunteers. However, to ensure that clinical trials continue to provide the highest quality evidence for treatments to prevent, mitigate, or cure disease, decisions to conduct clinical trials remotely should be made only after careful consideration about how these changes will affect the validity and integrity of the clinical trial.

Table. Proposed Remote Adaptations of Randomized Trials

Proposed remote adaptation[a]	Considerations potentially affecting trial integrity
Obtain informed consent	
Mailed or web-based	• Cannot observe or witness signature • May not facilitate staff assessment of the participant's comprehension and understanding
Video	• Participants must have and be able to use video equipment at home • Distractions at home may interfere with the informed consent process • Developing a strong connection with study personnel may be more difficult by video
Remote outcome measures	
Video instruction and coaching while self-administering	• Settings differ between homes, such as availability of an unobstructed walking course, differences in height of a chair for standing tests • Balance testing may not be safe
Self-administered without supervision	• Without supervision, the quality of data collection is unknown • Household members may help or substitute for the participant • The participant may forget or not bother to perform the measure • Additional burden on participant
Collecting data at a participant's home	• Traveling to participants' homes requires time and may be more costly than having the participant come to the medical center • Home environments differ and could affect standardization of some data collection methods • Some outcomes requiring sophisticated equipment may not be appropriate for home collection
Interventions	
Study pills mailed or delivered	• Relies on mail delivery, which can be problematic particularly in rural areas • Requires participant to return bottles if pill counting is used for adherence
Behavioral interventions	• Some evidence suggests that in-person behavioral interventions are more potent than remote[8,9]

[a] Each remote aspect of clinical trials has advantages that include greater convenience by eliminating the time, effort, and resources required for participant travel to a medical center and potentially facilitating participation by individuals living far from medical centers or who have disabling medical conditions that make travel particularly difficult.

ARTICLE INFORMATION

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