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Clinical Trials Without Clinical Sites

Steven R. Cummings, MD

Clinical trials conducted at clinical sites are limited to enrolling people who live nearby and are able to attend visits at clinics. Some types of clinical trials can be performed without clinical sites, which enables people to participate regardless of proximity to a clinical site or limitations that make visits difficult. Trials at clinical sites involve face-to-face relationships with in-person collection of informed consent, examinations, data, and specimens. In contrast, without clinical sites, informed consent and data are obtained online, limited examinations can be performed by telemedicine or visiting research nurses, biospecimens can be collected by visiting nurses or local laboratories, and treatments can be sent to homes or administered by nurses in participants' homes. Trials without clinical sites require internet access and must adapt to the lack of face-to-face interactions with study staff, with communication conducted by email, telephone, or video. Many trials cannot be performed entirely without clinical sites because they require examinations, tests, or treatments that must be given at a clinical site. However, some of the methods required for trials without sites, such as online data collection, follow-up visits by telemedicine or research nurses, and delivery of treatments to home, could reduce the need for visits to clinical sites and reduce the burden of participating in a clinical trial. When feasible, conducting clinical trials without clinical sites has the potential to expand participation and the generalizability of their results.

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Author Affiliations: San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, California; Department of Epidemiology and Biostatistics, University of California, San Francisco.

Corresponding Author: Steven R. Cummings, MD, San Francisco Coordinating Center, California Pacific Medical Center Research Institute, 550 16th St, 2nd Floor, Mission Hall, PO Box 0560, San Francisco, CA 94143 (scummings@sfcc-cpmc.net).

Conventional clinical trials of treatments are performed at clinical sites with face-to-face interaction between research staff and participants and access to procedures available in a clinical setting. However, participation in site-based trials is generally limited to people who live within reach of the sites, and visits can be challenging for busy participants or those with functional limitations. In contrast, trials conducted without clinical sites could expand participation by removing geographic limits and the inconvenience of in-person study visits. This broader participation might increase the generalizability of the results of trials.[1]

Although a few trials had been conducted without clinical sites before the coronavirus disease 2019 (COVID-19) pandemic, restrictions during the pandemic prevented many trials from having in-person visits and procedures at clinical sites.[2] With support from the US Food and Drug Administration (FDA), some trials adapted by conducting aspects of trials without visits, including research visits by telemedicine and delivery of treatments to the participant's home.[3] For example, because in-person visits were not possible, Lenze and colleagues[4] successfully conducted a trial of fluvoxamine maleate for symptomatic COVID-19 by sending an oxygen monitor to assess the outcome of treatment and the study drug to participants' homes. Successful experiences of conducting functions of trials without visits to clinical sites are likely to make trials less reliant on clinical sites after the pandemic ends.

Structure of Trials and Definitions

For trials conducted without clinical sites, the investigator and staff are located centrally and interact virtually with participants by internet or mail. All trial functions, such as data collection and distribution of treatments, are managed centrally. Research nurses may visit participants at home to perform examinations, collect biospecimens, and administer treatments. Trials can also be conducted in unconventional sites other than homes. For example, a successful trial of treatment of hypertension[5] was conducted by pharmacists stationed in barbershops.

Many terms are used for trials whose activities are performed partly or entirely without visits to clinical sites. Trials that have no clinical sites may be called *site-free* or *remote*.[6] The term *home-based trial* emphasizes the convenience of performing some trial functions at home, such as collection of blood specimens and administration of treatments by mobile research nurses.[7] The term *direct-to-participant*[8] indicates that a central unit communicates with and sends treatments directly to the participant rather than by way of local clinical sites. The term *virtual trial* indicates that communications and assessments are performed using digital technologies instead of face-to-face visits.[1] *Decentralized*, *hybrid*, and *disseminated* refer to trials that may or may not be based at clinical sites but use remote data collection, virtual communication, or home-based services to replace some in-person visits.

Table. Comparisons of Elements of Clinical Trials Conducted With and Without Clinical Sites

Element	Trials based in clinical sites	Trials without a clinical site
Structure	Assessment or treatment performed in a physical clinical site such as physician office or dedicated research site.	Assessments and treatment performed without a clinical site.
	Investigator and research staff located at the clinical site.	Investigators and staff located at the coordinating center.
	Participant has face-to-face relationship with staff.	Participants may establish relationship with staff by telephone, email, or video.
	In multicenter trials, functions are coordinated centrally by coordinating center, contract research organization, or sponsor.	All trial functions are managed by the equivalent of coordinating center or contract research organization.
Recruitment	Participants must live within a distance of the site that allows in-person visits.	Recruitment not limited by distance from a clinical site.
	Recruitment from any source but limited to the area near the clinical site. Examples: • Social media, online communities • From EMRs or clinical encounters • Community sources (eg, health fairs) People who are interested are referred to a clinical site.	Recruitment from any source. Examples: • Social media, online patient communities • From EMRs or clinical encounters • Community sources (eg, health fairs) People who are interested are referred to a study website or central phone number.
Data collection and entry	Instruments designed for staff to obtain and enter data in secure systems.	Data entered directly by participants online using secure systems.
	Data may be collected by mobile devices entered directly or by staff.	Data may be collected from mobile devices and wearable sensors.
	Monitors review documents at site visits or remotely.	No source documents at a clinical site to review.
Informed consent	Obtained in person including discussion with research staff.	Conducted online (e-consent). Must have opportunities to ask questions by telephone, text, or email. If the treatment carries more than minimal risk, a conversation with research staff may be required.
	May use paper forms or e-consent on a tablet or computer.	Electronic signature (eg, Docusign) in compliance with FDA regulations.
	The participant signature is witnessed by staff.	A written signature may be sent by photograph from cell phone, scan, or mail or obtained by a visiting nurse.
Examinations, measurements, and imaging	Physical examinations by physicians.	Telemedicine interview or examination, with limited examinations in home by research nurses.
	May include specialized measurements (eg, cardiopulmonary exercise testing).	Portable in-home tests (eg, oximetry, spirometry).
	Specialized research imaging, such as MRI, can be performed by the local facility.	Images acquired by nearby facility sent to reading center.
Treatments	Study treatments provided by a central pharmacy.	Treatments managed by a central research pharmacy.
	Treatments are sent to the site to be stored, tracked, and dispensed or administered at the clinical site.	Oral or topical treatments are shipped to a participant's home from a central pharmacy under a study physician's authorization. Identity may be confirmed by photographic identification and signature for delivery.
		Some parenteral treatments can be administered in home by research nurses.
Biospecimen collection and laboratory tests	Any type of specimen, including biopsies, are obtained and prepared by clinical site or nearby laboratory.	Blood, urine, saliva, or stool collected at home by nurses or phlebotomists or by a local laboratory. Can include some types of specialized preparation, such as cold centrifuging.
	Specimens may have specialized preparation, such as cold centrifuging, and frozen for storage.	Specimens are sent to central laboratory.
	May be analyzed locally or shipped to central laboratories.	In-home point-of-care testing (eg, eGFR by finger stick).
Adverse events and clinical outcomes	Medical oversight by clinical site investigator.	Medical oversight by central study investigator. Participant reports adverse events to coordinating center at any time by telephone, study website, text, or email.
	Participant reports adverse events to staff at scheduled visits.	Not limited by scheduled visits.
	Between visits, participants report events by telephone, text, or email.	Adverse event reporting and advice may be available 24/7.
	Medical care for adverse events might be provided by the sites in medical settings or referred to other local sources of care.	Medical care for adverse events is referred to local sources of care.
	Information about adverse events and clinical outcomes may be validated by review of local medical records with consent to obtain record.	Information about adverse events and clinical outcomes may be validated by review of medical records with participant consent to obtain records.

Abbreviations: eGFR, estimated glomerular filtration rate; EMR, electronic medical record; FDA, US Food and Drug Administration; MRI, magnetic resonance imaging.

How Trials Are Performed Without Visits to Clinical Sites

The **Table** compares how key components of trials are conducted with or without clinical sites. Because many functions of these trials are performed by participants rather than research staff, the protocol and procedures must be designed from the participant's point of view with input from potential participants.

Many observational studies and trials of behavioral or nutritional interventions have been performed without clinical sites. Some of the features of trials without visits, such as making measurements and collecting specimens from home, are useful in place of medical visits. However, conducting trials of drug treatments with-

out visits to clinical sites require special considerations about informed consent, delivery of treatments, and monitoring participant safety.[1]

Recruitment to clinical site-based trials draws on nearby populations, including recruitment of patients during medical visits, searches of electronic medical records, local advertising, and social media targeted to the area around the site; people who are interested then contact the clinical site. Trials that are performed without any clinical sites can use the same approaches but without geographic limits, and people who are interested are directed to a study website or central telephone number to enroll.[4,8-10]

Data collection performed without research staff must be designed so that participants can perform functions on their own with little or no assistance. Thus, the web-based questionnaires, data collection, and steps in the process must be simple, user friendly, and intuitive with readily available support online or by telephone. In addition, a variety of mobile technologies and wearable sensors can collect a wide array of data, from self-report of symptoms to monitoring of physiological functions outside of clinical sites.[10]

Without face-to-face interactions, informed consent is obtained online (e-consent).[11] It is particularly important that the consent document be easily understood and that the participant have ready access by telephone, text, or email with staff who can answer questions. Including a video illustrating key points about the trial may improve participants' understanding of it.[12-14] In place of signing in ink in person, participants establish an identification and password and use an electronic signature[15] to sign online, or they may sign and scan a paper version and submit it online or by mail.

The increasing use of telemedicine for clinical care may also expand its use in clinical trials. Telemedicine interactions with the staff or investigator could replace some follow-up visits to clinical sites, could be used to make diagnoses, such as Parkinson disease for enrollment in a trial, or make some type of measurements that require interviews, such as measurement of cognitive function.

Instead of collecting specimens at clinical sites, blood, urine, and stool specimens could be obtained by research nurses or phlebotomists at the participant's home, processed, and sent to a central research laboratory or repository. Participants can also go to a local laboratory to have specimens drawn. Alternatively, some tests, such as oxygen saturation and creatinine levels for estimated glomerular filtration rate, can be performed by devices or point-of-care tests in the home.[4,7]

Rather than dispensing study drugs in person, drugs are sent from a central pharmacy under a physician's authorization directly to participants' homes. Parenteral treatments can be also be sent to research nurses who then administer the study drug at home. For example, in the Trial of Parkinson's and Zoledronic Acid, a mobile nurse administered zoledronic acid or placebo intravenously at a home visit.[7] For treatments shipped to home, requiring a signature and photographic identification for the delivery confirms and tracks receipt of study drug by the trial participant.

To monitor the safety of treatments, staff ask about adverse events in person at periodic visits. Without visits to clinical sites, participants report adverse events at any time, by telephone, text, or a secure study website, to the coordinating center. Clinical sites that are in medical care settings may treat patients who have adverse events as needed and record that data or refer patients for care. Both clinical trial sites that do not provide medical care and trials without clinical sites triage patients, as appropriate, to local care and obtain data about the adverse event from medical records. Similarly, participants can be asked periodically about clinical outcomes in person in site-based trials; without local sites, a coordinating center may query for outcomes via internet-, telephone-, or mail-based surveys. In both approaches, medical records can be obtained to confirm the diagnoses.

Potential Benefits of Trials Without Visits to Clinical Sites

Potentially, people can participate in trials without clinical sites from anywhere at any time. Visits to clinical sites may require time off work, childcare, and costs of transportation, parking, meals, or overnight stays away from home that can be a financial burden to participants.[16] Visits may be more difficult for people with limitations in physical or cognitive function and might require that a family member, for example, take time away from work or bear the costs of accompanying the participant to a clinic visit. Trials that require a clinical site for some functions may be able to use alternative technologies and strategies (Table) to move some visits to the participant's home.

Slow recruitment is perhaps the most common and challenging problem of clinical trials. Clinical trials based at clinical sites have a limit on the rate of enrolling participants because a set number of sites have a limited number of study visits. Trials without clinical sites are not limited by the number of sites or availability of appointments and therefore can rapidly enroll participants from any geographic location. For example, the KALM trial of herbal supplements for insomnia and anxiety, the first trial performed entirely over the internet, enrolled 391 participants from 45 states in only 8 weeks,[8] and a trial of ω-3 fatty acid supplements for autism used a national autism community to enroll 57 families and 57 teachers from 28 states in 6 weeks.[17]

It can be difficult for patients with medical conditions and functional limitations to travel and tolerate visits to clinical sites, so trials without sites may avoid these barriers to their participation and thereby increase the generalizability of results to patients with multiple morbidities. Patients with rare diseases must often travel far to reach specialized clinical centers to participate in trials. Conducting many or all functions of trials from their homes may increase their access to trials of new treatments that would otherwise be out of reach.

Much of the costs of trials based at clinical sites arise from the cost of space and employment of research staff. Therefore, moving clinical trials from sites to homes and consolidating staff from many sites into a central organization could reduce costs. Research protocols designed to be conducted at clinical sites are prone to complexity because procedures are performed when the participant is already in the clinic. Designing a protocol for a trial without a clinical site might reduce costs by simplifying the protocol and substituting less expensive assessments performed at home for procedures ordinarily performed in clinic.

Limitations of Clinical Trials Without Clinical Sites

Many trials must be performed in clinical sites because they require specialized or complex assessments that are essential to the main aims of the study, such as magnetic resonance imaging to as-

sess cancer recurrence (Table). It may be necessary to administer some parenteral treatments, particularly new drugs whose potential toxic effects are not known, in a medical setting to monitor potential acute or serious adverse effects. Some trials involve patients being treated for medical conditions with assessments that are part of their clinical care and, therefore, are not suited for remote or home-based trials. Trials that require imaging generally require clinical sites, particularly to ensure that the imaging is obtained by standardized protocols. Trials that do not have procedures or treatments that must be performed at clinical sites might be feasible to design without clinical sites or with fewer visits to sites.

Participants in site-based trials develop relationships with research staff and investigators that are important to successful recruitment, complete follow-up, and adherence with study treatments. Relationships with physicians and staff who are enthusiastic about a trial encourage people to enroll and constitute a common reason that people participate in clinical trials. This lack of relationships with face-to-face interactions may diminish participants' enthusiasm to join and continue in a trial. To compensate for the lack of in-person visits, trials without sites rely on telephone calls, email, text, and video contact with staff in the coordinating center.

Home-based trials rely on familiarity with and use of technologies required for virtual trials, including mobile devices with internet access, computers, tablets, or, occasionally, video-enabled devices for telemedicine. Before the pandemic, about 80% of US adults had internet access.[1] In 2017, 77% of adults in the US had smart phones, including at least 50% in every age, educational, and major racial group.[1] However, access to the internet does not guarantee that potential participants can easily manage the virtual processes of a clinical trial. In particular, older patients and those with physical or cognitive difficulties using computers for long or complex tasks may not be able to enroll or complete follow-up processes online without assistance. As more people have turned to online sources and video to maintain connections and telemedicine instead of clinical visits during the pandemic, the ability to use these approaches in clinical trials may have also improved.

Trials without clinical sites should be designed for that approach rather than adopting protocols from trials based at clinical sites. Whereas staff at clinical sites can guide and assist potential participants through protocols with multiple assessments, complex protocols may create barriers to participation in trials without clinical sites. For example, the REMOTE (Research on Electronic Monitoring of Overactive Bladder Treatment Experience) trial of sildenafil citrate for overactive bladder attempted to implement a complex protocol that was designed for site-based trials in a trial without clinical sites.[6] Enrollment required that women go through many steps, including identity verification, screening, consent, and local laboratory testing, and then collect, measure, and report urine volumes for 2 weeks. At least one-third of eligible participants dropped out at each of the many steps so that of 1159 interested women who were initially eligible, only 18 were randomized, representing 1.5% of total and 6.4% of the goal of 283 women.[1] The experience emphasized the importance of keeping protocols for trials without clinical sites as simple as possible.

The FDA has not been a barrier to conducting trials without clinical sites.[1] However, no drug has yet been approved by the FDA to date based on findings of a trial conducted without clinical sites. Trials without clinic visits or sites may be more feasible for phase 4 trials of already approved drugs to test new indications than for phase 2 or 3 trials that require more measurements and procedures to meet regulatory requirements for approval of a new drug. If the FDA approves an investigational drug based on data that include results from a trial performed without clinical sites, the adoption of such trials by the pharmaceutical industry would likely increase. Most clinical trials of drug treatments are conducted internationally. However, regulatory requirements and local practices create barriers to conducting trials without clinical sites internationally. Thus, it is not yet possible to conduct a multinational trial of a drug for potential regulatory approval without clinical sites.

Research Needs

To test whether trials performed without sites expand participation by a broader spectrum of people with conditions of interest, trials performed without clinical sites should describe the geographic, socioeconomic, and racial diversity of the participants to allow for comparison with trials that have clinical sites and with the characteristics of people who have the condition of interest. Data are needed about the yield and cost of various approaches to recruiting participants to trials without clinical sites for various conditions and demographic groups. Trials without clinic visits have achieved 80% to 100% retention rates for 6 to 12 weeks.[4,8,17] Data are needed about adherence in longer-term trials, and studies about how to improve retention without face-to-face relationships would be useful. Trials without clinical sites could reduce the cost of trials. However, more data are needed about the overall cost and cost of components of trials without sites to compare with the standard site-based approach.

Conclusions

The use of methods that replace visits to clinical sites, including collecting data and consent online and delivery of treatments to the home, is expanding. Several trials of supplements or drugs have been performed or are under way, conducted largely without clinical sites.[6-9,17,18] The failure of the REMOTE Trial, achieving only 1.5% recruitment, was widely reported and may have inhibited pharmaceutical companies from adopting clinical trials entirely without sites. In contrast, the recent trial of fluvoxamine for COVID-19 provides a recent successful model of a trial without sites.[4] The number of trials conducted without sites has been reported to be growing[19] and may accelerate as additional successes are published and more investigators gain experience with the methods that enable conducting such trials.[1] The National Academies of Science, Engineering and Medicine[1] recently published a report that encouraged the use of virtual trials. Pharmaceutical companies may increase their use of these methods as confidence grows that the FDA will accept data from trials conducted without clinical sites as part of approval of new drugs or new indications for existing ones.

The COVID-19 pandemic requires clinical trials to find alternatives to in-person visits to clinical sites. The pandemic may have accelerated the adoption of methods for conducting at least some

activities without visits to clinical sites, thereby reducing barriers to participating in trials. When feasible, conducting trials without clinical sites could also substantially expand participation in clinical trials and increase the generalizability of their results.

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REFERENCES

1. National Academies of Sciences, Engineering and Medicine. Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation. Shore C, Khandekar E, Alper J, eds. Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop. National Academies Press; July 23, 2019. https://www.ncbi.nlm.nih.gov/books/NBK544217/

2. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *JAMA*. 2020;323(21):2135-2136. doi:10.1001/jama.2020.4689

3. US Department of Health and Human Services, Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: guidance for industry, investigators, and institutional review boards. Accessed November 12, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

4. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. doi:10.1001/jama.2020.22760

5. Victor RG, Ravenell JE, Freeman A, et al. Effectiveness of a barber-based intervention for improving hypertension control in black men: the BARBER-1 study: a cluster randomized trial. *Arch Intern Med*. 2011;171(4):342-350. doi:10.1001/archinternmed.2010.390

6. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp Clin Trials*. 2014;38(2):190-197. doi:10.1016/j.cct.2014.04.009

7. ClinicalTrials.gov. Trial of Parkinson's And Zoledronic Acid (TOPAZ). NCT03924414. Accessed January 23, 2021. https://clinicaltrials.gov/ct2/show/NCT03924414

8. Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore)*. 2005;84(4):197-207. doi:10.1097/01.md.0000172299.72364.95

9. Marquis-Gravel G, Roe MT, Robertson HR, et al. Rationale and Design of the Aspirin Dosing-A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial. *JAMA Cardiol*. 2020;5(5):598-607. doi:10.1001/jamacardio.2020.0116

10. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *NPJ Digit Med*. 2020;3:101. doi:10.1038/s41746-020-0302-y

11. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed consent. *N Engl J Med*. 2017;376(9):856-867. doi:10.1056/NEJMra1603773

12. Tait AR, Voepel-Lewis T. Digital multimedia: a new approach for informed consent? *JAMA*. 2015;313(5):463-464. doi:10.1001/jama.2014.17122

13. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA*. 2004;292(13):1593-1601. doi:10.1001/jama.292.13.1593

14. Rowbotham MC, Astin J, Greene K, Cummings SR. Interactive informed consent: randomized comparison with paper consents. *PLoS One*. 2013;8(3):e58603. doi:10.1371/journal.pone.0058603

15. US Department of Health and Human Services, Food and Drug Administration. Use of electronic informed consent in clinical investigations—questions and answers: guidance for institutional review boards, investigators, and sponsors. Published December 2016. Accessed May 17, 2016. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm436811.pdf

16. Vaswani PA, Tropea TF, Dahodwala N. Overcoming barriers to Parkinson disease trial participation: increasing diversity and novel designs for recruitment and retention.*Neurotherapeutics*. Published online November 4, 2020. doi:10.1007/s13311-020-00960-0

17. Bent S, Hendren RL, Zandi T, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):658-666. doi:10.1016/j.jaac.2014.01.018

18. Eilenberg KL, Hoover AM, Rutherford ML, Melfi CA, Segal S. From informed consent through database lock: an interactive clinical trial conducted using the internet. *Drug Inf J*. 2004;38(3):239-251. doi:10.1177/009286150403800303

19. Dolgin E. Industry embraces virtual trial platforms. *Nat Rev Drug Discov*. 2018;17(5):305-306. doi:10.1038/nrd.2018.66