Virtual Clinical Trials: Best Practices in Moving Toward a Patient-Centric Research Model

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Several decades ago, almost all clinical trials for new medications were conducted within the relatively small community of academic medical centers. Gradually, this practice began to shift, with community hospitals, free-standing research sites, and physicians in private practice becoming involved as research sites. Still, the model of clinical trials remained based at medical institutions. In the last few years, and in conjunction with the increase in patient involvement in the design and conduct of research programs, there has been a notable increase in the idea of "virtual" or "decentralized" clinical trials. While this term can be used in different ways, virtual clinical trials are fundamentally a movement of clinical studies away from medical institutions. In the virtual trial model, clinical studies are focused on bringing the clinical study directly to the participant and allowing data collection to be completed in a participant's home or local community. This paper examines the nature of virtual clinical trials, potential benefits and risks of this new paradigm, and best practices for maintaining regulatory and Institutional Review Board (IRB) compliance.

What does "virtual clinical trial" mean?

The term "virtual clinical trial" can encompass different organizational models. At one end of the spectrum is a pure virtual delivery model where all study activities and visits are conducted remotely at the participant's location. Even the informed consent process is conducted electronically, online or through a tablet or smartphone application. These studies also take advantage of mobile phone applications like the Apple ResearchKit[1], fitness trackers, and online patient reported outcome (PRO) assessments to collect data either passively (e.g., transmitting information such as sleep patterns collected by a fitness tracker automatically into the study database) or actively (e.g., through quality of life or other outcome measures completed online by participants).

The first virtual trial was the REMOTE study in overactive bladder disease sponsored by Pfizer, launched in 2011, which was entirely home-based for the participants.[2] Informed consent was obtained online and documented by electronic signature, study drug was delivered directly to participants' homes, and adverse event reports and efficacy outcomes were recorded using mobile devices and web-based measurement tools. Another example of a completely virtual clinical study was conducted by Sage Bionetworks, assessing the natural history of the symptomatic progression of Parkinson's disease in 9,500 participants.[3] In this observational study (which did not include administering any

investigational product)—the entire study—including documentation of informed consent, and recording of all measurements—was conducted through the mPower app on participants' iPhones.

Another delivery modality is a hybrid virtual trial which mixes remote data collection with clinical site visits, with the aim of reducing the burden on study participants. For example, initial study screening, or mid-study complex procedures are conducted at the clinical site, while study activities including intermittent check-in visits and routine blood draws can be completed via tele-visits or deployment of home health nurses.

What are the potential benefits of conducting a trial "virtually"?

Advocates of virtual clinical trials see many potential benefits. First, this participation modality can make involvement in research more feasible for a greater number of patients. Reorganizing trials around participant schedules may mean there is no need to drive to a medical center for frequent study visits, no waiting in line at the lab, and no juggling time constraints of work and family obligations. This, in turn, should lead to easier enrollment and higher rates of participant retention through study completion. Virtual trials certainly help avoid the common finding that on average, 20% of clinical sites that are opened for trial participation never enroll any participants.

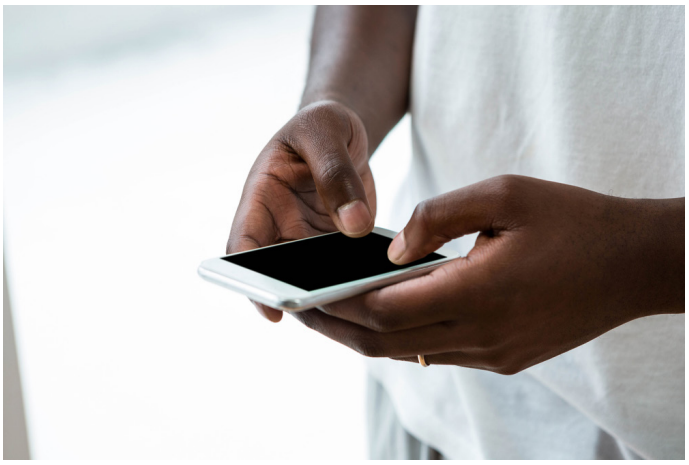
The virtual research model also means that study participation should be available to a broader geographic and demographic distribution of patients. There is hope that virtual trials can expand the racial, ethnic and age diversity of study populations, allowing for a more complete understanding of how investigational products work in more diverse, real-world settings. Since this research model is fairly new, we may have to wait for concrete data that show the impact on diversity in research across a broad spectrum of studies.

What are the potential downsides of conducting a study "virtually"?

It is essential to remember that digital devices, mobile applications and online communication methods are useful tools but are not complete solutions. The launch of Apple's ResearchKit facilitated the enrollment of thousands of participants into research programs on a wide variety of chronic diseases, but several weeks later, about 90% of initial enrollees had dropped out of the projects.[4] The Pfizer REMOTE study, mentioned above, was stopped early after failing to recruit sufficient participants. It did, however, provide important information to that study team and the research community about the need for greater participant support, resourcing to handle questions and participant concerns about sharing personal medical details online.[5] For these reasons, it will be important for companies that are initiating decentralized

clinical trial projects to work with partners who have experience in the actual conduct of virtual studies, and can offer an end-to-end solution, rather than relying on technology alone to make the study conduct flow easily.

Some patient populations may be uncomfortable with the technology of decentralized clinical trials. On the other hand, some patient populations may be ideal for this type of communication. For example, UCB and Science 37 are collaborating to conduct a study in restless leg syndrome which is planned to enroll 138 participants, age 13-17. UCB had delayed conducting this trial due to expected enrollment challenges to clinical sites of finding eligible patients in this age category. Using the decentralized model and targeting a group that is extremely comfortable with communication through modern technology, they project an enrollment time of 18 months.[6]



What is the regulatory oversight of virtual clinical studies?

There are no specific Food and Drug Administration (FDA) regulations or guidance related to virtual studies. However, the FDA is actively exploring this topic as evidenced by public docket FDA-2015-N-3579 on "Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs"[7]. Virtual trials must be conducted in accordance with the same regulatory standards as traditional trials.

One common question from sponsors who are considering or planning decentralized clinical trials is about FDA Form 1572, the form submitted to the FDA to identify the principal investigator (PI), clinical site staff, and facilities to be used for each clinical "site". When there are no actual physical clinical sites, sponsors struggle with whom to list as the PI. In some cases, they may decide to submit one Form 1572, identifying one person as the PI for the entire study. This may best reflect the decentralized model of study conduct, but the PI should be aware that they are then assuming training and oversight responsibility for all members of the study team. Other suggested models include identifying one PI for each state (and medically-licensed in that state) in which participants will be enrolled.

Are there specific ethical or IRB concerns in "virtual" clinical studies?

There are no specific regulations or guidance for Institutional Review Board (IRB) oversight of virtual clinical trials. Therefore, IRBs will apply the same regulatory criteria for the approval of research as they do for all studies (see sidebar). However, the application of these principles and relevant information the IRB may require to make determinations may differ from those of traditional trials. Sponsors and protocol authors should address the following points in the IRB application materials:

- **Informed consent:** While many IRBs are becoming comfortable with electronic informed consent tools, it is essential to remember that informed consent is a process, not a document. IRBs will want to ensure that the consent process includes the necessary elements of information sharing, comprehension of that information by the potential participant, and voluntary consent to participate. Potential participants must have the opportunity to ask questions about the study through an interactive mechanism, which should be described in the protocol or other documents.
- **Minimization of risks:** In a decentralized clinical trial process, it is still essential to ensure that risks to participants are minimized through a careful eligibility assessment before enrollment and study drug administration. If that eligibility assessment does not include any in-person contact with a study

Criteria for IRB Approval of Research

In order to approve the conduct of research, the IRB must find that these requirements are satisfied.*

1. Risks to subjects are minimized
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
3. Selection of subjects is equitable. If vulnerable populations are included, whether additional safeguards are necessary to protect their rights and welfare
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative
5. Informed consent will be appropriately documented
6. The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
7. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data

* Based on 21 CFR 56.111. The exact wording of the regulations has been shortened for clarity; please consult the CFR for the exact regulatory language.

team member, the protocol should be clear about how eligibility will be assessed with attention to ensuring that clinical signs and symptoms that might indicate potential safety issues are identified. When the study drug is one that has the potential for abuse, if the study drug distribution is remote (e.g., mailed directly to the participant's home), the protocol should describe how it will be ensured that the study drug is transferred securely.

Similarly, during the study, the protocol should describe how adverse events are being monitored, and what will happen if an adverse event is reported by a participant who may need medical attention for diagnosis or treatment. For example, if there is no clinical site and all outcomes are collected by self-report and the participant on study drug suddenly develops a significant rash which may be a drug reaction, how will they report it? Who will assess, diagnose and provide treatment?

- **Security of data:** The protocol should describe how any study data being collected online is going to be kept secure and confidential, and how access will be managed.

Conclusion

Virtual clinical trials offer potential advantages in moving toward a more patient-centric research model and a more diverse patient community representation in clinical trials, bringing trial data closer to real-world experience. Decreasing the burden on research participants may improve study enrollment rates, allowing for faster trials and the ability for biopharma and other study sponsors to reach decision points more quickly, optimizing research investments and pipelines. While there are an increasing number of internet-based and electronic tools to assist in the conduct of these studies, the tools do not provide complete solutions to study conduct. Experience in thinking about the unique design, conduct, and ethical challenges of virtual clinical trials will be essential as more researchers move toward this model of research.

References

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About the Authors

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Dr. Lindsay McNair has extensive experience in the pharmaceutical industry. Prior to joining WCG, she was a consultant to pharmaceutical and biotechnology companies, providing medical guidance on clinical development strategies and study designs for new drug studies, and medical oversight of all phases of clinical trials. Dr. McNair teaches graduate-level courses on the scientific design of clinical research studies. She has been actively involved in IRB work for more than 20 years, and has a Master's of Science in Bioethics with a concentration in research ethics.

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As Head of IQVIA ™ Virtual Trials, Bola Oyegunwa is responsible for leading innovative and patient centric virtual solutions that enable patients to participate in clinical trials from home, helping sponsors accelerate their time to market. Bola's key experience includes re-engineering and optimizing traditional delivery models for IQVIA's remote, technology-enabled virtual trial execution.

Prior to joining IQVIA, Bola was a Management Consultant at a Healthcare M&A Advisory Firm and an Associate at a Private Equity Firm. Bola holds a Masters in Molecular Genetics, PhD in Immunology and a MBA, all from North Carolina State University.

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