Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Mental Health Clinical Research Innovations during the COVID-19 Pandemic

The Future Is Now

Kelly B. Ahern, BS, Eric J. Lenze, MD*

KEYWORDS

• COVID-19 • Fluvoxamine • Remote • Trials • Decentralized

KEY POINTS

- The COVID-19 pandemic presented unprecedented challenges to clinical research.
- Telemedicine was frequently used to continue clinical care while prioritizing patient and provider safety.
- Using telemedicine technology, remote or decentralized clinical trials have risen to prominence during this era of "physical distancing."
- The feasibility of fully remote trials testing psychiatric medications was demonstrated by studies of the selective serotonin reuptake inhibitor fluvoxamine in COVID-19.
- Telemedicine and remote clinical trials are the future of psychiatric clinical research.

INTRODUCTION

The beginning of the COVID-19 pandemic brought most clinical research to a sudden halt. Enrollment in clinical trials per site plummeted by approximately 80% between April 2019 and April 2020.[1] When COVID-19 reached our institution, the Washington University School of Medicine, a multitude of restrictions were placed on clinical research. Research staff began working remotely, nonessential visits were canceled or postponed indefinitely, and most clinical trials became impossible to conduct without significantly modifying the study protocols. It soon became clear that the 2-week quarantine period would extend longer, with great uncertainty to this duration. Clinical researchers were faced with a daunting choice: cease research activity altogether or find new, innovative ways to move forward in these unprecedented times. In early 2021, more than 1 year since the pandemic first began, more than a thousand

Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA
* Corresponding author. Campus Box 8134, 660 S. Euclid, St Louis, MO 63110.
E-mail address: lenzee@wustl.edu

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trials were listed as suspended on ClinicalTrials.gov, most owing to the COVID-19 pandemic.[2] However, the time from 2020 to 2021 was also a period of incredible adaptation and innovation in psychiatric clinical research. This article summarizes some of the key changes and assesses their future impact.

TELEMEDICINE

One of the innovative tools with the most significant potential for use in clinical research during the pandemic has been around for more than a century. Little-used in psychiatric research before 2020, telemedicine has become prominent, in research and practice, during the COVID-19 pandemic. The umbrella of what could be considered "telemedicine" is broad and encompasses many types of remote communication, ranging from telephone consultations to videoconferencing sessions.

Telemedicine, which is becoming increasingly commonplace in our clinical and research practices, has a fascinating history worth reviewing. Because of the fluidity of the definition of "telemedicine," the exact date of the genesis of telemedicine is unknown.[3] Technological advances in telecommunications in the twentieth century continued to evolve the landscape of telemedicine. Casualty lists and medical supplies orders were communicated via telegraph during the civil war and there are reports of telephone wires being used for medical communication as early as 1906.[3,4] Radio communication opened new avenues for telemedicine after World War II and was followed by the development of television several decades later.[3] The first predecessor to the modern virtual appointment (now over Skype, Zoom, or other major teleconferencing software) occurred in 1964 via interactive video linking the Nebraska Psychiatric Institute to the Norfolk State Hospital. State funding for telemedicine research projects in the 1960s and 1970s allowed for testing the feasibility and clinical efficacy of telemedicine with somewhat positive results.[3]

NASA and the developing space programs further expanded the capabilities of telemedicine. One such example occurred in 1975 with the Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC) project, wherein television radio and remote telemetry were used to connect an Indian Health Service hospital to a mobile health unit in the Indian reservation.[5] Although the use of technology was more time consuming than in-person visits, the providers who participated felt that the STARPAHC program was successful in extending health care to the somewhat isolated population on the reservation. The development of modern internet in the 1990s, followed by subsequent widespread availability in the 2000s allowed for more widespread use of telemedicine.[5]

There are some advantages to telemedicine over the traditional model of face-to-face medical care. It allows physicians to treat patients in underserved areas who otherwise cannot attend in-person appointments owing to physical or logistical constraints. Additionally, virtual or telephone appointments can be more convenient for both parties and more cost effective in certain situations than traditional in-person appointments.[6,7] Although several arguments against telehealth cite a lack of interpersonal contact and a possible decreased quality of care, there is evidence to suggest that the accessibility that telehealth affords can lead to high levels of patient satisfaction.[6,7]

During the COVID-19 pandemic, telemedicine was used to provide health care in outpatient settings—especially in mental health—while decreasing risk of COVID-19 exposure and subsequent illness. The COVID-19 pandemic also saw the rapid and successful implementation of remote monitoring programs specifically for patients with COVID-19.[8,9]

TELEMEDICINE AND RESEARCH

Telemedicine has great potential in the world of fully remote or decentralized clinical trials, which are trials that do not require participant visits to clinical sites.[10] These trials rely on telephone communication, emails, texting, smartphone applications, videoconferencing, and many other technologies to deliver interventions and collect data. Although several significant challenges can affect these trials, the benefits they may deliver to current and future clinical trials merit their consideration.

In the prepandemic world, clinical research faced several significant hurdles to participant recruitment and engagement. In particular, rural populations have been historically difficult to engage in clinical trials. One potential driver of this phenomenon is the higher costs and travel time required to attend appointments at academic medical centers, which are often located in urban areas. A systematic review by Ross and colleagues[11] (1999) found that inconvenient travel and its associated expenses were a driver of trial refusal and participant attrition across many trials. Because of distance and a lack of exposure, rural populations may also be limited in their awareness and knowledge of clinical trials, which poses further obstacles to obtaining geographically diverse samples.[12,13] Telemedicine offers a workable solution to these problems, allowing investigators in a central location to easily reach and communicate regularly with participants, regardless of their geographic location.[14,15] Supporting this notion, a study by Sommer and colleagues[16] (2018) found that participants undergoing the decentralized model of their study had greater geographic diversity when compared with those who underwent the conventional (or in-clinic) arm. Additionally, the implementation of a decentralized study model also may increase convenience to those enrolled in the study by decreasing travel time.[15]

Coming to clinical trial visits poses burdens related to travel and potentially time off work, which may disproportionately affect individuals in minority groups that are historically underrepresented in clinical trials. One strategy to overcome this lack of diversity is to decrease participant burden, which decentralized trials can help accomplish.[17] In particular, the US Food and Drug Administration encourages the use of online recruitment strategies and electronic informed consent documents when needed to include underrepresented populations in research trials.[18]

Another important benefit of remote or decentralized clinical trials is the rate at which recruitment can occur.[16] As mentioned elsewhere in this article, studies do not require visits to a central site, so there are fewer geographic limitations on recruitment. With the help of online advertising, these studies can also quickly and efficiently reach and enroll many more people than an in-person study would, facilitating larger sample sizes and a greater impact of the study results. A wider study reach and faster recruitment can also be particularly advantageous when the study criteria are more specific or if the trial is recruiting patients with a rare condition.

There are also limitations of decentralized or remote clinical trials. First and foremost, it is important to consider that not all trials are well-suited to a remote or decentralized model. For example, more involved studies that require specialized medical tests and/or large or expensive equipment would be poor candidates for a decentralized model owing to the lack of acceptable remote alternatives. Second, privacy and data quality concerns accompany remote clinical trials.[15] By conducting a clinical trial remotely, the investigator relinquishes a great degree of control over the participant's physical environment and, subsequently, the trial participant's privacy. This lack of control, and its associated privacy concerns, lends itself better to some types of studies than others. For example, a simple online questionnaire can be completed discreetly on a mobile device in most settings. Conversely, neurocognitive or other

performance testing is significantly more difficult to conduct remotely and the investigator is unable to tightly control trial participant's immediate environment, which may lead to privacy concerns. Third, assessments requiring a participant to remain undisturbed for a length of time are particularly difficult to coordinate remotely and may require flexibility in the study protocol if the assessment is interrupted. Fourth, if a medication or intervention is riskier, it is more difficult to monitor adverse events and intervene if necessary if a participant is local and the study is in-person; interventions that are high risk (ie, early phase/phase I in human pharmaceuticals or invasive devices) or high intensity (ie, infusions or implants) likely need in-person contact with the investigative team. Overall, it is crucial that investigators critically evaluate the experimental intervention and trial requirements to determine if a remote or decentralized trial is the best option.

Additionally, there are legal limitations on remote clinical trials, although the status of these restrictions may be in flux. One such limitation, prescription privileges, can vary across different states.[15] This legal obstacle can limit a certain investigator's ability to recruit and may necessitate the foundation of additional sites in each of the states from which participants are being recruited. This hurdle can be overcome by involving investigators licensed in different states, including investigators licensed in multiple states, or by partnering with licensed mobile health care provider services.[19] Beginning in March 2020, most US states relaxed their intersite prescribing and telemedicine laws in the wake of the pandemic. It is unclear at this time how many of these states will continue to allow intersite prescribing over the long term. It is also anticipated that the US Department of Health and Human Services may continue to relax intersite telemedicine restrictions, thereby overriding any state-level restrictions. For example, on December 3 it was reported that the US Department of Health and Human Services instituted a new policy allowing telemedicine services across state lines during the COVID-19 emergency. Further, the US federal government's push for more decentralized trials, outlined in the 2021 Senate Appropriation Committee funding bills for US Department of Health and Human Services (including the National Institutes of Health) and the US Food and Drug Administration, included specific language furthering the use of decentralized trials. This wording may accelerate legal changes allowing interstate prescribing.

It is also important to keep the population of interest in mind when deciding to conduct a clinical trial, particularly a fully remote clinical trial. The technological requirements that often accompany decentralized trials may pose a high hurdle and learning curve for participants less familiar with technology. Although at least 50% of every age group (including older adults) possessed a smartphone in 2017, older participants and those who are cognitively impaired may struggle more with a technology-driven study than an in-person one.[10,20] Additionally, high-speed internet, reliable phone service, and other elements of technical infrastructure are luxuries for some people, posing a significant barrier to making clinical trials more universally accessible. Per the 2018 US census, thousands of households in each state were estimated to lack internet access.[21] In 2019, the Federal Communications Commission reported that 21.3 million Americans had no internet connection or internet connections with speeds lower than 25 Mbps/3 Mbps at the end of 2017.[22] Although deployment of broadband internet has improved in rural and tribal lands, as of April 2020, 22.3% of rural Americans and 27.7% of those inhabiting tribal lands still lack internet with speeds of more than 25 Mbps/3 Mbps.[23] These inequities present a quandary to equitable participant recruitment and adequate sample diversity for trials relying on the internet.

Although there is no single solution for including Americans who lack the technological literacy or infrastructure to fully participate in remote or decentralized clinical trials,

there are a few strategies that can be used to remediate the problem. Allowing various modalities for study assessments, including online questionnaires, phone questionnaires, and even carrier mail, may help to make study participation possible for those lacking reliable internet or phone lines. Depending on the nature of the study and the limitations of the participants, a hybrid in-person/remote approach may be more appropriate than a fully remote trial.[19]

Furthermore, even the safest interventions can still carry some degree of risk. In these cases, it is necessary to ensure that the trial participants are well-informed on what actions should be taken in the event of a health emergency. Such information can include a list of local approved providers, clear instructions on when to seek help, and how to inform the study team of any changes in medical care or study participation.[19]

Maintaining high levels of participant engagement from informed consent to study termination is critical to study success. Those of us who have read the Apple terms and conditions may already be familiar with a few of the significant difficulties of remote consent processes. For any study—whether remote, in-person, or hybrid—a thorough consent process is ethically desired and can decrease participant attrition in the future. The aforementioned systematic review by Ross and colleagues[11] (1999) found that participants across many studies desired more information about a trial than was provided to them by the trial team and called for a simpler, more readable consent form. For in-person clinical visits, it is much easier to keep the participant engaged. Those who consent participants should probe for questions and gauge participant understanding of the study. Although not necessarily the same as an in-person consent visit, ensuring that a study staff member is available to discuss the consent either by phone or email with the participant before enrollment can help to ensure a thorough consent process.

However, the hurdles to maintaining participant engagement in a remote clinical trial do not end with an interactive consent process. Trial participant attrition is a concern for in-person and fully remote trials alike, and thus it is important to maintain participant interest and engagement in the trial from consent to completion. Although extensive visits and procedures are objectively less convenient than answering a simple phone survey, they also require a high level of commitment to the study and the study mission. The ability to easily interact with study staff can also make a difference when it comes to improving recruitment outcomes and decreasing attrition. Corcoran and colleagues[24] (2015) found that social interaction from staff members helped to improve participant recruitment and retention rates. In contrast, Sommer and colleagues[16] (2018) compared decentralized and conventional/in-person clinical trial questionnaire administration and found that significantly more participants completed the decentralized assessments (89%) compared with the conventional or in-person assessment (60%).

INNOVATIONS IN REMOTE MONITORING

Remote monitoring has been a long-standing focus of our laboratory. Several of our studies have used ecological momentary assessment (EMA) technology, requiring participants to complete quick daily surveys on a mobile device. EMA is a type of assessment that prompts participants to evaluate their status in the moment (eg, “Right now I feel . . . ”), rather than retrospectively. Retrospective outcome measures, especially in mental health, which relies on subjective reporting, suffer from a variety of biases, particularly the peak-end rule. The peak-end rule refers to the human tendency to judge the entirety of a subjective experience by prototypical moments, most notably

the moments where the experience was the most extreme and the final moment.[25,26] Using EMA helps to mitigate the peak-end rule by encouraging contemporaneous evaluations rather than asking the individual to retroactively evaluate a period of time. It has been successfully implemented in several of our laboratory's current and former studies (eg, Moore and colleagues,[27] 2016). EMA also aids in examining the variability of symptoms (such as depressed mood) over a defined span of time. For example, Rodebaugh and colleagues[28] (2021) successfully used EMA to track the rapid individualized changes in COVID-19 symptoms that occurred over 15 days after illness onset. Additionally, before the onset of the pandemic, we had begun to explore mHealth research and recently founded an mHealth Research Core at our university to increase uptake in such measurement advances.

ANATOMY OF A FULLY REMOTE CLINICAL TRIAL: THE STOP COVID TRIAL

Before the pandemic, telemedicine was already implemented to a degree in some of our multisite studies, such as the OPTIMUM study.[29] However, perhaps our most unique and timely application of novel strategies to conduct clinical research remotely occurred in our laboratory's STOP COVID trial, which was a placebo-controlled randomized controlled trial testing fluvoxamine for COVID-19. For that reason, it makes an excellent example of clinical research adaptations to the pandemic, including psychiatric researchers repurposing themselves to fight the pandemic itself.

STOP COVID was motivated by basic research showing that the antidepressant fluvoxamine demonstrated effectiveness in preventing sepsis in mouse models, and its need was spurred by the urgent need for an effective acute treatment for outpatients with mild COVID-19.[30,31] Although many early pandemic research studies focused on new drug development, we instead explored repurposing an existing US Food and Drug Administration–approved medication.

Just as the urgent nature of the pandemic required many physicians to step out of their traditional specialties and roles, this trial was different from our other trials.[32] For this trial, we reached beyond our own department and partnered with the division of infectious diseases to approach a largely nonpsychiatric problem with a psychiatric medication.

We recruited exclusively from the St. Louis metropolitan area owing to challenges in recruiting, and getting study supplies to, participants. In the past, we have largely used advertisements, word of mouth, and referrals for study recruitment, but the isolation of the pandemic made it difficult for us to reach eligible patients within our limited window of time without us first initiating the contact. For this particular study, we advertised locally with signs at testing sites, emails to local physicians, and the news media. The bulk of our participants were identified via electronic health records (EHR) from the local hospital system, then screened and recruited by study staff via telephone and email. Additionally, traditional and social media were used as strategies for remote trial recruitment.

Once contact was initiated, participants were rapidly screened through a short prescreen on our database. If the prospective trial participant passed the prescreen, they were then emailed a link to a consent form under their identifying number in our database. We were ultimately successful in recruiting and consenting 152 participants.

Once participants consented, we had to quickly enroll them to get study medication started within the first week of being actively symptomatic. This meant getting participants randomized and on treatment within hours of first contact by the study team. Similar to the remote monitoring program led by Agarwal and colleagues[33] (2021), staff members carried out a no-contact delivery of the study medication (or placebo) and

required supplies to the participants' doorsteps. Participants were asked to complete brief online surveys twice daily for the first 15 days, followed by a short set of online surveys at the 30-day mark. These surveys requested the participants use their own supplies or provided study supplies to report their oxygen saturation, blood pressure, temperature, and pulse. They were also asked to report the presence and severity of their current dyspnea.

Our findings suggested that fluvoxamine, taken early in COVID infection, was effective in preventing clinical deterioration. In the placebo group, 6 of the 72 randomized patients (approximately 8%) met our criteria for clinical deterioration during the 15-day study. In contrast, no individuals in the fluvoxamine group (n = 80) deteriorated.

A key outcome of the STOP COVID trial was to demonstrate the feasibility of a fully remote clinical trial. The highly contagious nature of COVID-19 precluded any in-person interaction. We were working with an entirely remote study population with various levels of illness severity, technological literacy, and interest in our study. From a participant standpoint, we wanted the study to be high touch, but not high tech. We aimed to generate a simple, user-friendly interface for the participants to interact with.

We also tried to keep the study as simple and straightforward as possible. Cummings[8] (2021) discussed the difficulties that arise from complicating a participant's experience by adding additional measures to the primary outcome variable. In general, in-person clinical trial visits can easily fall prey to investigators' desires to screen patients extensively against a long list of inclusion and exclusion criteria or acquire as much data as possible. Although certainly burdensome for the participant, this is not always detrimental to in-person clinical trials. The Research on Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial, the first published fully remote trial of a pharmaceutical drug, demonstrates the pitfalls of a complicated enrollment and participation process. Although their initial aim was to enroll and randomize 283 participants, the study only randomized 18 participants, in part owing to attrition during screening that resulted from a time-consuming multistep process involving online questionnaires, laboratory testing, and additional medical screening.[34]

Also worth consideration is that fluvoxamine is not without side effects. For these reasons, maintaining adherence and compliance were crucial to having a good outcome with the study. The side effects of a selective serotonin reuptake inhibitor tend to be at their worst during the first few days of treatment, so to increase participant comfort, staff members would call the participants for the first 2 days and help them to manage any side effects they may be experiencing. This gesture had the dual purpose of keeping participants engaged, as well as allowing them to feel well-supported in our study, thereby likely decreasing attrition rates. From a participant retention standpoint, we were successful: only 9 participants dropped out before taking their first dose of the medication and 27 failed to complete the 15-day assessment; only 13% of daily surveys were left uncompleted.

With only 1 week from symptom onset to enroll each individual, we needed to be strategic in how we recruited and consented participants. Owing to the urgent nature of starting treatment rapidly in acute COVID-19, we instituted a mandatory 7-day window from onset of symptoms to first dose of study medication. For analyses, we developed a modified intention-to-treat group comprising all those included in the analyses meeting 2 distinct criteria: (1) they met all study inclusion and exclusion criteria and (2) they took the first dose of the study medication within the 7-day window from symptom onset. This modified intention-to-treat group is often seen in infectious disease studies, but is uncommon in mental health.

Our primary outcome variable was respiratory decompensation (operationally defined as an oxygen saturation of <92% and a dyspnea rating of >3), so it was important that we ensure that our randomized and then lost to follow-up participants had not decompensated. The study was designed so that all participants were in the St. Louis area, allowing us to first check our own EHR for emergency visits or hospitalizations. However, this process was not a complete solution because our EHR access was limited only to those who visited our own hospital. For the participants who were lost to follow-up and were not part of our EHR, staff members called them to ensure that they had not visited a hospital, emergency room, or urgent care after they left our study. This addition to the study protocol helped us to obtain the most complete dataset possible.

After the success of our pilot/feasibility trial, we set out to complete a nationwide confirmatory trial (STOP COVID 2). Although we were the sole site for the pilot trial and had the intention of keeping it remote, the larger workload necessitated bringing other institutions onboard as satellite sites. We partnered with the Fred Hutchinson Cancer Research Center, Northwestern University, the University of Utah, McGill University, and University of Toronto to recruit, screen, and monitor our study participants. This trial commenced in December 2020, during a peak in cases in the United States. The Pfizer and Moderna vaccines had just been made available to certain populations, but were limited in availability to the public. However, beginning in 2021, vaccination rates increased rapidly, and the number of eligible patients with COVID-19 eventually plummeted. Although the swift vaccine uptake and steep reduction in COVID-19 cases was a victory against the pandemic that had cost many lives and kept people physically distant for more than a year, it severely limited our ability to recruit individuals into STOP COVID 2. We also noticed a decrease in participant engagement, with noticeably higher levels of enrolled participant attrition in April compared with the earlier months of the year. As a result, we stopped recruitment in May 2021. Results are pending at the time of this writing.

ADDITIONAL COVID-19 CLINICAL TRIAL ADAPTATIONS IN OUR LABORATORY

As a clinical laboratory focused on geriatric mental health, the majority of our other studies work with adults 60 years and older. Although some studies were stopped entirely, others were able to proceed with significant modifications to protect the health and safety of our participants while also maintaining data integrity. For a study relying on neuropsychological testing, a remote neuropsychological test battery that bore similarities to the in-person battery was developed. This test, which could be administered over teleconferencing software, allowed testing to be continued remotely for participants with a webcam and stable internet connection.

Toward the end of the pandemic, we began inviting participants back into our laboratory for physically distant visits. Following university policy, masks were worn at all times by all parties involved, and surfaces were sanitized thoroughly before and after each testing session. The participant was placed in an empty office with a computer while the testing was administered remotely by staff through videoconferencing software. This protocol allowed us to exercise a greater amount of control over our participants' surroundings and equipment during neuropsychological testing without compromising their safety. No known cases of COVID-19 have been linked to these physically distanced, in-person visits.

SUMMARY

Much as the STOP COVID study repurposed medication to treat COVID-19, the pandemic forced us to repurpose existing technology to solve one of our most

pressing problems. Telemedicine has demonstrated clear strengths in the past, along with a few significant limitations that need to be overcome, but our STOP COVID studies have demonstrated that fully remote or decentralized clinical trials can be successful.

Looking Toward the Future

As the COVID-19 pandemic wanes, it is imperative that we look to the future and carry the lessons imparted to us by the pandemic forward. The COVID-19 pandemic has necessitated innovation in the area of remote clinical research. As our technology continues to improve, our capabilities and horizons continue to expand.

Sometimes the baseline tools to solve our most pressing problems already exist, and they just require creativity, courage, and good old-fashioned elbow grease to mold them into what we need them to be. Much like fluvoxamine itself in the STOP COVID study, remote and decentralized clinical research is an excellent tool that needed to be repurposed for the pandemic. The limitations that this pandemic has placed on in-person research have taught us the power and utilities of decentralized clinical research. Now, the onus is on us to figure out how we can take this lesson and use it to improve future clinical research.

CLINICS CARE POINTS

- Remote or decentralized clinical trials are an underused resource that can be used to reach out to difficult-to-recruit populations for greater sample diversity.
- Ensure that a decentralized model is the best fit for the topic of interest. Not all trials are well-suited for a decentralized model.
- When applied appropriately, a decentralized clinical trial design is a step forward in clinical trials, improving both efficiency and equitable access by patients.
- To promote equity and inclusion, make sure that study participation is straightforward and that you can provide necessary study materials to prospective participants if needed.
- Decrease attrition by frequently and consistently communicating with participants, ensuring that the study model is broad and not overly complicated, implementing an interactive informed consent procedure.

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