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Strategies for Behavioral Research in Neurology: Lessons Learned During the COVID-19 Pandemic and Applications for the Future

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Abstract

Purpose of Review Behavioral therapies are proven treatments for many neurologic conditions. However, the COVID-19 pandemic has posed significant challenges for conducting behavioral research. This article aims to (1) highlight the challenges of running behavioral clinical trials during the pandemic, (2) suggest approaches to maximize generalizability of pandemic-era studies, and (3) offer strategies for successful behavioral trials beyond the pandemic.

Recent Findings Thousands of clinical trials have been impacted by the COVID-19 pandemic, from undergoing protocol revisions to suspension altogether. Furthermore, for ongoing trials, recruitment of diverse populations has suffered, thereby exacerbating existing inequities in clinical research. Patient adherence and retention have been affected by a myriad of pandemic-era restraints, and medical, psychiatric, and other complications from the pandemic have the potential to have long-term effects on pandemic-era study results.

Summary In the development of post-pandemic study protocols, attention should be given to designing studies that incorporate successful aspects of pre-pandemic and pandemic-era strategies to (1) broaden recruitment using new techniques, (2) improve access for diverse populations, (3) expand protocols to include virtual and in-person participation, and (4) increase patient adherence and retention.

Keywords Behavioral research · Recruitment · Adherence · COVID-19 pandemic · Diversity in clinical trials

Introduction

Behavioral therapies, such as biofeedback, cognitive behavioral therapy (CBT), and relaxation techniques, are proven, non-pharmacologic treatments for a range of neurologic conditions. They offer benefit in individuals with headache, multiple sclerosis, epilepsy, and Parkinson's disease [1–5]. In related conditions, such as chronic pain, insomnia, and psychiatric disorders, a meta-analysis demonstrated that CBT alone had higher response rates than comparison conditions [6].

Clinically, behavioral therapies offer several advantages: They benefit a wide spectrum of patients, from children, to adults, to older populations [1, 7, 8]; they may be used as add-on therapies to standard medical treatments [1]; and additionally, they may provide successful monotherapy for individuals who are unable to undergo pharmacologic treatment, or for those disinclined toward typical medical therapies [1, 9, 10].

The high efficacy and wide-reaching potential of behavioral strategies underscores the importance of rigorous clinical trials to further establish therapeutic behavioral approaches. However, participation in behavioral clinical trials is often low due to participants' lack of knowledge about these therapies, negative beliefs about behavioral treatments, decreased motivation or support for new therapies, and poor self-efficacy [11–13]. This behavioral research conundrum has been further exacerbated by the COVID-19 pandemic, which has hindered or halted more than 20,000 clinical trials, affecting approximately 80% of non-COVID-related studies worldwide [14, 15•]. Of the ongoing trials during the pandemic, behavioral studies arguably have been disproportionately

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impacted by social distancing guidelines, as behavioral studies often involve face-to-face interaction for delivery of a therapeutic intervention. Furthermore, the pandemic's reduction in sheer number of clinical trials may disproportionally affect vulnerable patient populations [16]. Therefore, the authors suggest adopting strategies learned from the COVID-19 pandemic into current behavioral research practices both to avoid disruption in research in the future and to take advantage of successes devised during the pandemic.

Based on the authors' behavioral clinical research experiences during the COVID-19 pandemic and upon literature review, this article aims to (1) highlight the challenges of running behavioral clinical trials during the pandemic, (2) suggest approaches to maximize generalizability of pandemic-era studies, and (3) offer strategies for successful behavioral trials beyond the pandemic.

Study Design and Institutional Review Board Approval

Challenges During the pandemic, studies were affected by a range of institution-specific aspects of the Institutional Review Board (IRB) approval process. Many IRBs recommended human subject trials be conducted remotely to reduce the spread of the COVID-19 virus [15•]. Institutions, such as Columbia University, University of Michigan at Ann Arbor, Harvard University, and the California Institute of Technology, suspended (with limited exceptions) in-person human subjects research [17]. The inability to shift appropriately to virtual alternatives of in-person research contributed to the halting of many behavioral trials [18••]. Given the emphasis on in-person interactions in behavioral studies, these trials were at increased risk of being impacted.

Strategies In the development of post-pandemic studies, attention should be given to implementing protocols that allow for flexibility in offering both in-person and virtual options for face-to-face interactions (e.g., virtual interviews and behavioral interventions, online and/or telephone-based surveys). Study designs should allow for flexibility in visits (virtual and in-person) without requiring IRB protocol modification [19•]. To limit in-person interactions, researchers should consider electronic distribution of study materials (e.g., email or text messages) or postal service delivery to trial participants. Extra time should be allotted to the study protocol in case of delays in research. Research teams should become familiar with their IRB's updated, post-pandemic support systems, such as (1) educational and training sessions for investigators regarding updated IRB parameters, (2) expanded IRB virtual office hours, and (3) increased email news updates [19•].

Participant Recruitment

Challenges For years, trials in neurology have struggled to include underrepresented populations [20, 21, 22••, 23••], resulting in diverse groups receiving decreased access to therapies offered in studies, as well as limiting the medical field's ability to interpret study results [24]. The pandemic further impacted study recruitment, as traditional routes (e.g., flyers, brochures, and word of mouth, and routine in-person clinical visits) were affected by stay-at-home orders and social distancing [25].

Strategies Telemedicine visits surged during the pandemic, with some neurology practices experiencing at least a 500% increase in virtual operations [26•]. The ability of the medical field to adapt to such changes demonstrates promise in new and virtual enrollment methods. Post-pandemic strategies include expanded use of digital health platforms for participant recruitment [27••] and integration of recruitment into existing clinic telehealth structures. For example, at the completion of a patient visit, a research study team member may join the telehealth visit remotely to facilitate rapid recruitment (i.e., to explain the study, confirm eligibility, and expedite consent for those interested).

Furthermore, as the field aims to expand clinical trial enrollment of underrepresented and/or vulnerable populations to improve public health inequities [28•, 29, 30], social media advertisements have emerged as a powerful tool [27••, 31•]. The benefit of recruitment through social media has additional advantages: in one clinical trial on Parkinson's disease, recruitment via social media resulted in quicker and more cost-effective enrollment than even mass media techniques [32]. Therefore, public networks should be considered for the optimization of patient recruitment and enrollment, as in Table 1. Social media methods may include (1) advertising on Google, Facebook, and YouTube with web links to the clinical trial website; (2) implementing a Twitter campaign to raise research awareness; and (3) collaborating with online advocacy/peer-support groups related to the research topic (e.g., Parkinson's disease support groups).

Table 1 Alternative recruitment methods

Recruit electronically via your patient portal system
Utilize crowdsource internet marketplaces (e.g., MTurk, TurkPrime)
Advertise on social media groups (e.g., Facebook, Instagram)
Contact subjects via secured, online patient groups (e.g., ResearchMatch) and patient organizations (e.g., American Migraine Foundation)
Inform headache and other clinical providers within and outside your healthcare system about recruitment via email/listserv invites (e.g., Facebook invites)

Altered Demographics of Study Participants

Challenges The COVID-19 pandemic has variably impacted lives of many. Essential workers, parents, and others may have more demanding schedules, rendering them unable to participate in studies. Others have lost employment or no longer commute to work, resulting in perhaps more free time and interest in free access to behavioral therapies. Others who are less technologically savvy may have less interest in technology-focused studies. Patients with pre-existing health conditions may avoid in-person interactions during the pandemic. As a result, the demographics of individuals interested and able to participate in pandemic-era behavioral research may be skewed.

During the pandemic, a Pew Research Center survey of more than 5000 US full-time and part-time workers showed that most teleworkers had increased flexibility in their schedules since the start of the pandemic [33]. Although clinical research may benefit from participants with increased control over their schedules, attention to increasing diversity of recruitment is warranted. In addition, as clinical trials expand to include remote platforms, there is risk of further slanting a recruited population toward individuals who own digital tools and/or have the technical abilities to use them [15•]. One study revealed a stark digital divide in the nation: As of June 2021, about a quarter of adults with incomes below $30,000 a year did not own a smartphone; 43% did not have home broadband services; 41% did not have a computer [34]. Racial/ethnic minority community members may also be excluded disproportionately from studies, as Black and Hispanic Americans lag behind Caucasian Americans in internet adoption even after controlling for income [35•]. Therefore, relying exclusively on digital/virtual study recruitment and protocols risks exclusion of those of lower socioeconomic status and minorities.

Strategies When planning study protocols, consider minimizing the time commitment required for the study and favor home-based behavioral treatments. Choose technologies (e.g., headache diary applications) with which patients may already be familiar. To ensure demographic transparency in virtual studies, published protocol reports should include detailed demographic information [36] to clarify how interventions may impact those of many cultures and ethnicities. To improve inclusion rates of participants from wide range of economic statuses in virtual era studies, efforts should be made to provide temporary internet access and digital devices to low-income participants (e.g., purchasing mobile hotspots for participants). These efforts are relevant both during the pandemic and beyond, particularly as the field aims to improve equity across all arenas [36].

Participant Adherence

Challenges A range of psychological factors, such as lack of motivation, negative attitudes and beliefs, poor awareness of triggers, external locus of control, poor self-efficacy, low levels of acceptance, and engagement in maladaptive coping styles, have been observed to contribute to nonadherence in neurologic behavioral trials [11–13]. The pandemic arguably may have increased nonadherence rates, as influences of pandemic-related psychological changes (e.g., increased depression and anxiety) may affect patient motivation [37]. Limited in-person interactions also may contribute to decreased adherence, as communication and good rapport between researchers and participants are integral to patient retention, especially in underrepresented and/or vulnerable groups [38]. Poor adherence may contribute to inadequate participant retention, an established barrier to completing behavioral clinical trials in neurology [39].

Strategies Devise strategies to bolster patient adherence and retention. Establish rapport with study participants early on; consider initial virtual or telephone meetings with the study coordinator to further engage participants. Ensure participants are aware of several methods through which they can contact the study coordinator (e.g., telephone, text, email, or virtual platforms) during defined on-call hours. Request permission from patients to text and/or email reminders to complete behavioral therapies. Provide participants with electronic "study news" updates. Consider incorporating additional behavioral modifications, such as motivational interviewing and/or principles of behavioral economics to help with engagement.

Generalizability of Behavioral Treatments to a Non-pandemic Era

Challenges Conducting behavioral research during a pandemic raises concerns about generalizability of results to a non-pandemic era. In particular, the COVID-19 pandemic saw an increase in mood symptoms in the general population [37, 40]. In neurologic conditions, such as headache, comorbidities including stress, anxiety, and depression have a bidirectional relationship [41]; at the same time, therapeutic behavioral approaches used for headache also may impact mood [42•]. Therefore, pandemic-era behavioral study results may be dually confounded [43•, 44].

Furthermore, the neurological manifestations of COVID-19 (e.g., dizziness, headache, myalgias, hypogeusia, hyposmia) may overlap with the neurologic symptoms assessed in behavioral trials, affecting study results [44]. Certain medical comorbidities associated with COVID-19, including the

consequences of stay-at-home orders (e.g., decreased physical activity) and the long-term effects of the COVID-19 itself in some participants, may impact study results. Therefore, caution must be taken when analyzing and interpreting results of pandemic-era behavioral studies.

Strategies To increase generalizability to a non-pandemic era, incorporate measures to evaluate for mood- and anxiety-related comorbidities into statistical analysis. Consider studying behavioral approaches that are novel and interesting to the patient, so that patients will be engaged with therapy in both pandemic and non-pandemic times. Use behavioral techniques that are complementary to usual healthcare. Throughout the study, teach methods to incorporate behavioral strategies into patients' daily routines. Reinforce the clinical benefits with patients during the pandemic and thereafter.

Conclusions

The COVID-19 pandemic has influenced behavioral research in a myriad of ways, and ultimately, the pandemic's impact will be determined over time. However, the constraints of the pandemic encourage application of creative approaches to both study design and to the development of methods to improve participant recruitment, adherence, and retention, and generalizability of results in behavioral trials.

In particular, innovation in study design should be continued post-pandemic to optimize research while maintaining both in-person and virtual options for patients, as needed. Patient recruitment and retention strategies, including less traditional digital approaches, should be pursued to ensure enrollment of diverse patient populations, and to improve adherence and retention in studies. Focus groups may be performed to analyze patients' experiences in trials during and post-pandemic. As these strategies are integrated, more research is needed to devise methods to protect clinical trials from pandemic-related or other disruptions in the future.

Overall, the pandemic has created an opportunity for researchers and clinicians to re-evaluate the established norms of clinical behavioral research, and to take a leap forward, merging the most effective aspects of pre-pandemic- and pandemic-era studies. These new approaches may be applied both during the pandemic and beyond.

Declarations

Conflict of Interest Ami Cuneo and Kazi Maisha each declare no potential conflict of interest.

Mia Minen has received a grant from the National Institute of Health and contributed to developing intellectual property being used in this study that is co-owned by NYU and IRODY. If the research is successful, NYU and IRODY may benefit from the outcome.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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