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COVID-19 Clinical Trials: A Voice From the Front Lines

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Narrative Inquiry in Bioethics, Volume 11, Number 1, Spring 2021, pp. 16-19 (Article)

Published by Johns Hopkins University Press

DOI: <https://doi.org/10.1353/nib.2021.0005>

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to be involved was included, became a large part of my job during the months of April and May. We used RedCap to maintain the protected patient information in a database and monitored access to it to ensure compliance. The effort to maintain compliance could not have been done well without the invaluable work from our research team, including our research coordinator and research nurse.

During this time, the IRB deftly maneuvered and created new action items within the IRB submission process. These action items highlighted the specific needs related to COVID research in order to speed up the approval process. The only major institutional challenge we faced was when it came time to potentially collaborate with other institutions; the policies regarding data sharing when it came to COVID-19 patients were very restrictive initially. It took quite some time to arrange data user agreements in order to be able to look at these issues within a larger patient population.

I believe that, during the worst months of the pandemic, it was likely very hard for the IRB to ensure compliance for researchers actually conducting research. Despite these difficulties, maintaining an active IRB throughout the pandemic to support research endeavors was an essential part of understanding more about this illness. For our group, these endeavors ended up in many manuscript publications that likely improved our understanding of the disease.

Interestingly, however, research outside of COVID-19 did take a back seat. One clinical trial we were beginning to start up right before the pandemic began had to halt. This delay in enrollment lasted 3 months. The clinical research arena suffered, as did the clinical arena. Many patients with diseases not related to COVID-19 suffered as a consequence of this pandemic.

While the pandemic clearly did more harm than good, there were some important lessons learned through it. For one, the idea of in-person informed consent became a serious challenge as hospitals restricted visitors for a portion of the time. Transitioning to a remote world for clinical care and research will likely be invaluable, particularly in our arena of neurologic disease. Many stroke trials

involve patients that lack capacity and require a family member or health care proxy to enroll in studies. Finding these individuals when managing a condition like stroke, where every minute counts in order to save brain tissue, is a major challenge and barrier to enrollment in clinical trial research studies, particularly for disadvantaged groups, which often have complicated social structures.

Creating electronic applications for which e-consents can be performed and time stamped has the chance of increasing enrollment of patients with diverse social, racial, and ethnic backgrounds for whom in-person consent and enrollment may have previously been a barrier to inclusion. Of course, anything electronically driven comes with its own potential ethical risks as they pertain to data security and data permanence.

Sometimes it takes adversity in order to properly reassess the status quo. I am hopeful that through all of this, on the other end of the pandemic, it will be possible to conduct ethical research with less bias and increased accessibility.

COVID-19 Clinical Trials: A Voice From the Front Lines

Eric Lenze

Acknowledgments. Thanks to co-investigators and research staff in the STOP COVID trial.

Funding. COVID Early Treatment Fund (treatearly.org), Taylor Family Institute for Innovative Psychiatric Research, and FastGrants.

Getting Involved in COVID-19 Treatment Research

I am a clinical trialist because I believe that high-quality clinical trials save lives and improve health. They do this both by showing that new treatments are helpful and by determining that potential treatments are unhelpful and should

not be utilized. Both of these have occurred in the COVID-19 pandemic, due to clinical trial results (see <https://pubmed.ncbi.nlm.nih.gov/32673060/> and <https://pubmed.ncbi.nlm.nih.gov/32876694/>) and by the fall of 2020, new COVID-19 patients were getting more effective care than COVID-19 patients had received in the spring of 2020.

By March 2020, it was clear that COVID-19 was a major public health problem, possibly the largest and most urgent in our generation. Moreover, there was no proven treatment for it. Both policy-makers and medical researchers were proposing drug repurposing efforts to mitigate the negative effects of the illness. One good example of this is remdesivir, an anti-viral originally created to treat hepatitis C. There were, and still are, hundreds of potential candidates.

I lead a research team that conducts clinical trials for outpatients; for example, we recently repurposed an antidepressant medication to help age-related cognitive decline (See <https://pubmed.ncbi.nlm.nih.gov/32212856/>). So when my colleague Angela Reiersen approached me about an idea to repurpose the antidepressant drug fluvoxamine for early COVID-19 treatment, we decided to conduct a clinical trial.

The underlying idea was that fluvoxamine, a serotonin reuptake inhibitor, also activates the sigma-1 receptor. This receptor is involved in modulating the immune system, and a 2019 publication showed that fluvoxamine could prevent deterioration in sepsis by this mechanism (See <https://pubmed.ncbi.nlm.nih.gov/30728287/>). We hypothesized that fluvoxamine prescribed to COVID patients with mild symptoms early in their illness would prevent the clinical deterioration that is often seen around the second week of the illness due to an out-of-control immune response.

The Challenge to COVID-19 Research: We're All in This Together—Aren't We?

We first came up with the idea for the study in late March 2020, and by early April, we had created a study protocol and gotten it approved. The protocol called for a rigorous test of 15 days' treatment of

fluvoxamine for individuals who recently became symptomatic with COVID-19 but were not yet seriously ill. We would test fluvoxamine against a placebo comparator, providing more high-quality evidence than can be obtained from observational studies (See <https://jamanetwork.com/journals/jama/fullarticle/2773107>). We actually recruited our first participant only 16 days after our first conversation about using fluvoxamine for COVID-19. This rapid onboarding was due to the efficiency of our university's COVID-19 committee, which set up a system for rapidly reviewing clinical studies, and our Institutional Review Board (IRB), which accelerated their review process.

But then came the main challenge: recruitment. This has always been the bane of clinical trials. We had the staffing to randomize six patients per day and manage them in the trial, and we thought that recruitment would be rapid, estimating it would take approximately 3 weeks to randomize 152 patients. In the end, it took more than 4 months.

Our recruitment challenges were a two-fold problem: regulation and apathy. Regarding regulation, our IRB governs only one hospital in our hospital system (which is only one system among many in the region). Thus, it proved impossible to recruit within the wider ecosystem of the numerous hospitals and COVID testing sites in the region. We had no way to contact SARS-CoV-2 positive patients unless they were part of our university's medical school or its affiliated hospital.

We were also unable to get help from area organizations, who could have told patients about COVID-19 clinical trials but refused to do so. We were surprised by this because we thought there would be a community "esprit de corps," and the organizations would be interested in finding treatments that would diminish the virus's adverse effects and help everyone. Moreover, we were not asking for organizations to make much of an effort, such as recruiting and consenting (this is the most time-consuming and difficult task in clinical trials). Surprisingly to us, they were unwilling to participate even in terms of allowing us to post advertisements or to include a study flyer in their paperwork given to patients.

In some cases, my research team and I encountered hostility towards clinical trials. For example, when we approached the County health department, they stated they would not help and that it would be unethical for them to even tell patients about the existence of COVID clinical trials. They stated they would only tell patients about clinical trials if the patient brought it up first, even while acknowledging that this never happened. This decision, on their part, did not appear to be due to any departmental policy. They felt this was the most ethical position, but I wondered if their paternalism was ethical; after all, by not informing a patient of the opportunity to participate in a clinical trial for their condition, they were removing autonomy from that patient. Another example was at COVID-19 testing sites; in one encounter, they told us to keep lawn signs advertising for the study away from their site.

More often, the problem was apathy; “not my job” was the default. This was not universal, and a few providers not only expressed enthusiasm for the research but actually helped by referring patients. But it was far too few, compared to the providers who failed to inform their patients about the availability of clinical trials or even discouraged them from participating.

These two problems—fragmentation and apathy—exemplify the US health care system when it comes to research. Indeed, we don’t have a health care *system* in this country, but rather a complicated patchwork of independent operators. This contrasts with the RECOVERY study in the UK, a large platform trial testing repurposed drugs for serious COVID-19. There, they were able to get the entire country’s hospitals to work together on this large RCT, randomizing hundreds of patients daily. The Chief Medical Officers of England, Wales, Scotland and Northern Ireland, and the Medical Director of the National Health Service wrote to all doctors and encouraged participation in COVID-19 trials. Unsurprisingly, then, most of the early findings about COVID-19 treatment came out of the UK: the effectiveness of dexamethasone, and the lack of effectiveness both for hydroxychloroquine and for lopinavir-ritonavir, for reducing morbidity and

mortality in patients with serious COVID-19 (See <https://www.recoverytrial.net/>).

Ethical Challenges in COVID-19 Research

Aside from recruitment challenges, three ethical challenges arose. The first was that our primary recruitment method involved “cold-calling” individuals who recently tested SARS-CoV-2 positive. This is a highly-successful recruitment technique that is often approved by university IRBs. But some individuals express discomfort about it, usually articulated as “If I were a patient and you called me out of the blue, I’m not sure I would like that.” However, we did not see any concerns or complaints in our COVID-19 trial, despite screening over 1300 individuals and randomizing 152. This may be because our study focused on outpatients who are not gravely ill and not in a position of possibly limited decisional capacity. We also avoided individuals with dementia or in nursing homes or assisted living facilities.

The second ethical challenge was how to manage patients in our trial. Since they had COVID-19 and were self-quarantined, there was no face-to-face contact. Instead, all aspects of the study had to be conducted remotely. We resolved this by emphasizing a high-touch approach whereby participants were e-consented via the phone and REDCap. Then study supplies (including medication) were delivered to their house, whereby they began participation. We checked on them frequently during the study with phone calls, supplementing the primary source of data collection for outcomes and adverse events, which was a REDCap survey. Another fully-remote trial for COVID-19 outpatients, which tested hydroxychloroquine (and found it ineffective), used a low-touch approach that was almost entirely automated and had a similar experience (see <https://pubmed.ncbi.nlm.nih.gov/32673060/>). So I would conclude that fully-remote trials with no face-to-face contact can be conducted safely and ethically, at least when the drug being tested is amenable to this technique.

A third interesting ethical issue was that we initially excluded pregnant women, but we were

approached by maternal-fetal medicine doctors who urged us to reconsider this position. There is a controversy about excluding pregnant women from clinical trials and whether doing so creates a disparity. It hadn't occurred to us that excluding pregnant women might be unethical. However, the Coalition to Advance Maternal Therapeutics, a consortium of about 20 organizations (such as the American Academy for Pediatrics), actually sent a letter to the directors of NIH and FDA, calling for the inclusion of pregnant and lactating women in COVID-19 clinical trials. As a result, we decided to include pregnant women. However, ultimately none participated in our study. Nevertheless, this experience calls into question the assumptions that researchers (and IRB reviewers) often make about excluding "vulnerable" individuals; there may be advocates for those same individuals who strongly feel it is unethical to exclude them without good reason.

Recommendations

There needs to be more cooperation in the US to support and advocate clinical trials. For that to happen, two things should change.

First, the federal government could clarify that one and only one IRB can and will govern a research study no matter where in the US it is conducted, whether it is at one hospital or in every hospital in all 50 states (and 14 territories), including within the VA system. This is a simple, long-overdue change. I cannot overstate the amount of unnecessary bureaucracy and idiosyncratic decision-making (all of which impede progress towards new treatments and increase the cost of testing them) that could be swept away with the stroke of a pen.

Second, there needs to be a cultural change in our country's default position in providing medical care, which is anti-clinical research (with a few exceptions, such as cancer care). Leaders in health care at all levels could make this change by stating clearly that clinical trial participation is the standard of care for medicine. Hospitals and providers that refuse to tell their patients about clinical trials, or actively prevent patients from

participation, are not providing the standard of care for treatment. Instead, providers could point their patients to clinicaltrials.gov (or even look on the site on their behalf); and, they could give an unbiased opinion about whether their patient should participate.

As a clinician, I can help people with treatment only because those treatments were demonstrated effective in clinical trials. Perhaps medical training needs to instill this way of thinking. Perhaps payers should reimburse providers for the time they spend assisting patients in learning about and deciding about participating in trials. Policy-makers have the sticks and carrots needed to change behavior at the provider level. Of course, ultimately, it should be the patient's decision.

In the end, our trial succeeded. In August 2020—five months after Dr. Reiersen first contacted me with the idea—we unblinded our results and found none of the 80 fluvoxamine-randomized COVID-19 had deteriorated, vs. 6 of the 72 placebo patients (see <https://jamanetwork.com/journals/jama/fullarticle/2773108>). This exciting but preliminary finding led to a larger, confirmatory trial, which is just starting at the time of this writing, in December 2020. Still, I can't help thinking we would have finished already if the US system was geared towards helping rather than impeding clinical trials. And the new trial may be a failure because of some of the problems described in this article that make clinical trials unnecessarily inefficient and challenging to conduct. It is my view that the changes I've recommended would make clinical trials faster, less expensive, and more likely to succeed.

Related Work.

Lenze, E. J., Mattar, C., Zorumski, C. F., Stevens, A., Schweiger, J., Nicol, G. E., . . . Reiersen, A. M. (2020). Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA*, 324(22), 2292–2300. doi:10.1001/jama.2020.22760