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Commentary

Research During the Pandemic: Views from Both Sides of the Fence

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Abstract. The SARS-CoV-2 pandemic has affected practically every aspect of life across the globe for the past year or more; the practice of clinical research not the least. Clinician scientists attempting to start or continue work both related and unrelated to the disease itself have faced ethical, oversight, or regulatory challenges. No aspect of the clinical trial enterprise was unaffected. These narratives detail some of the barriers encountered and how the investigators coped (or didn't cope). Common themes emerged, ranging from a need to contribute, which drove the researchers to frustration with real and perceived obstructions (both old and new). The narratives disclose common ethical issues related to research during a pandemic: issues both qualitatively and quantitatively different from other human subject research; challenges both new and novel, as well as those previously seen, but writ large in the face of the crisis. The narratives also offer words of advice from the trenches and speak to successes, both large and small, and to the value of teamwork and focus on a common goal.

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Introduction

"Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China in November 2019, and its designation by the World Health Organization (WHO) as a Public Health Emergency of International Concern on 30 January 2020, the coronavirus disease 2019 (COVID-19) pandemic has significantly affected

the economic and social fabric of virtually every country" (Singh, Bandewar, & Bukusi, 2020).

Oddly, the most difficult part of writing this commentary has been devising an introductory paragraph that sums up the dramatic effect of the COVID-19 pandemic on clinical research, much less on the "economic and social fabric" of the world. The COVID-19 pandemic has "created massive disruptions to clinical trial research across the world.

As in other aspects of life, the virus has severely affected the ability to conduct trials in safe and effective ways” (van Dorn, 2020).

These narratives describe the challenges faced by researchers during the COVID-19 pandemic when conducting both COVID-related or unrelated human subject research. Authors were asked to describe any ethical, oversight, or regulatory challenges that they experienced during the pandemic, how they addressed the challenges, and offer recommendations to IRBs, other oversight bodies, or other researchers when reviewing research during a pandemic.

I was asked to provide this commentary because I sit in a rather odd position. I was trained as a pediatric oncologist and clinical researcher. Midway through my career, I made a hard left turn and ended up first an IRB member, then chair, then director. Though I function within the IRB and research ethics world entirely now, I retain my experience with (and therefore perhaps some insight into) the challenges associated with conducting clinical trials in a population with a life-threatening disease.

Further, my institution has always been at the forefront of health security and response to bio-emergencies. With the largest biocontainment unit in the country and the sole federal quarantine unit, we took care of Americans with Ebola virus disease (EVD) evacuated from western Africa during the 2014 epidemic and worked with quarantined US citizens airlifted from China during the start of the coronavirus pandemic. During these twin infectious disease events, our investigators led a variety of national and local human subject research projects, which were reviewed by our IRB.

In these stories, I can see the motivations, frustrations, and in some cases, ethical challenges faced by these investigators, both from the point of view of a researcher and an IRB director.

Had to Do Something . . .

A theme in many of these vignettes is the author’s (and the researcher’s) desire to “do something” in the face of an unprecedented health crisis. Paul Monach says, “I knew I would be low on the list of people to be called in for ‘risky’ inpatient work . . . but I had to do something; . . . I had to enlist.” As

Rebecca Wells noted, “The question kept nagging inside my head, ‘How can I best help others?’ When the pandemic began, I was overwhelmed with a deep desire to serve . . . I felt an urgent need to provide this help as rapidly as possible.”

They were certainly not alone. Scientists and medical personnel across the globe who were not directly involved in the care of patients have volunteered time, supplies, and expertise. As research labs and research protocols were halted, the health care workers and scientists who ran and staffed those labs and conducted that research sought ways to help, and online databases of volunteers with technical skills and equipment (like crowdfightCOVID19.org and covid19sci.org) have arisen.

The desire to serve, so clearly shown in the setting of COVID, is not new, nor should it be surprising. We in the IRB world are often leery of the investigators who use people as a means to an end (laudable as it may be). This protectionist view, and the regulatory system under which we operate, arose as a direct consequence of abuses of human beings: in the concentration camps of the Second World War, in the halls of Willowbrook State School and Brooklyn’s Jewish Chronic Disease Hospital, and in the fields of Macon County, Alabama. The regulations that arose sought to “protect human subjects” from unethical research and unethical researchers. But we must remember that the vast majority of investigators want to conduct ethical research that produces good quality information to help others. They want to serve, as do the researchers that composed these narratives. COVID-19 has made that more apparent and desperate.

In these vignettes, the “something” the writers chose to do was research. Some researchers sought to develop therapies to treat the virus, or to ameliorate the clinical syndrome affecting multiple organs. Some attempted to treat the psychological effects and stress related to the pandemic, or a consequence of caring for those with the disease. Some sought to better understand the long-term sociologic effects of COVID-19. In some cases, the research was directly related to studies the writers had been performing prior to the pandemic, or represented only a change in subject population; other researchers completely changed their focus, and used the tools they had available in new and novel ways.

And the act of carrying on, of participating, and helping, also helped scientists cope with the fear and trauma of the pandemic. As Todd Seto notes, “Many of us found value in ‘carrying on’ in the midst of uncertainty and unease. We found that our clinical trials had a galvanizing effect—they built a common cause for our providers to rally around; they provided a sense of order and purpose; they reaffirmed our identity as scientists contributing knowledge to the larger community.”

Though these are mostly stories of success—little successes in terms of being able to continue day to day, or big successes that altered the course of a patient’s disease or provided a better understanding of the pandemic or its consequences—those victories were not always easily won.

Non-COVID Research Came “Second” (or Not at All)

The effect of COVID-19 on clinical research has been enormous, with thousands of trials—around 80% of non-COVID-19 trials—being stopped or interrupted (van Dorn 2020). Stay-at-home orders, institutional and sponsor (including NIH) policies, supply shortages, disruption of support services, and altered priorities have all contributed to dramatic slowing or halting of research activities not directly related to the pandemic. Though the need for these halts is entirely understandable, the frustration this engendered is amply displayed in the vignettes

David Altschul notes, “research outside of COVID-19 did take a back seat . . . The clinical research arena suffered, as did the clinical arena in that many patients with diseases not related to COVID-19 suffered as a consequence of this pandemic.”

Even research that might have impacted the consequences of the pandemic (such as that related to mental health and stress) became much more difficult to conduct. Studying the delivery of mental health services, Patrick Romani notes, “At a time when mental health research was perhaps most important, universities placed significant restrictions on research practices.”

The long-term effects of research halts on the subjects directly involved in these projects, or on the patients who might have benefited from results

of the trials, is not yet clear. Gary Schiller, a medical oncologist, laments “the closure of studies for some of our most vulnerable patients.” He notes, “diseases don’t disappear by virtue of a pandemic. Even during a crisis, cancer does not take a break”.

Barriers to Research

The vignettes present a litany of barriers to conducting any research, even that related to COVID; some have already been noted above. In some cases, the challenges were related to the necessity to avoid contagion and protect subjects, staff, and researchers themselves.

Personnel issues / working from home

Challenges included attempting to conduct trials with diminished staff numbers, or staff working from off-premises. Schiller notes, “not having the regulatory staff on-site proved very difficult. Although they worked from home, many things were not done in a timely manner, documents were not signed, and amazingly, there were no easy electronic options.” More generally, and reflecting the theme of the importance of continuing even non-COVID related research, he notes with regret “safer-at-home orders . . . did not define research personnel on clinical trials as essential workers.”

The need for the researchers themselves to work from home was seen by most as a barrier. Laleh Coté notes, “Being mostly confined to the home isn’t conducive to writing or inspiration, and so it takes me a lot longer to produce something (anything!) than it normally would.” But Romani saw a positive side: “My co-investigators and I could meet, develop the surveys, and execute the project at home, at night, or on weekends, whichever was most convenient.”

Recruitment challenges

Many authors expressed frustration with barriers to recruiting subjects to trials. Some of these concerns arose from perceived regulatory and “bureaucratic” barriers; we will discuss them later. Others, however, found apathy, or fatigue, or competing interests to blame. Coté, for example, noted, “While recruiting, many people were supportive of these

studies, but explained that there were already plans to survey their own community about their experiences. Others explained that they had too much else to deal with, or simply did not respond.”

In contrast, Eric Lenze, conducting a randomized clinical trial of fluvoxamine to reduce immune-mediated complications of COVID, states, “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 everyone would be interested in finding treatments that would diminish its adverse effects would help everyone . . . In some cases, my research team and I encountered hostility towards clinical trials . . .” Although Lenze offers speculations as to the reasons for this antipathy, I wonder if some part might be related to hesitancy about the “risk” of being assigned to a placebo arm of a clinical trial (as will be discussed below).

Informed Consent

Informed consent is central to the ethical and regulatory framework of human subject research, including clinical trials. Informed consent, in its traditional (and perhaps most effective) form, involves face-to-face contact and conversation between the prospective subject and the investigator. The COVID pandemic has cut right to the heart of this interaction, by interfering with, and indeed, prohibiting, that direct contact, and by requiring the development of new paradigms for the conversation. Altschul notes, “the idea of in-person informed consent became a serious challenge as hospitals restricted visitors for a portion of the time.”

Interestingly, some researchers described the need for these novel mechanisms to obtain informed consent as a challenge (most often resolved through cooperation with the IRB and out-of-the-box thinking); however, the complementary need for documentation was often reduced to a “bureaucratic burden” before being resolved as well.

Barbara Yawn notes, “For many sites, the use of e-consent was a barrier requiring new formats,

new tools, and in some cases, extensive work with local IRBs . . . We had to redo our consent forms not just to accommodate the e-consent format but to include information on protecting participants from study-related spread of COVID and to accommodate mixed virtual and in-person visits.”

Regulatory Burden / Bureaucratic burdens

Not surprisingly, some authors cited regulatory (or stated less kindly, “bureaucratic”) burden. Westyn Branch-Elliman and Paul Monach note, “we were forced to develop more complicated and cumbersome processes, all in the name of collecting proof of a wet signature on a page from the patient or legally authorized representative.” Monach bemoans, “cumbersome and changing recommendations, put in place by people who never have to interact with a patient or treating physician, has made the conduct of our trial nearly impossible. Everyone who could influence the trial from a distance slowed it down.”

Seto notes that “the bureaucracy of research regulation and compliance, built over decades to minimize institutional risk and maximize human subjects protection, was poorly suited to match the rapidly evolving clinical milieu of the early pandemic.”

What was surprising though, was the infrequency of the complaint. When I was asked to read a series of narratives by researchers describing the ethical, oversight, or regulatory challenges they faced during the COVID-19 pandemic, I anticipated a certain amount of fault attributed to the overly bureaucratic, obstructionist tendencies of regulators and IRBs in particular. Such complaints are often well-grounded, but nonetheless sting. I was grateful to find remarkably little in these stories.

There is certainly truth in the observation that regulations and regulators slow the pace of research. There is also truth in the assertion that some of these barriers are unnecessary. However, there is, in some of these narratives, a sense that research is good, and therefore, anything that stands in its way (including protections for subjects) must be bad.

Also apparent in a few of these narratives is a related ethical trap; that is, the expectation that whatever intervention is being proposed in the research is better than nothing. This is the classic formulation of therapeutic misconception; that is, some authors seem to “deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself” (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987). It is perhaps forgivable among medical practitioners desperate to offer something to their patients, but this must always be guarded against by scientists.

Teamwork

As a counterpoint to concerns about bureaucratic barriers and burdens, many narratives spoke of the ultimate triumph of teamwork between researchers and the IRB and human research protection programs.

Various authors spoke of “the efficiency of our university’s COVID-19 committee . . . and our Institutional Review Board (IRB) which accelerated their review process” and “*ad hoc* meetings to help expedite our study reviews.” Rebecca Wells notes, “the IRB office was open, operational, and studies related to COVID-19 were receiving top priority . . . Efficient responses and anticipation made me feel like we were working on the same team, side-by-side, all of us together.”

In the face of a bioemergency, the need for rapid, responsive and quality ethics and regulatory review is well recognized (Saxena et al., 2019). During the Ebola virus epidemic in 2014, our IRB utilized a rapid review model to review and ultimately approve the use of investigational drugs for critically ill patients with the disease. During COVID, we utilized the same paradigm, now as the single IRB for the Special Pathogens Research Network of the National Emerging Special Pathogens Training and Education Center (NETEC). That other IRBs and HRPPs were able to function in this manner is gratifying, and speaks to what we have called the “all hands on deck” approach to this sort of crisis (Lowe et al., Submitted).

Central to successful rapid review is preparation and communication. Recognizing this, Romani advises, “I would heavily encourage researchers to connect with their IRBs early and often to ensure understanding of preferred formatting characteristics of applications and to communicate idiosyncrasies of applications to ensure rapid review.” I could not agree more.

Ethical Issues

I am not a trained bioethicist (but I have, through osmosis and contact with greater minds, acquired the fundamentals of research ethics). However, all astute observers recognize that research during a pandemic poses ethical issues both qualitatively and quantitatively different from other human subject research; challenges new and novel, as well as those previously seen, but writ large in the face of the crisis (Nuffield Council on Bioethics, 2020; World Health Organization, 2010). Two of these issues recurred in several of the narratives and are worth mentioning.

Research vs. compassionate use

The use of new or repurposed drugs as “therapy” in the setting of a life-threatening illness has been a feature of the coronavirus pandemic, a result of the lack of effective therapies in the face of a mounting global death toll (and exacerbated by the flurry of uninformed tweets and weaponized misinformation).

The ethical argument in favor of off-label (and off-clinical trial) use of drugs is similar to that offered for “right to try” laws and programs: patients (and in their fiduciary role, physicians) should have a right to mitigate extreme suffering and to enhance self-preservation. “As rational actors, patients . . . should be entitled to utilize their own risk-benefit thresholds in deciding whether to consume such products” (Darrow, Sarpatwari, Avorn, & Kesselheim, 2015).

However, using these drugs outside the context of a randomized clinical trial impacts the ability to learn about both benefits and risks associated with

these therapies and use them more effectively and more safely (Kalil, 2020). The failure to generate useful information about therapeutic interventions during the EBOV epidemic in 2014 highlights the risk here.

Branch-Elliman and Monach observe in their trial of IL-6R inhibition as an adjunct treatment for COVID, “The question was whether to use medications off-label based on limited anecdotes or to conduct a clinical trial . . . There was a desire by many, both among research leaders and some clinicians, for a “clinical trial” banner, so that patients would be appropriately informed about the potential for a lack of benefit—and potential for harm—associated with almost any COVID-19 intervention.”

Seto noted in his trial of hydroxychloroquine and tocilizumab “For some of us, clinical equipoise—when there is professional disagreement among the community of expert practitioners as to the preferred treatment—was sufficient to justify enrolling patients into randomized clinical trials. For others, it was not.”

Ethical study design / use of placebo

Similar angst arises when considering the justification for a placebo (or more accurately, a “best supportive care”) arm.

In the narratives, Lenze chose to use a placebo-control design since it would result in “providing more high-quality evidence than can be obtained from observational studies”; and Branch-Elliman and Monach because it would result in “bolstering scientific validity for subjective outcomes.”

However, the latter authors note, “we witnessed psychological distress not only among patients and their relatives, but also among treating physicians as evident in immediate abandonment of the scientific principles that they had supported during design of the trial. When patients were randomized to standard care, physicians quickly revolted, and requested open-label use of the unproven study drug”.

The ethics of using a placebo arm (or again, more accurately, about using a “best supportive care” arm) in a randomized clinical trial has been debated

for decades; and similar arguments arose during and after the 2014 EVD epidemic (Adebamowo et al., 2014). The ambivalence expressed may represent the fundamental contradiction between the dual roles of physician and scientist, and as noted above, may lead to hesitancy to enroll patients in randomized clinical trials (or even to discuss those trials).

Conclusions

Describing the effect the coronavirus pandemic has had on the fabric of society remains, for me at least, an exercise in futility: it defies mundane language. In these narratives, though, we see glimpses into the human drama around a narrow slice of the activities of my life, and the lives of other practitioner-scientists. And so, perhaps, we can see a shadow of the bigger picture.

These narratives are in some ways strikingly similar to each other, and in other manners, very different. We see this defining moment of a generation through different lenses, and we take away different lessons. Within the very narrow scope of this series, the effect of the pandemic on researchers, I believe I see cooperation, teamwork, and a joint understanding of the importance of both the subject of the research and the research itself.

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