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Personal Narratives IRB Members and Research Administrators

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Walter Dehority

The first reports of a novel SARS coronavirus emerging from China in early January of this year did not capture my attention as they should have. This, I reasoned at the time, was a virus halfway around the world, probably an oddity of interest only to virologists in East Asia. I would soon learn, however, that this would evolve into a plague, the likes of which had not been seen in a generation. As inconceivable as it seemed at the time, this virus would eventually affect my work as an Institutional Review Board (IRB) chair in New Mexico. Warily, I watched as the virus entered Europe and the rest of the world. Soon, curiosity in the West transformed into worry, which rapidly gave way to terror. Images of overflowing intensive care units in New York City filled my cellphone screen. Health care workers were forced to use garbage bags for protection after supplies of personal protective equipment (PPE) disappeared. Hospitals ran out of ventilators. (These equipment shortages can be seen documented on the CBS *60 Minutes* segment “Sick doctors, nurses and not enough equipment:

NYC healthcare workers on the fight against the coronavirus.”) Still, the virus moved further and further west from New York, eventually heading for my own borough.

I watched as panicked physicians, patients, and media outlets turned to the research community for answers, desperately hoping cures, vaccines, and preventive measures could be produced. Repurposed drugs and experimental agents with in vitro activity against the virus were rapidly identified. Small, uncontrolled studies began to appear in the literature, many bypassing peer review, feeding scraps of pilot data to a frightened medical community. Clinical trials materialized overnight, as the website ‘ClinicalTrials.gov’ exploded with hundreds of new COVID-19 studies. At the local level, our investigators, clinicians, hospital administrators, and the populace they served advocated for the initiation of clinical trials in our hospital. Researchers wished to contribute their expertise to help generate data. Administrators hoped to offer our hospital as a trial site for a number of coveted experimental therapies for the community, while patients were willing to volunteer for studies of these new treatments. From one perspective, such efforts were laudatory, and a remarkable demonstration of determination and altruism. From

another perspective, the clinical trials arising from these efforts would soon force me to confront the idea of therapeutic misconception and misestimation as never before.

Therapeutic misconception—as defined by Henderson, Churchill, Davis, et al. in the journal *PLOS Med.*—is the failure to appreciate the distinction between the goals of research, which are to collect data to contribute to scientific knowledge, and the goals of clinical medicine, which are to improve the health of patients. Pentz, White, Harvey, et al., in the journal *Cancer*, define therapeutic misestimation as the misestimation of the level of risk and chance of benefit in a clinical trial. As in other hospitals around the country, patients in our hospital wanted cures, and many were willing to be the recipients of untested drugs in their quest for such cures. This simple fact kept me awake many nights before an IRB meeting that Spring. Would any of our potential research subjects actually consider the warnings in a consent form about the possible risks and lack of proven benefit for an investigational therapy when offered the chance to participate in a COVID-19 clinical trial? Particularly after these potential study subjects had viewed the same images of death in New York that I had? For that matter, would our worried health care workers be able to objectively appraise the opportunity to participate in trials of preventive measures against the virus, such as vaccines and prophylactic drugs, after they had viewed the images of health care workers in New York using garbage bags as PPE? Internet and media sources continually promulgated a steady stream of real-time updates on seemingly every development in the ongoing search for a cure or a vaccine. No longer restricted to the esoteric domain of medical journals, major media outlets now trumpeted the results of clinical trials and obscure phase 1 studies with breath-taking abandon. Co-workers frequently stopped me in the hallways to ask if we would be a trial site for many of these proposed therapies or vaccines, a hidden glimmer of fear (and hope) in their stares. Hope may arise from fear, whether or not that hope is misguided. A drowning person will reach for any lifeline thrown their way, whether or not that line is secure. How could our IRB best ensure subjects would be able to make informed

choices as to whether they should grab these experimental lifelines and not just reach for them blindly out of fear? Therapeutic misconception and misestimation, which I previously associated with the use of investigational therapies in early phase oncology trials, were now suddenly front-and-center and affecting our entire community.

Therapeutic misconception and misestimation do not just affect study subjects, however. During troubling times, as I learned, these thought processes may also affect IRB members (myself included). In my case, they assumed a different guise, which was harder to recognize, namely a self-imposed pressure to make experimental therapies rapidly available to our patients, and to quickly facilitate the opening of our hospital to clinical trials to do our part to aid a community (and nation) in crisis. Hindsight now permits an appraisal of the many ethical issues this raised (both locally at our hospital and nationally). These were issues that I did not adequately appreciate while in the throes of the pandemic's first months. Many studies were, by necessity, hastily constructed and targeted critically ill patients who may have been most at risk of therapeutic misconception or misestimation, as well as worried health care providers looking for prophylactic medications as they entered the front lines in the fight against the virus. Given these concerns, did the medical community really need 104 trials of hydroxychloroquine that April (all presumably IRB approved, two from our institution), many of which were single-site, underpowered, or uncontrolled studies? (The number 104 was cited in an article by Dehorty, Spence, and Dinwiddie in the journal *Pediatric Allergy, Immunology, and Pulmonology*.) To better protect these study subjects, would waiting for the results of larger, well-designed, multi-site controlled trials have been wiser, allowing us to maximize scientific gain and minimize exposure of desperate subjects to risks borne out of fear?

Nonetheless, proposed trials kept appearing on our committees' agenda, though not without concerns. Did sufficient data exist to support an interventional trial at that point in time for many of these therapies? Were the hastily assembled study teams and data safety monitoring boards qualified to conduct or adjudicate these studies? Were the

waivers of informed consent we granted for some single-arm therapy trials necessary (in intubated, critically ill patients whose families were not allowed into our increasingly locked-down hospital to provide consent)? Were such waivers acts of beneficence, providing opportunities to receive potentially life-saving medications for those unable to request them, or attacks on those subjects' autonomy? Time for such deliberations was often sacrificed upon the altar of speed and efficiency. I sifted through preliminary data from studies in rodents and small, underpowered and uncontrolled trials, looking for kernels of hope that may suggest a new modality was ready for a proposed trial in humans, while over my shoulder, in my workplace, and in my home, the specter of COVID-19 grew ever larger, challenging my impartiality. At times, hope, influenced by therapeutic misestimation, may have prevailed over caution or scientific reason in my mind. Such insight, more easily achieved after the fact, is difficult to rely upon when a pandemic finally reaches your borders and comes knocking on your door.

The difficult decisions and ethical balancing acts did not end with the approval of such research. Scientific data that could impact the conduct of these trials were being published daily. Studies, which several weeks prior we hurriedly approved during emergency IRB meetings, were now being hurriedly assessed for closure or suspension due to newly identified risks in the rapidly expanding medical literature. The perceived beneficence behind the initial decisions to approve such studies could quickly transform into an attempt to ensure non-maleficence. Studies constructed to test the efficacy of the drug hydroxychloroquine came into question almost overnight following the publication of a study in the *Lancet*, demonstrating a potential increased risk of mortality with use of the drug. However, less than two weeks later, the same study was retracted by the journal. This left IRB's (including ours) to ponder the best course of action for their local hydroxychloroquine trials, and to wonder whether the original approval of these studies may have arisen, at least in part, from the influence of therapeutic misconception or misestimation.

Experience adjudicating emergency research in my role as an IRB chair was something I was

lacking at the time COVID-19 arrived, which is perhaps why I continue to reflect on these events. I believe that during such challenging times, IRB's may find themselves caught in the middle. They have a genuine desire and responsibility to rapidly approve clinical trials that will facilitate the study of novel drugs, vaccines, and diagnostic modalities that may produce urgently needed data. However, in competition with this responsibility is an equally important need to slow down during what is a time of relative urgency and critically evaluate each proposed trial in order to ensure the protection of the human subjects enrolled within it, even if that means asking difficult questions that may delay the start of a trial, or lead to disapproval or modification of a study. At the core of therapeutic misconception and misestimation is an understanding that interventions with proven clinical benefit do not need clinical trials. Interventions without proven benefit do. It is those interventions that may either help or harm our study subjects. Adjudicating and evaluating clinical trials during a rapidly evolving pandemic, when hope and fear are present at all levels of the research community, is a challenge to which IRB's must adjust. Perhaps, I now realize, it is during such demanding times that the research subjects we work so hard to protect actually need us the most.

Eight Seconds of Panic

Edith Paal

Little daily emergencies are common in IRB offices. The one that hit our IRB office the week ending Friday, March 13, 2020 (of course a Friday the 13th was involved, right?) quickly evolved from a "little emergency" to something requiring an urgent rethinking of the full scope of our human subject research program and its oversight.

Our standard practice, when emergencies hit, is to allow ourselves about 8 seconds to panic. Then,