Title: Decisions on Innovation or Research for Devastating Disease

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Open Peer Commentary

In their paper, "Helpful Lessons and Cautionary Tales: How Should COVID-19 Drug Development and Access Inform Approaches to Non-Pandemic Diseases?" Holly Fernandez Lynch and colleagues have presented a valuable account of treatment and research decisions made during the COVID-19 pandemic. (Lynch et al. 2021) Their discussion focuses on patients with other serious diseases and their families who ask “what about us?” They wonder why the conditions important to them have not received similar research attention. While we largely agree with the authors’ account and their insightful observations, we want to highlight the manifest tension between innovation and research which they did not emphasize.

We turn our attention to the critical question of whether initiating treatment with promising interventions or initiating research is the right course. As Lynch and colleagues note, the FDA, clinicians, patients, and others all jumped on the hyped bandwagon to promote hydroxychloroquine and convalescent plasma as COVID treatments. If it is important to first conduct robust randomized trials with concurrent controls, even in the face of a life-threatening disease, then all of those who eschewed rigorous research chose the wrong course.

Facing an emergent pathogen without effective treatment, clinicians in 2020 were desperate to save their COVID-19 patients. Some repurposed drugs previously

approved for other indications. Others tried interventions postulated to work by physiological reasoning or based on clinical experience in similar scenarios. Unfortunately, numerous heroic efforts turned out to be ineffective. Some drugs (e.g. hydroxychloroquine) even proved harmful. (Singh et al. 2021 This understandable desire to help patients in dire straits can, however, impede the investigation of urgently needed potential therapies in placebo-controlled randomized trials. The COVID-19 pandemic made that common predicament, a glaring and urgent ethical issue.

Last year, in a move that was distinct from its usual approval process, the FDA issued several Emergency Use Authorizations (EUA) for COVID-19 that were not based on rigorous evidence. Some of those EUAs were later rescinded (e.g., for Hydroxychloroquine, convalescent plasma) because they were subsequently found to be either unsafe or ineffective. (Singh et al. 2021; Piechotta et al. 2021) During the intervening period between the EUA issuance and its being rescinded, convalescent plasma was distributed to over 97,000 people at cost reported to be $800 million. Regrettably, that tremendous effort was undertaken outside a controlled clinical trial, and therefore did not provide any useful evidence on clinical benefit.(Rogers, 2021)

In effect, the FDA departures from their standard procedures did acknowledge that some circumstances merit special consideration and a non-standard ethical approach to research. Those actions by the FDA also raised a significant issue that has been largely unaddressed by current research ethics guidance.; for the most part, existing ethical guidance takes a one-size-fits-all approach (Emanuel et al. 2000) and the rules for assessing risk of harm and potential benefits are vague. Yet, there are tremendous differences in the conditions that require new or improved treatment, the circumstances in which they arise, and the kinds of treatment that require study.

Some conditions are mild and have minimal effects on the quality of life (e.g., toenail fungus), others are life-threatening. Some short-lived diseases have minor consequences (e.g., the common cold), others can have devastating long-lasting effects (e.g., polio) or unknown long-term effects (e.g., COVID-19). Some diseases are chronic with life-altering consequences (e.g., diabetes, allergies). Some diseases progress slowly, others rapidly, some affect millions of people, others affect just a few, but may afflict predominantly marginalized and minority populations. These radical differences raise ethical issues about whether differences in factors such as urgency, prognosis, the number and circumstances of people affected require different responses, and whether ethical guidance should be more nuanced and specific to the situations that actually arise. The current direction on balancing risks and benefits does not address number of important issues. For instance, they ignore issues such as what might happen to people who are enrolled in a study and not offered an untested intervention, and the issue of whether knowledge gained about a chronic illness should be considered a significant direct benefit to people outside of a study living with that condition.

COVID-19 is a devastating disease, that is, a seriously life-altering or life-threatening disease for which no adequate effective treatment is available. Such

diseases seem to make clinicians especially reluctant to initiate rigorous placebo-controlled trials. Devastating diseases also make the research ethics community reluctant to allow research. That reluctance is evident, for example, in the 2002 and 2016 versions of CIOMS Guidelines (CIOMS 2002, 2016) which have governed research practices in many parts of the globe. The Commentary on Guideline 5 of the somewhat more tolerant 2016 standards still holds that, “The use of placebo controls in clinical trials … [is allowed when doing so] exposes participants to no more than a minor increase above minimal risk.” In other words, it appears that CIOMS guidelines do not accept placebo-controlled studies for devastating diseases because the risks associated with the disease include “serious or irreversible harm to the subjects.”

Clinicians facing patients with devastating diseases without effective treatment recognize that the consequences for their patients are likely to be catastrophic. Yet, because the stakes are high, the angst is intense. The powerful emotions of fear and despair may impair the thinking of patients. Of particular concern, however, are the extreme feelings that may distort the judgment of clinicians, influence institutional decision makers, and sway the judgment of those who create research ethics policies.

A recent account by Kahneman, Sibony, and Sunstein in their new book, *Noise: A Flaw in Human Judgment,* describes how both systematic distortions, i.e., biases, and random and irrelevant reactions, i.e., noise, may have driven well-meaning parties to flawed decisions. Noise can be produced by random unrelated factors including the weather, time of day, hunger, a good meal, or most anything else. In deliberation on whether or not to provide treatment with unstudied interventions for a devastating disease, it is certainly possible that judgment is affected by noise from exaggerated results of low-quality studies, emotions, or entrenched but unexamined ethical positions.

Yet, at some institutions, and in some countries, such as Britain, and in some disciplines such as pediatric oncology, we consistently see rigorous research conducted on devastating disease. In the US during the COVID-19 pandemic, however, the most common response was "do something!" In the face of devastating disease, either we should accede to the emotional compulsion to try anything that might work or abide by scientific best practices. If one is the right course in the face of devastating disease, following the opposing course is an error. Both approaches cannot be correct.

Contemporary reactions to the COVID-19 pandemic raise challenging moral issues and questions that have not been adequately addressed in the research ethics or clinical ethics analyses. One question is whether standards for offering an unproven intervention as treatment should be different from those for initiating research. Another question is whether those enrolled in studies should be most or least vulnerable to the devastating effects of the disease. Given the disparity with which COVID-16 affected immigrants, minorities, and underprivileged populations, questions of justice, burdens of risk and benefits reemerged, and the perspective of under-served groups remain. (Raven-Gregg et al., 2021) Other questions concern specific issues about where, when, and how research should be conducted, and who should receive innovative

interventions outside of research. Repeated calls for normative and empirical analysis on how innovation and research should be integrated, have led to remarkably few empirical studies or moral deliberations with bioethicists and other key informants.

At this point, with the threat of new infectious diseases on the horizon and numerous devastating diseases that have no adequate treatment, we cannot afford to punt. We need clear answers to the core issues of research ethics, answers that can be endorsed by an overlapping consensus of clinicians and investigators. We need to investigate the biases and noise that impact decisions of those who make the choice to pursue treatment with unstudied remedies or undertake conscientious and rigorous research. We need to identify institutional structures, mechanisms, and commitments that allow people to overcome the emotional barriers that interfere with good judgment as well as the arrangements and pressures that inhibit research initiatives. And, in line with the recommendations from Kahneman and colleagues, we have to bring those findings to the attention of astute and experienced leaders of the research ethics community, in concert with leaders from the pharmaceutical industry, and representatives of organizations that advocate for people who are stricken with devastating diseases.

In the tradition of The Belmont Report, we have seen similar working groups take on important issues in research ethics to produce valuable guidance. An interdisciplinary stakeholder working group led by Diane Hoffman from the University of Maryland School of Law, used a series of iterative discussions to develop recommendations on probiotic regulation. Using a similar process, Christine Grady, colleagues at the NIH, and others with extensive experience in research ethics, convened a working group to develop a consensus position on broad consent for research with biological samples.(Grady et al. 2015) We now need another such conserted effort to forge new guidance for integrating innovation and research for devastating disease.

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