

**The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard
Bioethics Collaborative**

Monday, June 1st, 2020 | 12:00PM-3:00PM EDT
Virtual Meeting

**COVID-19 and Ethical Challenges for Clinical Research
Executive Summary**

Introduction

The COVID-19 pandemic has raised novel ethical issues and intensified existing ones in clinical research. Some issues relate to clinical research generally, such as determining if and how research can continue under social distancing measures. Other issues relate specifically to COVID-19 research, such as whether it is ethically sound to include vulnerable populations (e.g., children, pregnant women) in COVID-19 research so that results from the research can be applied to them. The standards for prioritizing clinical trials based on rapidly evolving evidence need to be delineated. Additionally, issues such as the fair allocation of therapies and vaccines that have been approved or granted an Emergency Use Authorization (EUA)—and thus no longer require clinical trials—may affect clinical research. The MRCT Center selected several issues to discuss at the June 1st Bioethics Collaborative. The selected topics included the proliferation of uninformative COVID-19 clinical trials, the inclusion or exclusion of vulnerable populations in COVID-19 research, and the appropriate standard-of-care (SOC) for COVID-19 research. The convened meeting of the Bioethics Collaborative considered strategies for addressing the theoretical and practical challenges these issues raise for clinical research stakeholders.

Meeting Summary

The COVID-19 pandemic has led to a proliferation of poorly coordinated, often underpowered, and/or single arm clinical trials that are uninformative or are at risk of becoming uninformative. Uninformative clinical trials are unethical in that they subject participants to the risks of research without providing the possibility of either personal benefit or generalizable knowledge. As of May 31st, 2020, there were 1833 COVID-19-related clinical trials registered in ClinicalTrials.gov, of which 207 studied hydroxychloroquine and 29 studied remdesivir. Similar patterns were observed in Europe. Many of the European trials were small: 46 trials enrolled less than 50 subjects (Eichler et al., 2020). Several factors appear to contribute to the proliferation of COVID-19 clinical trials, including the rapidity of the pandemic's onset, poor pandemic preparedness, a lack of infrastructure for trial coordination, and a lack of incentives for collaboration. One attendee with experience on an Institutional Review Board (IRB) of an academic medical center noted their efforts to merge two similar research studies occurring at the



institution. While their efforts in this instance were successful, compelling researchers to merge studies more generally would be an unpopular action and beyond the remit of the IRB.

The onset of the COVID-19 pandemic strained resources in research and clinical care settings, forcing difficult decisions about how scarce resources should be allocated to support research efforts. As a result, many institutions established research prioritization committees that aimed to determine which trials should be initiated or continued and which trials should be delayed or halted altogether. Prioritization of trials remains important as the local incidence and severity of disease wanes, and organizations look towards reopening normal research operations. Trial prioritization committees examine parameters such as trial feasibility, unmet need, and the social value of a trial, among other factors when making a determination. Attendees considered whether trial prioritization committees should also consider the risk of COVID-19 infection that a trial poses to research staff and others who may come in contact with participants. Attendees agreed that this consideration matters but speculated that a significant proportion of clinical research stakeholders might disagree.

The same conditions that force the need for trial prioritization may also indicate a need for trial deprioritization as the evidence base surrounding different therapies for COVID-19 evolves, and thus the informativeness of a given clinical trials changes. For example, if a research study is published demonstrating conclusively that drug X is an ineffective treatment for COVID-19, it would be unethical to continue similar studies on drug X. While attendees agreed that trial deprioritization would preserve research resources and protect participants from unnecessarily bearing the risks of uninformative trials, it was noted that trial de-prioritization does not appear to happen currently. The locus of responsibility for reexamination of trial appropriateness also remains unclear.

Meeting attendees linked questions of trial prioritization to the issue of providing expanded access to experimental COVID-19 drugs, considering whether it may also be appropriate to restrict or foreclose expanded access to experimental COVID-19 drugs when there are ongoing clinical trials testing that (or another) therapy for COVID-19. Among other criteria, the FDA states that expanded access may be appropriate when “providing expanded access will not interfere with development of the drug for the expanded access use” (Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER), 2016). The FDA considers the availability of ongoing clinical trials for the drug, the size of the patient population, and the potential impact that expanded access will have on trial accrual for research on the drug (CDER & CBER, 2016). However, the FDA does not consider how expanded access to one drug will affect the development of other therapeutic (or investigational) products for the same disease. In light of the pandemic, should this perspective be widened to account for the potentially negative consequences that expanded access programs may have on the development of other therapies? One attendee noted that it is unrealistic and unethical to limit expanded access to a drug based on what might or might not be happening at other companies or institutions. One attendee suggested that the indirect effects of expanded access could be mitigated through inter-



institutional platform clinical trials that alleviate patients of the need to choose between multiple trials and expanded access. While inter-institutional platform trials have been designed, their coordination remains difficult.

Given the wide availability of COVID-19 clinical trials and the large patient population willing to enroll in COVID-19 research, meeting attendees asked if and how an institution should play a role in determining which patients enter into which trials. On one hand, potential research participants could be permitted to review the various clinical trials available to them and choose one for themselves, upholding autonomy. However, there may be too many clinical trials for a potential participant to realistically review or understand before making a decision, and it places the burden of sorting through available clinical trials inappropriately upon the potential participant. On the other hand, an institution could play an active role in determining which participants are offered which specific clinical trials and thereby help to ensure that none of its clinical trials are underpowered. Attendees suggested that institutions could randomize which clinical trials are presented to potential participants based on some arbitrary factor such as the weekday that the potential participant arrives at the institution. Some participants suggested that limiting the options available to potential participants appears ethically problematic. There may be, for instance, pragmatic reasons that a participant would prefer one trial over another that are impossible for an institution to predict (e.g., one trial may have a study visit schedule that makes it more accessible to an individual). One attendee emphasized that institutional influence on clinical trial selection can coexist with participant autonomy. Even if the number of trials makes it difficult to explain in detail each trial for which a potential participant is eligible, an institution could still be transparent about how they are selecting which trials to present.

Attendees considered several IRB challenges during the COVID-19 pandemic. First, attendees asked if IRBs should be responsible for preventing or limiting duplicative clinical trials. While this would protect research participants from potentially uninformative clinical trials and would therefore fall within the scope of IRB responsibilities, it would also require burdensome and frequent landscape analyses to filter through the rapidly changing, preliminary, and sometimes unreliable information on the COVID-19 pandemic. Second, what options should the investigator or informed consent document describe as alternative therapies for a COVID-19 research participant? As information is changing rapidly, how often should participants be reconsented? Third, traditional documentation of informed consent involves the exchange and signature of paper forms, which raises a risk of COVID-19 transmission. IRBs and research study staff must define new standards for the informed consent process and for documenting consent during the pandemic. Fourth, children and pregnant women have been largely excluded from COVID-19 research and are often underserved and underrepresented in trials. Should IRBs permit, or even encourage, the inclusion of these groups in COVID-19 research? Finally, should prisoners be included in COVID-19 research, particularly given their increased risk of COVID-19 infection? Are health care employees a vulnerable population, and what are the implications of designating them as such?



The sprint for an effective COVID-19 vaccine has prompted some researchers to consider human challenge trials as a potential method to accelerate vaccine development. In human challenge trials, healthy individuals receive an experimental vaccine against SARS-CoV-2 and are subsequently infected with the virus. Attendees noted that vaccine development will be slow whether or not challenge trials are utilized and research stakeholders should be careful not to assume that the hypothetical social benefit of speeding vaccine development will be realized by challenge trials. Attendees questioned whether the prospect of challenge trials will evolve as COVID-19 infection rates decrease and companies are no longer able to conduct vaccine field trials.

Attendees commented on how the politicization of science has affected the COVID-19 response in clinical research. Vaccine development has been influenced by political pressures: whichever region receives the vaccine first will have a significant health and economic advantage over the rest of the world. Unwarranted political attention on hydroxychloroquine diverted resources from research on other therapies. An emergency use authorization (EUA) for hydroxychloroquine was granted in late March and rescinded by the FDA on June 15th, 2020 (Hinton, 2020). Political leaders played an active role in defining the standard of care for COVID-19 research before research data on the named intervention was publicly available (Lovelace, 2020). With early data on an investigational product, what is the evidentiary base that would modify standards of care? How should early news announcements be evaluated in the absence of timely publication of data? Attendees suggested that the MRCT Center could provide leadership to the clinical trial enterprise at a time when governmental institutions have faltered. For example, the MRCT Center could promote standardized research criteria for COVID-19 data acquisition and endpoint assessments.

The inadequacy of government guidance and the resulting impact on clinical research was manifest by the issuance of EUAs for COVID-19 diagnostic tests, many without robust evidence for their reliability. The EUAs challenged investigators and IRBs to evaluate the risk and benefit of COVID-19 research proposals given that the diagnostic tests resulted in both false positives and false negatives with consequences to data integrity and interpretation. Larger questions about the purpose of EUAs extend beyond the example of diagnostic tests. What is the role of an EUA, and how should an EUA be considered by patients, researchers, and the general public? As the example of hydroxychloroquine shows, EUAs can have an unintentional impact on the public's understanding of scientific evidence and may even result in the erosion of public trust in science. Should these factors impact the purpose and effectiveness of EUAs?

Attendees acknowledged and appreciated the positive aspects of the clinical research response to the COVID-19 pandemic. There has been an unprecedented drive for collaboration (most notably across industry and regulatory authorities) and resource sharing. One attendee participated in a collaborative COVID-19 study that was completed rapidly, attributing the trial's success to the drug manufacturer's willingness to work with a variety of institutions as well as the culture of infectious disease doctors accustomed to collaborating in the treatment of infectious diseases.



Other positives include decreased non-essential study visits for clinical trial participants, increased decentralized and hybrid clinical trials, flexibilities in study conduct, and increasing patient-centeredness in trials.

Potential Future Work

- Address trial prioritization by defining criteria for assessing the scientific value of a research study and by creating tools for conducting and assessing landscape analyses
- Explore the implications that trial prioritization may have for expanded access during a global pandemic
- Establish evidentiary standards for defining the standard of care in COVID-19 research
- Call for data transparency in COVID-19 research
- Publish the argument for considering the risk of COVID-19 infection that research poses to others when assessing research proposals
- Propose solutions to the lack of clinical trial coordination
- Identify ‘success stories’ from the pandemic and distill lessons that can be applied broadly to other situations

References

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