



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

Thursday, February 3, 2022 | 2:00PM-4:30PM ET
Virtual Meeting

**Ethical Complexities with Human Challenge Trials
Meeting Summary**

The February 2022 Bioethics Collaborative explored ethical complexities in human challenge studies and Controlled Human Infection Models (CHIM). These study designs have a long and complicated history, figuring in notorious cases of research abuse (Willowbrook, Guatemala STI experiments) but also as important components in treatment advances for conditions that tend to disproportionately impact the world's worst-off, such as dengue and malaria. The potential for CHIM studies to be leveraged ethically in relation to Sars-CoV-2 has been a matter of significant debate in the bioethics community. While the conversation touched on many issues relevant to the analysis of CHIM research generally, the viability of CHIM studies specifically in the context of the Sars-CoV-2 pandemic was a major focus.

After a brief presentation reviewing the history of CHIM research and raising some questions for reflection, discussion turned toward the distinction between CHIM models and specific tests or applications of the model. A CHIM model is developed with a particular strain of pathogen in the service of yielding an appropriate dosage (i.e., one that minimizes risks to participants while also permitting evaluation of relevant objectives) and route of administration that can then be tested in the service of particular aims, such as evaluating specific vaccines or therapeutics in different populations. While CHIM models are strain-specific, insights gained in the development of one model may be leveraged in the development of subsequent models. The viability of leveraging CHIM studies in the contexts of Sars-CoV-2 and future pandemics may depend on how quickly an acceptable model can be developed. It was also noted, however, that CHIM studies do not require the development of a model. It is possible to construct CHIM studies that mimic the natural processes of infection (e.g., by isolating someone known to be sick with a communicable virus in close proximity to volunteers) and that such designs may have certain scientific advantages, insofar as they more closely approximate real-world routes of transmission.

There appeared to be agreement that, when evaluating the ethics of CHIM studies, it is important to be precise about what they are being designed to accomplish and to compare them along relevant axes (including risk and benefit) to other possible designs that could be used to evaluate the same or similar objectives. Along similar lines, multiple participants noted

that CHIM research is likely to be most valuable, and should be viewed as, one particular component in a portfolio of research that also includes observational and other types of studies. The aims of CHIM studies will often not be the same as the aims of wider field studies, the latter of which serve important purposes of confirming safety and efficacy in large populations, in ways that can also garner public trust. The question for CHIM studies may thus often be what value they add to a portfolio of research, not what value they have in isolation, and whether that value is enough to justify them.

Risk to participants occupied a central place in the discussion. The idea that there should be a ceiling on permissible risk independent of benefit in CHIM studies was contrasted with views on which any amount of risk could be tolerable provided that the expected benefits were great enough and participants were supported in providing informed consent. The matter of uncertainty arose in connection with risk at several points in the discussion. Participants discussed, with apparent lack of consensus, whether the level of uncertainty regarding predictors of severe disease, frequency of long-term sequelae, and the like in the early days of the Sars-CoV-2 pandemic, and perhaps still, was too high to ethically conduct CHIM studies. Analogies were drawn between the level of uncertainty and risk found in traditional first-in-human drug studies and CHIM studies, but there was apparent disagreement on whether the degree of uncertainty and risk in each were comparable. Discussion also touched on how informed consent should handle uncertainty and what strategies exist for best communicating and ensuring genuine understanding of uncertainties and unknown risks.

Several important issues were raised in connection with the recently completed Sars-CoV-2 challenge study in the United Kingdom (UK). The case of a participant losing their sense of smell through 180 days post-participation provided an interesting test case on the threshold for acceptable risk. Several participants stated that they did not believe the value of the UK study's findings were significant or added greatly to what was already known. Along similar lines, some participants, looking back at the last two years of the Sars-CoV-2 pandemic, expressed skepticism that CHIM studies could have accelerated vaccine and therapeutic development, although it was recognized that some of the factors responsible for this (exceptionally efficient vaccine development via field studies; factors that delay development of CHIM model and publication of results) may not always be present. This gave way to a discussion of whether the main benefits of CHIM studies should be construed as accelerating timelines for vaccine and therapeutic development, with some participants expressing skepticism that speeding product development was a main benefit of CHIM research.

The issue of public trust was considered. Even if ethically justified *ex ante*, CHIM studies, like any research, can have bad outcomes. Given the already significant challenges with vaccine hesitancy among the public, a death in a CHIM study at the beginning of the Sars-CoV-2 pandemic, or even now, may have set back public trust significantly, at a time when it was needed most. An analogy was drawn to the death of Jesse Gelsinger, which set back public



perception and trust in gene therapy research enormously. By contrast, it was also suggested that one potential benefit of CHIM studies is helping to familiarize and educate the public about CHIM research designs, in ways that might be beneficial to the long-term public acceptance of appropriately designed and conducted CHIM research. It was noted that future outbreaks of new infectious diseases worse than Sars-CoV-2 are likely and that CHIM research may be the best or even a necessary component of combating future pandemics, making it prudent to work out the ethical issues and familiarize the public now so that CHIM research can be done as quickly as possible in such a scenario. However, doubts were also expressed over whether CHIM research is really the right fit for use in the face of a pandemic caused by a novel pathogen, given the time lag needed to create the model and the uncertainties likely to characterize the situation, noted earlier.

A number of additional interesting and important issues were raised in passing, but time constraints prevented the group from discussing them in depth. These included the concern that the lack of guaranteed compensation for research injury in the United States is a problem for CHIM research; the potential impact of CHIM research in infectious diseases for third-party bystanders; the role of advocates for healthy research volunteers; questions about how lay advocacy may or should shape research, as evidenced by the 1DaySooner campaign; and the potential viability for CHIM studies to be leveraged in relation to the Zika virus.