HEALTH CARE POLICY AND LAW

Are SARS-CoV-2 Human Challenge Trials Ethical?

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A clinical trial is underway in the UK in which young, healthy participants are exposed deliberately to SARS-CoV-2 to assess the viral inoculum needed to produce an infection and to test vaccine efficacy (NCT04740320). Each participant will be paid approximately $6200. Although the very idea of such a study might seem unethical, there is a long history of deliberate infection of humans for research. Such studies are called challenge studies or controlled human infection trials and involve deliberate exposure to pathogens to study the natural history, treatment, or prevention of infectious diseases.

Challenge trials have a checkered ethical history, such as German and Japanese experiments during World War II, US sexually transmitted disease experiments in Guatemala after the war, and the Willowbrook hepatitis experiments that only ended in 1972. Yet most recent studies have been conducted ethically, ensuring consent and participants' welfare. Challenge trials have contributed to important medical advances, such as the yellow fever vaccine. They can speed the development of treatments and cut research costs and have the potential to help many people, perhaps hundreds of millions in a pandemic. Yet the end does not necessarily justify the means. The importance of having ethical principles in the first place is that they can be relied on, especially under extraordinary circumstances. Pandemic exceptionalism should be avoided.

Some have advocated strongly for SARS-CoV-2 challenge trials. Therefore, it is important to examine how the UK COVID-19 challenge trial measures up against ethical criteria.

Informed consent is a necessary, but not a sufficient, protection for research participants, particularly for a challenge trial. Although intended to advance medical knowledge rather than to benefit participants clinically, human medical research is a part of the medical enterprise, which is conditioned by the ethics of medicine as a profession. Physicians have recognized since Hippocrates the ethical importance of avoiding harm. In challenge trials, the participants are deliberately put at risk for the sake of helping unnamed future patients, and there is a special obligation to limit the likelihood and potential magnitude of the harm they might face. Importantly, challenge trials add the risk of the infective agent to the already substantial risks of the experimental intervention being investigated. The ethical mandate to limit the harm to those who volunteer for such trials is very strong.

Consent is but one of several ethical considerations that ought to govern a decision to permit a challenge trial. Broadly speaking, these considerations also include the social and scientific warrant for the trial, nonmaleficence, and justice. These ethical considerations also be used to assess the UK COVID-19 challenge trial.

First, the social and scientific warrant for a challenge study should be strong: the disease must be important, with high morbidity and/or mortality, or at least a high prevalence. The study must address an important unanswered question. The proposed intervention should have a reasonable prospect of success. Alternative methods of giving an adequate answer to the trial question should be ruled out.

Regarding the UK study, COVID-19 is prevalent, morbidity and mortality are high, and vaccines and are an important intervention. However, the warrant for a challenge trial is diminished by the fact that there are already several safe and effective vaccines. As the pandemic is ongoing, the alternative of standard population vaccine trials is still available. Moreover, to make the trial safe, a young, healthy study population was selected; therefore, results may not generalize well to those most at risk, namely elderly individuals and those with predisposing conditions.

Second, everything reasonable should be done to mitigate risks to participants, and the level should be set so that the most likely risk is of mild to moderate symptoms of a short duration; for example, equivalent to a day or 2 of fever, chills, and malaise. Not only should the probability and magnitude of known risks be considered, but also the unknown risks associated with an incompletely understood disease. Attenuated infective agents or strains with low pathogenicity should be used preferentially. Testing in subpopulations at low risk of severe disease should be considered. Finally, a rescue option, an effective treatment in case a participant contracts moderate to severe disease, is ethically necessary.

On one hand, the UK study admirably has selected participants who are at low risk of severe disease. On the other hand, COVID-19 is still new and poorly understood. Occasionally, even those in low-risk groups can become severely ill, and the long-term risks are unknown. Moreover, there is no good rescue therapy should a participant contract severe disease.

Third, justice rules out conducting such studies in vulnerable populations such as prisoners. It is also unjust to recruit participants heavily from socioeconomic and racial/ethnic groups that are already disproportionately burdened by the disease. Ideally, the population from which participants are selected will be assured access to the intervention if it proves valuable. Justice also requires compensation for those who are harmed as a result of participation, and their medical care should be assured. Notably, the US does not have a system of compensation for injured research participants, and the Vaccine Injury...
Compensation Program does not cover research. Above all, it is unjust to conduct a challenge trial merely because it offers an inexpensive research design.

The UK study does not present any overt justice problems. The medical care of participants who become ill is assured in the UK. The trial is advertised widely and not targeted at marginalized groups. Nonetheless, the relatively high payment is likely to be more attractive to those experiencing economic adversity.

Finally, informed consent for challenge studies must be performed carefully, ensuring that potential participants understand the risks (including how much is unknown) and are making an autonomous choice. Proxy consent should not be permitted. Volunteers are the optimal participants; remuneration in a challenge study beyond compensation for incidental costs carries the special dangers of manipulation and/or exploitation. An admission that “no one will do this if we don’t pay them” proves the point.

The UK study has adequate mechanisms for informed consent. Nonetheless, the remuneration is hefty enough to raise concerns about exploitation and manipulation.

The COVID-19 pandemic does present urgent needs, but this analysis suggests that the ethical justification for this (or other) challenge studies using SARS-CoV-2 fall short of the mark: there are alternatives; the study population may not give generalizable results; there is no rescue therapy; the long-term risks of infection are unknown; and the level of remuneration is suspiciously high. However, this does not mean that there might be conditions in the future under which SARS-CoV-2 challenge trials would be better justified. As Aristotle once wisely counseled, an ethical decision always rests with the particulars.

ARTICLE INFORMATION

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REFERENCES