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Shah, S.K., Miller, F.G., Darton, T.C. orcid.org/0000-0003-2209-9956 et al. (19 more authors) (2020) Ethics of controlled human infection to study COVID-19. Science, 368 (6493). pp. 832-834. ISSN 0036-8075

https://doi.org/10.1126/science.abc1076

Responding to the COVID-19 pandemic: Ethical considerations for conducting controlled human infection studies

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Word Count: 2000

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Conflicts of Interest: The authors have no conflicts of interest to report.

Disclaimer: The opinions expressed in the article are the authors' and do not reflect the views of organizations with which the authors have affiliations, including the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Acknowledgements: This work was primarily supported by a Making a Difference Grant from the Greenwall Foundation, along with support from the Wellcome Trust, Brocher Foundation, and NIH Clinical Center Department of Bioethics. The authors would also like to thank Katherine Littler, Cecilia Chui, Melissa Kapulu, Michael Yu, and Punnee Pitisuttithum for their contributions.

A novel coronavirus (SARS-CoV-2) has caused a global pandemic with more than 1.1 million confirmed cases and 60,000 deaths.[1] To reduce the surge of seriously ill patients,[2] governments have issued strict physical distancing orders for half of the global population.[3] These public health measures[4] are difficult to sustain and have unintended negative consequences for health, well-being, and justice.[5] Development of an effective vaccine is the clearest path to controlling this pandemic, [6] but will take at least one year.[7]

Vaccine development could be accelerated by conducting controlled human infection (CHI) studies with SARS-CoV-2.[8] [9] The idea is being pursued by some researchers, and hundreds of people are interested in participating.[10] In CHI studies, a small number of participants are deliberately exposed to a pathogen to study infection and gather preliminary efficacy data on experimental vaccines or treatments. CHI studies have a long, complicated history that includes unethical research.[11] Yet they have enabled significant improvements in clinical and public heath practice, have been conducted safely for many infectious diseases, and recently were instrumental in obtaining licensure for two vaccines.[12]

Under what conditions would CHI studies with SARS-CoV-2 be ethically acceptable? Building on existing ethical analysis[13] [14] and recent developments in research ethics,[15] our international, multidisciplinary group of ethicists, CHI researchers, policymakers, and social scientists has been developing a state-of-the-art ethical framework for CHI studies.[16] Based on this framework, members of our group agree that the following conditions should be met to conduct SARS-CoV-2 CHI studies ethically (Table 1). However, we differ as to whether these conditions are met at the present time, while acknowledging that the situation is rapidly evolving. Rather than arguing for or against SARS-CoV-2 CHI studies, we therefore provide guidance for research sponsors, communities, participants and the essential independent reviewers considering such studies.

1. Sufficient social value

Given that SARS-CoV-2 CHI studies would involve major uncertainty and controversy, they should have high social value compared to the alternatives. This requires that studies address the most relevant scientific questions in rigorously designed and conducted experiments; results are published quickly and widely accessible; and data, samples and challenge strains are appropriately shared.

Crucially, SARS-CoV-2 CHI studies should have the potential to significantly accelerate vaccine or treatment development. Timely vaccine development would likely result in faster control of the pandemic and reduce the need for, and associated costs of, physical distancing measures.

Over 50 investigational vaccines and 100 experimental treatments for COVID-19 are currently in development.[17] Scholars estimate that SARS-CoV-2 CHI studies with previously uninfected participants could expedite vaccine development, notably by selecting the most promising candidates.[18] To accelerate development, regulatory authorities, researchers and research sponsors must collaborate. Stakeholders should, for example, standardize data collection and share data for better aggregation across studies—especially if multiple vaccines are tested.[19] Stakeholders should also plan how CHI data could be used for launching or modifying larger trials.[20] This type of coordination is difficult, and was not achieved for proposed Zika virus challenge trials in 2015-16.[21] Finally, stakeholders should address barriers to widespread, equitable access to any proven effective products.[22]

SARS-CoV-2 CHI studies also have the potential to yield unique scientific insights. While animal models for COVID-19 are being developed and validated, CHI studies could illuminate who is infectious, when, and how—which are key, poorly understood parameters for modelling the course of the pandemic and improving the response. This information is difficult to collect by observation alone. Vitally, CHI studies could identify correlates of protection, clarify disease mechanisms, and study potential disease enhancement in previously-infected individuals, which could inform vaccine and treatment development, testing and introduction. Depending on who is enrolled, however, CHI study results may not generalize to all populations.

Alternatives include conducting CHI studies with attenuated SARS-CoV-2 strains or related, milder coronavirus strains.[23] While these alternatives could reduce the risks to participants and study personnel, it is unlikely that their results alone would be sufficiently relevant to address the current pandemic. Additionally, CHI studies could be conducted with previously-infected participants only, but these may be significantly less valuable for developing vaccines and treatments. Finally, standard vaccine efficacy studies could be conducted with at-risk populations, such as healthcare and other essential workers. These studies would be less ethically complex, but would likely take more time.

2. Reasonable risk/benefit profile

For SARS-CoV-2 CHI studies to be ethically permissible, risks to participants, study personnel and third parties should be minimized, reasonable in relation to the social value of the research, and below the upper limits of acceptable research risk.[24] [25] There are both scientific uncertainties about SARS-CoV-2 and moral uncertainties about the upper limits of research risk. These uncertainties warrant a cautious approach to evaluating the risks and potential benefits of SARS-CoV-2 CHI studies and will require revisiting risk-benefit judgments as new evidence emerges.

Risk minimization should focus primarily on reducing the risk of serious outcomes. To minimize risks to participants, SARS-CoV-2 CHI studies should recruit young people without underlying medical conditions who face lower mortality risks from COVID-19.[26] [27] [28] To minimize risks to study personnel, participants should be in inpatient isolation, contact with participants reduced to the extent possible, and robust personal protective equipment provided. Participants and personnel should also be carefully monitored, promptly managed when symptomatic, and be provided any proven effective targeted treatments (if any) or offered enrollment into an appropriate clinical trial. To minimize risks to third parties outside the research, participants who decide to withdraw should be confined as needed to prevent transmission. Advance coordination with public health authorities would facilitate confinement (which might not differ significantly from current physical distancing measures).

Participants might experience benefits from controlled infection and/or vaccination if they become immune to SARS-CoV-2. However, the degree and duration of naturally-acquired and vaccine-derived immunity needs further study. Moreover, some participants might receive placebo vaccines, and investigational vaccines may prove ineffective. Because these potential benefits of participation remain speculative, a cautious approach to risk-benefit evaluations requires that they be given limited, if any, weight. Insofar as potential direct benefits do not justify the risks to participants, they must be justified by the social value of the research, with higher risks requiring higher social value.

Finally, even when research has high social value and enrolls competent consenting adults, there is substantial consensus that risks to participants should not exceed an absolute upper limit. While

regulations and ethics guidance do not clearly delineate this limit,[29] commentators have argued that it should not exceed a 1% risk of death[30] or the risks posed by activities similar to research, such as living kidney donation or volunteer emergency assistance.[31 32] Some suggest higher risk limits might be permissible for research in an emergency.[29]

While data about COVID-19 outcomes are still emerging, and current data come from relatively small samples with missing data points and are still being vetted, existing population data suggest healthy 20-44 year-olds could have a mortality risk of up to 0.2%.[33] One model that attempts to account for current testing limitations and asymptomatic infections estimates adults ages 20-29 have a 0.03% risk of death and a 1.1% risk of hospitalizations.[34] The mortality risk could be further reduced by limiting eligibility to the youngest women and men (e.g. ages 18-25), carefully monitoring and promptly treating participants, and adding exclusion criteria as improved knowledge of risk factors emerges.[35] A <0.2% mortality risk is higher than in most other research or from common seasonal infections (Table 2). However, it falls below the upper risk limits proposed for research even under normal circumstances.[36] For third parties, there is no recognized upper risk limit;[14] however, with the above safeguards, these risks could be minimized to a very low level.

3. Context-specific stakeholder engagement

CHI studies have a checkered history,[37] and it can be counterintuitive for the public that researchers would infect people with diseases. Because of uncertainty and worries about public trust, SARS-CoV-2 CHI studies require early public engagement. Such engagement should convey that CHI studies can generally be ethically acceptable and highlight the high social value of SARS-CoV-2 studies specifically, alongside risk-mitigating measures taken in these studies. Given unprecedented physical distancing measures worldwide and the need for robust, yet swift engagement, novel engagement methods may be needed. For example, researchers could convene virtual advisory groups and disseminate information through social media. Clear channels for engaging communities and the public during and after studies would also be needed to mitigate possible mistrust in research and the health system. Rapid and robust engagement might be easier to achieve when the communities and the public are already familiar with CHI studies.

4. Suitable site selection

Selecting suitable sites for SARS-CoV-2 CHI studies requires considering risks to participants, study personnel, and third parties; feasibility of recruitment; availability of necessary infrastructure; and potential effects on the local pandemic response. Sites should be selected for sound scientific reasons and not based on vulnerability or mere convenience.[38] For example, CHI studies could be performed in locations with high community spread of SARS-CoV-2 in order to facilitate recruitment. Given that participants could require testing, medical attention, and treatment, and research personnel would require personal protective equipment, sponsors would also need to demonstrate that CHI studies will not unduly compete for scarce resources and thereby compromise the local pandemic response. All sites should have sufficient capacity to conduct rigorous studies, provide high-quality care to participants, and minimize research risks. Sites experienced with conducting CHI studies might be favored to ensure studies and engagement efforts can be launched quickly and responsibly.

5. **Fair participant selection**

Selecting participants fairly for SARS-CoV-2 CHI studies primarily requires considering fair distribution of research risks and burdens and generalizability to relevant populations. Because of the uncertainty and potential high risk involved, participants who are at relatively low risk and have capacity to give their own consent should be selected (i.e., young, healthy and competent adults). Healthcare professionals and other essential workers at increased risk of infection might be especially interested in enrolling, so as to develop immunity while receiving care in a controlled setting. However, as discussed, long-lasting and highly-protective immunity from infection or vaccination in SARS-CoV-2 CHI studies is currently uncertain. Moreover, enrolling essential workers during this pandemic could keep them from their jobs. In selecting participants, SARS-CoV-2 CHI studies therefore should avoid undue negative impacts on the local pandemic response.

6. **Robust informed consent**

Researchers should use enhanced consent procedures to ensure understanding and voluntariness for SARS-CoV-2 CHI studies, including engaging approaches to disclosure and testing potential participants on key information.[39] In this context, key information includes that participants will be deliberately infected, the associated risks and burdens, the study's purpose and social value, areas of uncertainty, possible restrictions on withdrawal to protect third parties, and that the study has undergone independent review. Ongoing informed consent will be especially important as information continues to evolve rapidly, for example about longer-term risks.

7. **Proportionate payment**

As SARS-CoV-2 CHI studies require confinement and additional follow-up, participants should be compensated for their time. Assuming this compensation reflects a fair minimum wage for unskilled and potentially risky labor,[40] U.S. participants might receive several thousand dollars in total. While high payments or compensation can be controversial, expecting participants to volunteer without compensation risks exploiting them.[41] Moreover, worries that high payments cloud understanding have generally not been supported by data, which instead suggest payment can help draw attention to risk.[42] Incentive payments beyond compensation might not be unnecessary, given the number of people already interested in participating in CHI studies.

CONCLUSION

If SARS-CoV-2 CHI studies were to advance, several ethical conditions must be met—but none of these are insurmountable. Given the extraordinary nature of the current situation, even for those who harbor ethical concerns, our framework supports laying the groundwork for SARS-CoV-2 CHI studies, such as developing and registering a challenge strain and engaging stakeholders to maximize the potential benefits of SARS-CoV-2 CHI studies. However, before such studies commence, independent ethical review—preferably by a specially convened committee[14]—should be required to determine that a given study meets these conditions, maintains the public's trust in research,[43] and is likely to help hasten the end of this pandemic.

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TABLE 1: Framework for ethics of challenge studies applied to COVID-19

Sufficient social value

- CHI studies should address relevant, unresolved scientific questions in rigorously designed and conducted experiments; results should be published quickly, in open-access; and data, samples and challenge strains should be appropriately shared for future research
- Coordination among stakeholders required to standardize data collection, ensure regulatory authorities are willing to accept data from CHI studies to accelerate licensure
- Valuable scientific questions for COVID-19 pandemic include: (1) identifying correlates of protection, (2) rapidly testing efficacy of interventions, (3) selecting the most promising vaccine candidate(s), and (4) improving understanding of disease pathogenesis.

Reasonable risk/benefit ratio

- Enroll participants ages 18-25 with no comorbidities
- Monitor closely and confine participants for at least 14 days
- Have personal protective equipment, mechanical ventilation, medical support staff available to minimize risk to study personnel and avoid interfering with outbreak response

Appropriate site selection

- Consider feasibility of recruitment, risk, availability of infrastructure, potential effects on outbreak response
- Conduct in region with ongoing transmission and available expertise, but bring in extra resources to protect participants and research staff so as not to hamper outbreak response

Fair participant selection

- Enroll younger participants (18-25) who are able to give consent and are at relatively low risk of mortality
- Consider enrolling essential workers who are likely to be exposed if their participation will not remove them from their essential roles when they are needed

Context-specific stakeholder engagement

- Media and social media strategy to engage wider community in a time of physical distancing
- Gather community input about concerns through surveys, interviews, or creation of virtual community advisory board

Robust informed consent

- Key criteria participants shoudl understand: (1) that they will be deliberately infected, (2) the risks and burdens, (3) the purpose of the study, and (4) any restrictions on liberty necessary to protect others
- Develop evidence-based, context-specific materials, test participant understanding and require high level of understanding for enrollment

Proportionate payment

- Participants should be compensated for their time and not exploited

Table 2: Comparison of mortality risks for otherwise healthy individuals

SARS CoV-2 for healthcare workers in China[43]	SARS CoV-2 in individuals 18-25 years of age[43] [43]	Challenge study with SARS-CoV-2 (assume participants 18-25 years of age)	Influenza (data from 2019)[43]	Influenza challenge study	Participation in phase I healthy volunteer study[43]	Malaria challenge study[43]
0.67%	0.003-0.2%	<0.2%	0.01%	<0.01%	0.003%	None reported

Highest estimated risk---------->Lowest estimated risk