Ethical Considerations for International Recruitment in COVID-19 Human Challenge Trials

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Abstract

Ongoing and anticipated COVID-19 human challenge studies in the UK may advance our understanding of COVID-19 and facilitate the licensure of safe, effective, and easily deployable next-generation COVID-19 vaccines and boosters. We argue that international volunteer recruitment for COVID-19 human challenge trials can help promote diversity in these trials and ensure a sufficient number of eligible volunteers, both of which will increase the benefits of challenge research. We explore the ethical ramifications of dealing with unfair background conditions of global vaccine injustice to expand medical research, and conclude that international recruitment for COVID-19 human challenge trials can be conducted ethically provided that several robust protections are in place for volunteers.

Keywords: human challenge trials, research ethics, COVID-19

Background

The world's first COVID-19 human challenge study, led by a consortium of hVIVO, Imperial College London, and the UK Vaccine Taskforce, began in March 2020. Several follow-up studies are being planned or considered: the University of Oxford has received ethics approval to conduct a reinfection challenge study with up to 64 seropositive volunteers, and researchers at the Leiden University Medical Center in the Netherlands are preparing for the first COVID-19 challenge study outside of the UK (University of Oxford, 2021; Reuters, 2020).

As SARS-CoV-2 virus variants are reshaping the COVID-19 pandemic, human challenge studies may be of significant utility by yielding data on viral activity in the upper respiratory tract, COVID-19 reinfection, and correlates of immune protection (Medicines and Healthcare products Regulatory Agency, 2021). Most importantly, challenge studies can gauge the efficacy of boosters and next-generation vaccines that may be needed to protect the world against emerging virus variants, such as the Beta and Delta variant (Rohrig and Eyal, 2021). This is especially important for developing countries that are in need of rapid next-generation vaccine authorization, since mRNA vaccines— which have alone been shown to be effective against the B.1.351 strain— have been overwhelmingly prepurchased by wealthy countries and have proven difficult to handle for LMICs due to their cold chain requirements (Duke Global Health Innovation Center, 2021). Identifying a correlate of immune protection would also expedite future vaccine efficacy trials by enabling surrogate endpoints for efficacy.

However, because volunteer recruitment is only taking place in the UK, COVID-19 human challenge studies may have limited public health value. This is for two reasons. First, UK-only recruitment means that COVID-19 human challenge trial participants are not representative of global genetic, environmental, behavioural, and microbiome diversity. Not only is the UK not demographically reflective of the world, but Black and Ethnic Minority (BAME) populations are systematically underrepresented in British medical research (Ijoyemi, 2021). We explore this limitation in greater detail in subsection 2.1, *Promoting Trial Diversity.*

Second, UK-only recruitment may preclude an adequate number of trial participants. Several challenge study designs may require unvaccinated volunteers, which is a problem since as of July 10th, 2021, over 88% of Britons have already

received their first dose (Public Health England, 2021). This may limit trials for next-generation vaccines, in which volunteers will likely need to be seronegative before they are exposed to the challenge agent, as well as COVID-19 reinfection studies like the one planned by the University of Oxford, which needs to recruit unvaccinated volunteers to control for the effect of previous vaccination on re-exposure to the virus.

As time passes, the share of eligible volunteers will continue to decrease under the current schema. The UK has the highest COVID-19 vaccine willingness rate in Europe—91% as of June 2021 (YouGov, 2021). Those who elect not to get vaccinated once vaccines are readily accessible are presumably the least likely to partake in a COVID-19 human challenge trial due to mistrust in the medical system. The greatest population of eligible volunteers for COVID-19 human challenge trials will increasingly be found internationally, and in low and middle income countries (LMICs) in particular, where vaccination rates are extremely low.

We argue below that international recruitment could improve the value of the resultant challenge trial data and fulfill an ethical obligation to promote global inclusion in medical research. We consider some of the key protections that must be put into place to ensure that international recruitment for challenge trials is conducted ethically.

Ethical considerations for international recruitment

While allowing international recruitment of unvaccinated volunteers may have significant public health value by enabling COVID-19 human challenge studies to test boosters and next-generation vaccines, such recruitment would likely draw increased scrutiny from the global health research community, mindful of the checkered history of the profession that has been marked by exploitative and extractive research practices (Washington, 2006).

We explore three unique ethical considerations presented by expanding the inclusion criteria of ongoing and planned COVID-19 human challenge trials in the UK to include international volunteers, with a particular focus on recruitment from LMICs, and conclude that with robust protections in place for volunteers, these trials can remain ethical.

2.1 Promoting trial diversity.

The imperative duty of ethicists reviewing challenge proposals is to minimize risks to volunteers and maximize the societal benefits of research. While international challenge trial volunteer recruitment would affect both sides of the risk-benefit analysis, we think that the benefits of increased international diversity in COVID-19 human challenge trials outweigh the risks, provided that this recruitment includes robust protections for volunteers.

For young healthy volunteers, Manheim et al. find that the risks of participating in a COVID-19 human challenge trial are lower than other commonly acceptable medical procedures such as living organ donation (Manheim et al., 2021). Some evidence shows that BAME populations are at greater risk of severe disease and death due to COVID-19; however, the differences in risk are small relative to other comorbidities (White, 2020). For instance, a 22-year-old Black woman would be at lower risk in a COVID-19 human challenge trial than a 29-year-old white man, holding other comorbidities constant.

On the other hand, the benefits of including BAME volunteers in COVID-19 human challenge trials would be significant. The lack of global volunteers from various ethnic backgrounds in current COVID-19 challenge trials could limit the generalizability of the resultant data (Kafuko, 2021). This is especially problematic, since the data accrued from challenge trials will have the most public value if they can be used to support the authorization of vaccines in developing countries. Given that efficacy and viral transmission data in challenge trials is being inferred from a relatively small challenge cohort, it is especially important for the sample to include volunteers with diverse genetics and microbiomes, as well as environmental and behavioural stressors (Hagan et al., 2019). Notably, this is a reason for COVID-19 human challenge trials to include volunteers *both* from wealthy countries and LMICs to optimize for trial diversity, not to include solely volunteers from LMICs.

A final ethical argument in support of COVID-19 human challenge trial diversity is an opposition to medical paternalism and the obligation to foster global inclusion in medical research. It seems contrary to the spirit of equity-centered research to needlessly restrict volunteers living in LMICs from exercising the opportunity to voluntarily participate in the research and the development of therapeutics which may be distributed to them in their host countries[19]. Over 2,000 people from LMICs have expressed interest in taking part in COVID-19 human challenge studies with the non-profit 1Day Sooner. Giving people in LMICs equal opportunity to partake in global research is respectful of their agency as prospective research volunteers, and may alleviate vaccine hesitancy and the suspicion of medical institutions that exists in many BAME and LMIC communities as a result of historical exploitation, exclusion from research, and a lack of readily available information about the vaccine development process among people in LMICs (Hawkins and Emmanuel, 2008). International recruitment of participants from LMICs also fulfills the principle of justice: sharing of burdens and resultant benefits between the rich countries and LMICs.

2.2 Capitalizing on unfair background conditions

International recruitment from LMICs is desired for human challenge trials precisely because volunteers from LMICs are disproportionately unvaccinated, a phenomenon that only exists due to an unjust global vaccination scheme in which rich countries have cornered the market for effective vaccines. One may therefore worry that international recruitment would be complicit with a morally impermissible public health landscape on one hand, and damaging to volunteers and host countries on the other by entrenching structural inequalities in research capacity.

While these concerns are well-founded, we argue that international recruitment for COVID-19 human challenge trials may be less exploitative than field efficacy trials to gauge the efficacy of next-generation vaccines for three reasons. We use the definition of exploitation provided by Emmanuel et al., in which "A exploits B when B receives an unfair level of benefits or unfair burden of risks as a result of interacting with A" (Emmanuel et al., 2014).

Firstly, many LMICs have under resourced healthcare systems, meaning that if someone becomes infected with COVID-19, which may be inevitable due to low vaccination rates, serious disease may go untreated. Oppositely, in human challenge trials in the UK, participants would be offered the highest quality care available globally in specially constructed and staffed medical centers, at no monetary cost to themselves.

Second, COVID-19 challenge trials last only a couple of weeks for trial participants (Imperial College London, 2021), whereas field trials can last several months, and in some cases could require volunteers to withhold receiving authorized vaccines to ensure efficacy results.

Third, challenge trials only require around one hundred trial participants to gauge vaccine efficacy against infection, whereas field trials may require tens of thousands of participants, creating a far larger research burden for involved communities.

Further protections to minimize exploitation are ethically necessary, as the COVID-19 pandemic has seen problematic dynamics between researchers in developed countries and potential trial participants in LMICs, in which developing countries bore the costs of research without receiving the benefits. For instance, researchers at the University of Oxford moved part of their Phase III vaccine study to South Africa and Brazil in mid-2020, where COVID-19 transmission was greater, to expedite efficacy results after transmission waned in the UK. The Oxford vaccine was ultimately of little use in South Africa due to the prevalence of the B.1.351 strain, meaning that South Africans bore the costs of research without receiving any of the benefits. If it was not for the B.1.351 variant, South Africa could have benefitted from the trial by, for example, getting preferential treatment during allocations of the resultant vaccine.

In the context of human challenge trials, if volunteers did not receive a vaccine in the trial, all trial volunteers should be offered an authorized COVID-19 vaccine at the completion of the trial to protect their safety thereafter. As is the case with ongoing challenge studies, high-quality, cost-free medical care must be available for international volunteers in the case of any adverse events.

The primary justification of COVID-19 challenge research is to speed the approval of next-generation vaccine candidates and boosters, many of which are well-suited for distribution and application in LMICs, where the current authorized vaccines that have been overwhelmingly prepurchased by wealthy countries are limited and in some cases not accessible. Conditioning the ethical approval of the trial on guaranteeing a certain share of vaccine delivery resulting from the research to LMICs would ensure that the benefits of research are shared in earnest by volunteer host countries.

The informed consent procedures for the trial must be monitored by an independent entity from LMICs to guarantee that trial participants fully understand the risks of the trial. Advocates from LMICs must also be available to represent volunteers during the course of the study. Lastly, in contrast to the ongoing COVID-19 human challenge study in London, the protocol for international recruitment and challenge study design should be made public before the first volunteer is recruited to ensure transparency and accountability.

2.3 Volunteer Payment

Payment for participation in medical and pharmaceutical research, including challenge studies that recruit volunteers from endemic settings are particularly controversial. There is a live debate amongst bioethicists about which framework for determining monetary incentives should be used, and which view of the distinctions between different types of payments is most appropriate (Ndebele et al., 2008; Fernandez-Lynch et al., 2021).

One novel ethical consideration presented by these challenge trials is whether research participants from LMICs should receive equal compensation as participants from developed countries in the same trial. These trials may be the first instance when international research participants will be transported to a single site to participate alongside one another, rather than research happening simultaneously across multiple locales. It would be egregious if two participants from different countries, doing the same "work", in the same place and at the same time, were to receive significantly different amounts of money on the basis that they are citizens of different countries. While this consideration should be duly weighed against legitimate concerns about exercising undue influence over people in LMICs through compensation, we agree with

Blumenthal-Barby and Ubel that underpayment is a greater concern than overpayment for COVID-19 human challenge studies (Blumenthal-Barby and Ubel, 2020).

Perhaps the most unique circumstance surrounding the existing COVID-19 challenge trials with respects to worries about undue financial inducement is the fact that more than 2,000 people from LMICs have already volunteered to participate in COVID-19 challenge trials without any expectation of financial gain with the non-profit 1Day Sooner. Whether or not these volunteers are ultimately eligible for a challenge trial, we should view this as evidence that there are many young people from a diversity of LMICs who have good faith altruistic intentions when it comes to contributing to this research (1Day Sooner, 2021).

Conclusion

Next-generation vaccines are likely necessary to end the COVID-19 pandemic worldwide, and human challenge trials may be a key step toward trialing vaccine candidates. Recruiting international volunteers for COVID-19 human challenge studies in the UK can improve these trials both scientifically and ethically by increasing trial diversity and solving for a possible lack of volunteers.

Notes

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Conflict of Interest:

K.A., A.R., Z.K., P.N., and J.M. all report affiliation with 1Day Sooner throughout the writing of the article.

References

Blumenthal-Barby, Jennifer, and Peter Ubel. "Payment of COVID-19 Challenge Trials: Underpayment Is a Bigger Worry than Overpayment." Journal of Medical Ethics, 12 Oct. 2020, p. medethics-2020-106901, jme.bmj.com/content/early/2020/10/11/medethics-2020-106901, 10.1136/medethics-2020-106901. Accessed 19 July 2021.

"COVID-19 | Launch and Scale Speedometer." Duke Global Health Innovation Center. Launchandscalefaster.org, 2021, launchandscalefaster.org/COVID-19. Accessed 19 July 2021.

Data.gov.uk, 2021, coronavirus.data.gov.uk/details/vaccinations. Accessed 19 July 2021.

"Data on COVID-19 Vaccination in the EU/EEA." European Centre for Disease Prevention and Control, 19 July 2021, www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea. Accessed 19 July 2021.

"Dutch Researchers Preparing for 'Human Challenge' COVID-19 Vaccine Trial." Reuters, Thomson Reuters, 25 Nov. 2020, www.reuters.com/article/health-coronavirus-challenge-virus/dutch-researchers-preparing-for-human-challenge-covid-19-vaccine-trial-idUSKBN2852VM.

Emanuel, Ezekiel J., et al. "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research." The Journal of Infectious Diseases, vol. 189, no. 5, Mar. 2004, pp. 930–937, academic.oup.com/jid/article/189/5/930/810459, 10.1086/381709. Accessed 19 July 2021.

"Guidance on Strain Changes in Authorised COVID-19 Vaccines." Medicines and Healthcare products Regulatory Agency. GOV.UK, www.gov.uk/government/publications/access-consortium-guidance-on-strain-changes-in-authorised-covid-19-vaccines/guidance-on-strain-changes-in-authorised-covid-19-vaccines.

Hagan, Thomas, et al. "Antibiotics-Driven Gut Microbiome Perturbation Alters Immunity to Vaccines in Humans." Cell, vol. 178, no. 6, Sept. 2019, pp. 1313-1328.e13, www.sciencedirect.com/science/article/pii/S0092867419308980, 10.1016/j.cell.2019.08.010. Accessed 19 July 2021.

Hawkins, Jennifer S, and Ezekiel J Emanuel. "Front Matter." Exploitation and Developing Countries, Princeton University Press, 2008, p. [i]-[vi]. JSTOR, www.jstor.org/stable/j.ctt7s3f4. Accessed 19 July 2021.

"Human Challenge Trial Launches to Study Immune Response to COVID-19." University of Oxford, www.ox.ac.uk/news/2021-04-19-human-challenge-trial-launches-study-immune-response-covid-19.

Ijoyemi, Timothy. "Fixing the Underrepresentation of BAME Participants in Medical Research | RACE.ED." RACE.ED, 7 May 2021, www.race.ed.ac.uk/fixing-the-underrepresentation-of-ba

me-participants-in-medical-research/. Accessed 19 July 2021.

Kafuko, Zacharia “UK COVID-19 Human Challenge Trials Need Participants. International Volunteers Are Ready to Heed the Call | Journal of Medical Ethics Blog.” Journal of Medical Ethics Blog, 26 Apr. 2021, blogs.bmj.com/medical-ethics/2021/04/26/uk-covid-19-human-challenge-trials-need-participants-international-volunteers-are-ready-to-heed-the-call/. Accessed 19 July 2021.

Manheim, David, et al. "Exploring Risks of Human Challenge Trials for COVID-19." medRxiv (2020).

Ndebele P, Mfutso-Bengo J, Mduluza T. Compensating clinical trial participants from limited resource settings in internationally sponsored clinical trials: a proposal. Malawi Med J. 2008;20(2):42-45. doi:10.4314/mmj.v20i2.10955

“Promoting Ethical Payment in Human Infection Challenge Studies.” The American Journal of Bioethics, 2021, www.tandfonline.com/doi/abs/10.1080/15265161.2020.1854368. Accessed 19 July 2021.

Rohrig, Abie and Eyal, Nir. “The Ethics of Human Challenge Trials Using Emerging SARS-CoV-2 Virus Variants.” Philpapers.org, 2012, philpapers.org/rec/ROHTEO-3. Accessed 19 July 2021.

“SARS-CoV-2 Human Challenge Characterisation Study - Full Text View - ClinicalTrials.gov.” Imperial College London. *Clinicaltrials.gov*, 2021, clinicaltrials.gov/ct2/show/study/NCT04865237. Accessed 19 July 2021.

Washington, Harriet A. Medical apartheid: The dark history of medical experimentation on Black Americans from colonial times to the present. Doubleday Books, 2006

White, Chris. “Model Estimates of Deaths Involving the Coronavirus (COVID-19) by Ethnic Group for People in Private Households, England.” Ons.gov.uk, Office for National Statistics, 16 Oct. 2020.

1Day Sooner. “1Day Sooner.” 1Day Sooner, 2020, www.1daysooner.org/. Accessed 19 July 2021.