COVID-19 controlled human infection studies: worries about local community impact and demands for local engagement

Kyungdo Lee,[1] Nir Eyal [2]

[1]Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, New Jersey, USA
[2]Center for Population-Level Bioethics, Department of Philosophy (SAS) and Department of HBSP (SPH), Rutgers University, New Brunswick, New Jersey, USA

Correspondence to
Professor Nir Eyal, Center for Population-Level Bioethics, Dept of Philosophy (SAS) and Dept of HBSP (SPH), Rutgers University, New Brunswick, New Jersey, USA; nir.eyal@rutgers.edu

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ABSTRACT

In spring, summer and autumn 2020, one abiding argument against controlled human infection (CHI) studies of SARS-CoV-2 vaccines has been their impact on local communities. Leading scientists and bioethicists expressed concern about undue usage of local residents' direly needed scarce resources at a time of great need and even about their unintended infection. They recommended either avoiding CHI trials or engaging local communities before conducting any CHIs. Similar recommendations were not made for the alternative—standard phase III field trials of these same vaccines. We argue that the health effects of CHI studies on local residents not participating in the study tend to be smaller and more positive than those of field trials. That is all the more so now that tested vaccines are being rolled out. Whether or not local community engagement is necessary for urgent vaccine studies in the pandemic, the case for its engagement is stronger prior to field trials than prior to CHI studies.

A DISTINCTIVE WORRY ABOUT CONTROLLED HUMAN INFECTIONS: A LOCAL COMMUNITY IMPACT

The UK government started a dose escalation interlude for the controlled human infection (CHI) study of SARS-CoV-2 vaccines.[1] In such a study, several dozen volunteers would typically be randomised to receive the vaccine being investigated versus control (an authorised vaccine, an experimental vaccine or dosage, or a placebo). Participants would then be exposed to live SARS-CoV-2. Comparisons of rates of infection and of infectiousness between different arms could reveal the protective effect of the vaccine being investigated. For their own safety, in a typical SARS-CoV-2 CHI, participants would all be young and healthy, a population in whom the chance of adverse COVID-19 outcomes or hospitalisation is small.[2]

While safe and highly efficacious vaccines are already being rolled out in some countries, it remains important to test whether these vaccines block infections (a crucial role not yet fully elucidated)[3] and how long that protection lasts,[4] yet further large-scale field trials of these vaccines would face complications in recruiting, as well as ethical complications.[5] In addition, the world needs to test whether next-generation vaccines, and especially vaccines easier to store, deliver or procure worldwide than current vaccines,[6] competitively block infections.

Elsewhere, one of us has argued that CHIs have important scientific value, can overcome various practical concerns and that done right, they remain fair towards study participants.[7–12] Here, we would like to tackle a particular concern about CHIs, raised by different author groups in spring, summer and fall 2020.

In spring 2020, an interdisciplinary expert group worried that

> Selecting suitable sites for SARS-CoV-2 CHIs requires considering … potential effects on local pandemic responses. … Given that participants would require testing, medical attention, and treatment, and research personnel would require personal protective equipment, sponsors should also demonstrate to ethics review boards or public health authorities that CHIs will not unduly compete for scarce resources and thereby compromise the local pandemic response.[13]

Their next sentence seemed to signal a way to address this worry, namely, 'to ensure that … local public engagement can be launched quickly, effectively, and responsibly'.[13] That article and others additionally recommended wider public engagement (which, in light of the global stakeholders in pandemic trials, it was plausibly proposed, could take the form of electronic surveys).[13 14] In light of the unusual nature of CHIs, such wider public engagement may make sense, and the results of the only deliberative workshop[15] and global survey[16] of which we are aware indicate strong global public support for CHIs. In the quoted passage, however, the public engagement recommended was 'local', presumably addressing the alleged adverse effects on 'local' pandemic response. Authors from the same group (along with colleagues) elsewhere seemed to recommend local community engagement before any CHI.[17–19]

In summer 2020, a public–private partnership advising the National Institutes of Health warned that 'Minimizing risk to … the community' is a 'critical consideration' concerning CHIs.[20] What worried them were potential infections: 'Even with strict facility engineering controls, stringent discharge criteria, and experienced personnel, there is a potential risk of community spread of the challenge virus. Thus, [CHIs] require active community engagement throughout the project.[20]

In autumn 2020, a third group repeated the second group's warning about 'the potential for unintentional release' of infections to the local community.[21] It also repeated the first group's concern about capture of a struggling local community's COVID-19 response resources:

> As part of a risk minimization strategy, [CHI] sites should be geographically located in high prevalence areas to reduce the risk associated with intentional infection. Unfortunately, these are areas with the most demands on essential public health resources… We believe that the unique impact that a SARS-CoV-2 [CHI] places on scarce and already strained resources during a pandemic must be given considerable weight in any justification of these trials.[21]

This third group explicitly compared CHIs with field trials in that respect:

> In contrast to community-based field studies, which are effectively outpatient rather than inpatient trials, a SARS-CoV-2 [CHI] will place greater demands on medical resources …[21]

While less explicit, the groups mentioned earlier never seemed to express quite the same worry about community impact and a related call for community engagement in relation to conventional field trials. And while there are various reasons to engage wider communities (eg, reducing public mistrust and vaccine hesitancy by enhancing transparency, and gaining knowledge about local bottlenecks to successful trial completion), in our view those would not seem to apply more to CHIs than to field trials.

All clinical trial designs, including CHIs and field trials, may affect people well beyond trial participants, including communities surrounding trial sites.[22–25] One standard way to partially mitigate and justify those risks is community engagement.[18 26–29] We shall argue, however, that in the particular case of SARS-CoV-2 vaccine trials, the health effects on area residents not participating in the study are actually smaller in CHIs than in field trials, and at this advanced point in the pandemic, significantly less adverse. Accordingly, setting aside the general question whether clinical trials always require local community engagement, we propose that such a requirement has been misapplied in our setting. If any of these two designs requires local community engagement, it is field trials before CHIs. The distinctive fears instigated about added risks to local community in CHIs and not in field trials, as well as the onerous distinctive requirement for local public engagement, foisted on CHI and not on field trials, were misplaced.

Let us address CHIs' two cited potential adverse effects on local communities—the potential capture of COVID-19 response resources and the potential risk of augmented community spread, arguing that both are larger and more negative in field trials.

RISK OF ADVERSE IMPACT ON COVID-19 RESPONSE IN THE COMMUNITY

A field trial *must* take place in a concurrently high transmission area and would tend to affect its response efforts dramatically. Earlier in the pandemic, its dramatic effect on COVID-19 response could have been either negative or positive overall. The negative element would come from giving its many trial participants and cases priority access to care, potentially at the expense of local patients, during a likely surge in demand—there is a limit to how much even special added governmental funding can create intensive care unit wards and trained staff overnight. But there is also a positive element, by infusing the area with high-quality resources and by reducing surge through inoculation of many residents with an experimental vaccine that might turn out to be efficacious or even create local pockets of herd immunity.

The size of a CHI's effect on local response tends to be smaller. The participants whom a CHI recruits are fewer than a hundredth the number a field trial recruits, and none is likely to develop severe COVID-19. It was recently calculated that in a 50-person CHI, the chance of having simply no hospitalisation is 98.4%.[2 30] The chance that not a single intensive care bed would be occupied should be even higher.

CHIs also need not take place in concurrently surge areas, where local systems for COVID-19 response can be overwhelmed, and one factor in selecting a CHI site could be minimising interference with concurrent COVID-19 response. It is true that there is something to be said for recruiting CHI participants from areas where high transmission is expected at some future point anyhow (not necessarily during or immediately after the trials, which would be harder to predict), thereby reducing participants' relative risk.[10 31 32] But that point could come after the trial,[10] and rather than holding the trial near such communities, it is smarter to safely transport a few dozen participants from such communities to a site elsewhere—an undersized task given the stakes.[10]

If trials seek to prioritise their participants for improved access to top-level COVID-19 care and to the follow-up and resources that may turn out to be valuable for long-term COVID-19 sequelae, that is far easier to achieve with small group of participants and a small number of (severe) COVID-19 cases. It should therefore be easier to achieve for a CHI than for a field trial's (tens of) thousands of participants, usually at high risk of infection, including many at high risk of severe COVID-19.

The worry that in a CHI 'participants would require testing, medical attention, and treatment, and research personnel would require personal protective equipment'[13 21] arises at least as much for field trials, which are far larger and notoriously resource-intensive. Like a field trial, a CHI would bring in external resources (eg, from the UK government's generous budget for CHI studies)[33] to address any such impacts. Such external resource investment in either trial type is prudent given the global financial and humanitarian impact of COVID-19. It also renders concerns about taking resources away from the local community less relevant, for either trial.

RISK OF AUGMENTING COMMUNITY SPREAD

It is true that a field trial does not deliberately infect any participant, so by its design it involves no secondary transmission from core trial procedures. It is also true that while a properly conducted CHI keeps participants isolated until no longer infectious[8] and applies our increasing knowledge on how to prevent SARS-CoV-2 transmission, secondary transmissions of its viral strain, for example, through unintended infection of research staff, cannot be completely ruled out. However, we shall argue that overall, CHIs' impact on community spread is far smaller and more positive than that of field trials, especially from autumn 2020 onwards.

SARS-CoV-2 already circulates in almost every potential trial site. Communities everywhere see exposures from travel, essential work, gatherings and so forth. In comparison with these background contributors to pandemic spread, any added risk for communities around the isolated CHI site from the rare unintended transmission is, relatively speaking, very small. So while this added risk of infection stemming from core trial procedures does not exist in a field trial, that addition is a drop in an ocean of risk factors for community spread, and from a public health standpoint, wholly tertiary.

Indeed, some immunity to SARS-CoV-2 may follow either infection (which CHI participation may introduce and field trial participation normally does not) or vaccination (introduced by

either trial). That would make participants in either design less likely to infect contacts than they would have if they did not participate. So the overall risk of community spread would tend to decline in the surrounding community under either design and, inasmuch as infection is driving it, especially under a CHI.[14]

There actually is some added risk of infection from field trial participation. Any tendency among these respective trial participants to risk exposure once injected with either vaccine or control would have much worse effects on community spread in a field trial. There, such risk behaviour would translate into up to thousands of risk-takers, going about their daily lives in the community without any special restrictions. In a CHI, such risky predilection would translate into only up to dozens of risk-takers, already exposed, remaining isolated while infectious. It would jeopardise no one.

Although trial risks should be minimised, the sheer need to travel to trial sites, wait in line and interact with staff may add small risk of exposure that is always not entirely eliminable. In a benign cohort study at our university, participants seem to have gotten infected (potentially infecting other community members) when they did not wear masks on the train to a check-up at the study site notwithstanding advice to keep safe. When a typical field trial recruits thousands of patients, such small risks are replicated over thousands of participants. In a CHI, it is true that participants also must arrive to the trial site, but with less than a hundredth the participants of a field trial, cumulative risk is smaller. It can be affordable to provide costly but robustly safe transportation to all.[10]

Since fall 2020, approved vaccines are fast becoming available in rich countries. In communities where approved vaccines are already being rolled out, field trials would now tend to have a large adverse effect on community spread around the site. A field trial would now assign participants from communities at high concurrent risk of viral exposure to one of the following three options: an experimental vaccine, an approved vaccine and a placebo. For all participants who would otherwise have accessed an approved vaccine, the high chance of being assigned to either an experimental vaccine or a placebo in the field trial dramatically increases their risk of getting infected and of increasing spread in their local community. This is replicated over thousands of participants, giving field trials from this point onwards a large and adverse effect on spread around trial sites.

That local public health footprint is so large and so negative that it raises serious ethical questions about conducting field trials from this point forthwith.[34] Justifying the resulting potential exposures of a great many non-participants in that community who never authorised that added risk would be difficult and may well require community engagement.

By contrast, a CHI would continue to recruit only dozens of participants, and not necessarily ones hailing from areas of high spread. When its participants forego approved vaccination outside the trial, that would have only a limited effect on total spread in their communities.

Thus, the overall impact on community spread is likelier to be larger and worse in a field trial. And now that a vaccine has become available in rich countries, that impact of field trials is likely to be very bad indeed. Solutions proposed thus far are only partial.[35 36] For example, field trials could instead take place in communities with no vaccine access because they have been unjustly deprived of vaccines that are available to stronger communities or to hoarder nations. But that background injustice would mar trial ethics and, in the very least, require intensive community engagement.

Table 1 Risks from each study type to the surrounding community, based on the authors' arguments.

		CHI	Field trials
Risk of adverse impact on COVID-19 response in the community		1 to -1	2 to -2
Risk of augmenting community spread	Risk of unintended infection from the viral strain	1 to -1	0 to -1
	Risk of other added SARS-CoV-2 infections in the community	-1	3 to -3 before approved vaccines were available; now that vaccines are available, 5
Overall added risk from the trial to the local community and the consequent urgency of local community engagement		*Lower*	*Higher, especially from now on*

The higher a number, the greater the risk.
CHI, controlled human infection.

It is true that if the experimental vaccine proves efficacious in blocking infections, then having given it to thousands of participants in a field trial would reduce spread more than having given it only to dozens in a CHI. But it is hard to put numbers on that reduction in communal risk in advance of testing the vaccine, and for some ethicists, the prevention of some infections would not condone other infections and the harmful capture of scarce COVID-19 response resources, for example, because benefits and harms are not always commensurate.[37]

It is also true that only in a CHI, any adverse impact on community spread would come from an intentional exposure in the trial. While opponents did not argue as much, one might try to claim that that intentionality makes CHIs more problematic. But any adverse impact on community spread in CHIs (from, for example, *un*intended infection of staff) would be as *un*intentional as any infection resulting from a field trial.

SUMMARY

As table 1 recapitulates, effects on adverse impact on COVID-19 response in the community are possible under each of the designs, with a somewhat wider range in field trials. Effects on community spread are both larger and worse in field trials, especially now that approved vaccines are becoming available outside trials. The rare added risk of infection by the CHI's viral strain would be drowned by larger and more adverse effects on community spread from the field trial.

Overall, both small and large negative effects on struggling communities are likelier in field trials than in CHIs. In that respect, local community engagement, which has value but also generates financial cost, delay and uncertainty, is somewhat more urgent in field trials than in CHIs. Ironically, the latter, and not the former, were targeted for suggestions of local community engagement before trials can proceed.

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ORCID iD

Nir Eyal http://orcid.org/0000-0003-1056-6609

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