

Controlled human infection with SARS-CoV-2 to study COVID-19 vaccines and treatments: bioethics in Utopia

Søren Holm  ^{1,2}

¹CSEP, Department of Law, School of Social Sciences, The University of Manchester, Manchester, UK

²Center for Medical Ethics, HELSAM, Universitetet i Oslo, Oslo, Norway

Correspondence to

Professor Søren Holm, CSEP, Department of Law, School of Social Sciences, The University of Manchester, Manchester M13 9PL, UK; soren.holm@manchester.ac.uk

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ABSTRACT

A number of papers have appeared recently arguing for the conclusion that it is ethically acceptable to infect healthy volunteers with severe acute respiratory syndrome coronavirus 2 as part of research projects aimed at developing COVID-19 vaccines or treatments. This position has also been endorsed in a statement by a working group for the WHO. The papers generally argue that controlled human infection (CHI) is ethically acceptable if (1) the risks to participants are low and therefore acceptable, (2) the scientific quality of the research is high, (3) the research has high social value, (4) participants give full informed consent, and (5) there is fair selection of participants. All five conditions are necessary premises in the overall argument that such research is ethically acceptable. The arguments concerning risk and informed consent have already been critically discussed in the literature. This paper therefore looks specifically at the arguments relating to condition 3 'high social value' and condition 5 'fair selection of participants' and shows that whereas they may be valid, they are not sound. It is highly unlikely that the conditions that are necessary for ethical CHI trials to take place will be fulfilled. Most, if not all, CHI trials will thus be well intentioned but unethical.

'There's this emerging consensus among everyone who has thought about this seriously,'¹⁵ said Professor Nir Eyal, the director of Rutgers University's Center for Population-Level Bioethics in the USA.

The prospect of infecting healthy individuals with a potentially deadly pathogen may sound counterintuitive, but according to Eyal the risk of death from COVID-19 for someone in their 20s is around 1 in 3000—similar to the risk for live kidney donation. In this case, the potential benefits would extend not to a single individual, but to thousands or millions who could be protected by a vaccine.

'Once you give it thought, it is surprisingly easier to approve than dispatching volunteers as part-time medical workers and other practices that we've already accepted,' he said.¹

A number of papers have appeared recently arguing for the conclusion that it is ethically acceptable, perhaps even laudable to infect healthy volunteers with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as part of research projects aimed

ⁱIt is very tempting to comment on the implicit *ad hominem* argument here, but I will refrain even though as will become evident later I am one of those who must not have 'thought about this seriously' because we reach a different conclusion.

at developing COVID-19 vaccines or treatments.^{2–8}

This position has also been endorsed in a statement by a working group for the WHO.⁹ These papers and their conclusions have already received considerable media attention and as is often the case the nuances of the arguments justifying the conclusions have got somewhat lost in that process, as in the quote from a reputable UK newspaper above.¹ In this paper I will argue that even if we accept that the arguments supporting controlled infection of healthy volunteers for research are valid, they are not sound because some of the necessary premises will be false in practice. That is, the arguments may be sound in Utopia, but they are unsound in any plausible future of the real world. This makes the arguments dangerous in the sense that policymakers and decision-making bodies such as research ethics committees (REC) may rely on the conclusion and not realise that it is not fully justified, except in the best of all worlds.ⁱⁱ

The arguments in the papers arguing that controlled human infection (CHI) can be justified have a very similar form in that they argue that controlled infection of volunteers for COVID-19 research is ethically acceptable if a long list of conditions are fulfilled, most importantly that (1) the risks to participants are low and acceptable, (2) the scientific quality of the research is high, (3) the research has high social value, (4) participants give full informed consent, and (5) there is fair selection of participants. The shorter papers contain some of these considerations, whereas the longer papers and the WHO statement cover most or all of them. There is also a strand in the literature arguing that risks can be high as long as they are outweighed by social benefits, and there is valid informed consent.¹⁰ I will not engage directly with this line of argument in this paper, but my argument about social value is relevant for any balancing of risks against benefits of challenge studies.

All five conditions are necessary premises in the overall argument put forward that CHI is ethically acceptable. The arguments showing that the conditions are fulfilled therefore have to be valid and sound for the overall argument to go through. The arguments presented in the literature in relation to the five conditions can all be problematised, and the arguments about risk and consent have already been criticised.^{11 12} It is worth to note in passing that

ⁱⁱThe literature on the topic discussed in this paper is developing very fast and the paper is, for obvious reasons, only engaging with the literature available at the time of final submission, 15 June 2020.



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some who now argue for the acceptability of CHI trials in the COVID-19 context have previously endorsed conditions about risk that would render such trials unethical, for example, arguing for ‘the following risk threshold for challenge studies, namely that: under no circumstances the research exposes volunteers to risks of irreversible, incurable or possibly fatal infections’¹³ (p 98). This paper will therefore specifically analyse the arguments relating to condition 3 ‘high social value’ and condition 5 ‘fair selection of participants’.

CHI RESEARCH HAS HIGH SOCIAL VALUE

Controlled infection with SARS-CoV-2 in a situation where there is no effective rescue treatment entails that a small number of research participants will be hospitalised, some of these will require intensive care, some will have long-lasting, potentially permanent after-effects, and it is likely that some will die from COVID-19. Or to put it more simply, some CHI research participants will suffer significant and permanent harm. In order to justify causing this harm we therefore need to be able to show that the harm is outweighed by the high social value of the research.

The social value or benefit in the current context is not knowledge per se, but knowledge which is likely to lead to effective vaccinations or treatments being widely available earlier than they would have without CHI research taking place. The high social value is primarily lives saved through the effective prevention or treatment of COVID-19, either directly or indirectly through the healthcare system not being overwhelmed with COVID-19 cases but being able to continue treating other patients as normal. Understanding high social value in this way is to understand it primarily as related to public health. There is a wider conception of social value encompassing benefits to the economy as a component of social value. This is a legitimate conception of social value, but it is unlikely to be one that most of us are willing to suffer and die for, and it is not the one that is emphasised in most of the papers justifying CHI research. They explicitly base their argument on the benefit side primarily on the public health conception of social value.

It is undoubtedly true that the earlier we can achieve wide availability of vaccines or treatments the better. Early wide availability will mean that more lives are saved and more suffering alleviated. This is also the argument used by one of the organisations already signing people up for future CHI trials. One day sooner on its front web page estimates a saving of 220 000 lives for each month vaccine development is sped up, based on a calculation involving the global incidence of SARS-CoV-2 infection¹⁴ However, the time at which wide availability is achieved depends on many factors. Establishing the evidence base that allows for the development and confident licensing of vaccines or treatments is a necessary step, but so is adequate scaling up of production, a reasonable pricing structure and a well-functioning distribution network. We will not have wide availability if some healthcare systems in low and middle-income countries (LMIC) do not have effective access to the products, or the funding and logistics necessary to deliver them to those citizens who need them. Unless we have such wide availability we will not realise the full promise of the vaccines and the treatments, and the high social value may not be so high after all.

Shah *et al*³ realise this problem and make it part of their ethical framework that a part of ensuring ‘Sufficient Social Value’ is to: ‘Realize benefits by facilitating equitable access to proven safe and effective products’ (p 833). They suggest that this can be achieved through various mechanisms that make it possible to

negate the normal effects of pharmaceutical patents through compulsory licensing and other means. This solution raises a number of questions.

First, there is a question about whether using existing legal mechanisms for compulsory licensing is the best mechanism to achieve the desired goal of equitable access. Why not simply require any owner or producer of intellectual property whose product is part of a CHI study, to sign a legally binding agreement to license to any willing and able producer of the product? This would be voluntary and less likely to be subject to later legal opposition.

Second, and perhaps more importantly merely making parallel production and marketing of an effective vaccine or treatment possible by negating the effects of any applicable patents and other intellectual property protections does not in itself ensure wide availability or equitable access. Despite years of effort there are still billions of people in LMICs, and even some in high-income countries who do not have effective access to vaccines and essential medicines that are long out of patent and can be manufactured relatively simply and cheaply.¹⁵ We do not have any reason to expect this to be different for any vaccine or therapy developed as a result of CHIs. We also already see some state actors trying to get preferential early access to vaccines and some not engaging with international organisations and initiatives aimed at ensuring wide, equitable access.^{16–19} So when estimating the social value of CHI research we need to apply a rather steep discount for the likely lack of wide, equitable availability leading to fewer lives saved than could theoretically have been saved; as well as potentially subtract some social value for the increase in social injustice created by differential access between LMICs and high-income countries, and differential access within some high-income countries.

It could be counterargued that wide availability and/or equitable access are not necessary for high social value in the context of CHI research, despite it being claimed to be necessary in the literature (eg, Shah *et al*, quoted above). If, for example, country X pays for the development of a vaccine, produces it at home and excludes all other countries from access to the vaccine there could still be high social value if the population of country X is large enough. A CHI trial could therefore be justified in country X if it made a large enough difference in the time at which the vaccine would be available. This would still raise questions about equitable access and fair selection of participants within country X, but will the lack of access outside of country X subtract from the high social value? The answer to this question depends on how we, in general, conceptualise and evaluate situations where access to essential goods is deliberately restricted, and where we locate the exact ethical problem or problems raised by such deliberate restrictions. A full discussion of this is outside the scope of this paper, but if the world where a country acts in the way X does in this example is a world with less value in it than a possible world where X had not acted in this way, then X’s actions do subtract from the social value generated by the development by X of the vaccine. This would be true even if we came to the very unlikely conclusion that X’s actions were ethically justified.

There is also an intriguing issue of how to balance risks and benefits and of how to ensure that RECs and other decision-makers choose the right ‘numbers’ on both sides of the equation. This is nicely illustrated in the newspaper quote above, where the risk-benefit calculation is characterised in the following way:

The prospect of infecting healthy individuals with a potentially deadly pathogen may sound counterintuitive, but according to

Eyal the risk of death from COVID-19 for someone in their 20s is around one in 3000—similar to the risk for live kidney donation. In this case, the potential benefits would extend not to a single individual, but to thousands or millions who could be protected by a vaccine.¹

The risk of death to a single participant is compared with the likely benefits in terms of protection to many generated by CHI research. But that benefit is not generated by a single CHI research project, or a single research participant being permanently harmed, but by all the CHI projects necessary to develop an effective vaccine. The comparison is therefore misleading for a number of reasons. First, there will be many participants, some of whom will suffer significant, permanent harm without dying; and what is prevented is not ‘thousands or millions’ dying but thousands or millions getting COVID-19 infection and some of those dying. It is difficult to estimate the numbers on both sides of the equation. Eyal *et al*² suggest that we probably need 100 participants in a challenge study, and quote figures for the risk of hospitalisation of 1% and a risk of dying at 0.03% if participants are recruited from the 18–30 years age range. If we accept those estimates for the sake of argument a challenge study will lead to about one hospitalisation and probably no deaths. But, there is a conflation between the individual research project and the whole research programme in the argument. As of 9 June 2020 there are 10 vaccine candidates already in clinical development and 126 at various stages of preclinical development, so there are many potential candidates for CHI trials in the pipeline.²⁰ If CHI trials become the standard we should therefore expect that a significant number will be conducted which will increase the number of participants harmed.

Second, the development of many vaccine candidates based on a range of very different vaccine technologies, which is in itself very positive, because it increases the chance of one or more being effective and safe, nevertheless also creates a problem in relation to how to assess the benefits of an individual CHI trial. We necessarily approve research projects based on an *ex ante* evaluation of the balance between risks and benefits, but because that balance is *ex ante* it is a balance between likely risks and likely benefits. Given that our knowledge about the SARS-CoV-2 virus and the disease(s) it causes is still incomplete there is larger than usual uncertainty about the risk estimation, but there are also large uncertainties relating to the benefit estimation. One of these large *ex ante* uncertainties concerns which of the many vaccines under development that will actually come into use, if any. This is determined by the quality of the science, including a possible CHI trial, and by many other factors. There might in theory be some pivotal CHI vaccine trial that on its own would push the time for having sufficient evidence for licensing of a particular vaccine back some months because the trial shows the vaccine to be effective and safe enough for licensing. But we have no way of *ex ante* identifying the particular CHI vaccine trial that will produce the high social value, from the other CHI vaccine trials that will be taking place at the same time and which will produce knowledge but much less social value. They will be scientifically good trials but produce less social value either because they show a particular vaccine candidate not to be effective or safe, or because despite the trial showing the vaccine being effective and safe enough, the vaccine is nevertheless not submitted for licensing or not marketed. And, furthermore, trials are presented to RECs one by one and not as a suite of similar trials where the REC can choose to approve only the one that looks most promising in terms of social value and most ethical in terms of fully meeting all the criteria for an ethically

acceptable CHI. It is therefore more than likely that CHI trials will be approved and conducted which are scientifically sound but which, if a comparative perspective could be applied, could be identified to have likely low social value.

It is argued in the papers advocating for the permissibility of CHI that the value of allowing CHI increases if the community infection rate has been brought under control and is low. If the community infection rate is low, it will make it more difficult to run vaccine trials in the community because it will take a long time for enough trial participants to be infected ‘naturally’ to reach a firm conclusion about the effectiveness of the vaccine. The difference between the duration of a conclusive CHI trial and a conclusive community trial of the same vaccine will therefore go up as the community infection rate goes down. However, if the community infection rate can be kept low by effective test, track and trace policies, the need for speed in the development of vaccines and treatments also decreases, since the number of COVID-19 cases can be kept low indefinitely. Effective test, track and trace does not remove the need for developing an effective vaccine, but it decreases the urgency whether or not we apply a public health or a wider economic conception of social value, because it is much less disruptive of both the function of the healthcare system and of the economy than general lockdown and social distancing measures.

CHI RESEARCH WILL HAVE FAIR SELECTION OF PARTICIPANTS

Participation in CHI research will require a significant time commitment from participants who will have to be in a controlled environment until they eventually become non-infective. They should be compensated for this time and for any other burdens involved in the research. These other burdens in terms of blood taking and other unpleasant tests might well be substantial since it is argued that we should generate as much knowledge about aspects of SARS-CoV-2 infection as we can from the CHIs. The amount of compensation may therefore ‘... total several thousand dollars in the United States’.³ Providing compensation will satisfy one of the requirements of fair participant selection by creating a situation that avoids or minimises ‘... inequities in access to CHIs’.³ Only those who will lose more income than ‘several thousand dollars’ over the relevant period if they participate will find it financially difficult to access CHIs. Those who are excluded from access in this way are probably likely to be a small group, given that the risk considerations point to only recruiting young people to CHIs. Thinking about high earners being excluded might sound puzzling. But it is important to note that high earners are not necessarily asset rich, for example, they may have large mortgages they have to service. This means that they may not be able to afford a loss of income involved in participation, and are therefore *de facto* excluded. However, some of the envisaged CHIs have little potential for benefiting the participants, so the fairness question they raise is not one of fairness in access, but fairness in actual participation. The WHO working group recognises that this raises issues of social justice and argues, rightly in my view that:

Those whose background risk is high as a result of social injustice should be excluded from participation because their inclusion could be considered unethical exploitation (ie, taking advantage of those who have already been wrongly disadvantaged). (pp 13–14)⁹

But, exploitation explicated as ‘taking advantage of those who have already been wrongly disadvantaged’ does not only apply to those ‘whose background risk is high as a result of social

injustice' (pp 13–14).⁹ It applies to anyone who finds research participation very attractive as a result of being in a socioeconomically disadvantaged position as a result of social injustice.

There is ample evidence from both LMICs and from high-income countries that recruitment to phase 1 pharmaceutical trials in some instances involves the exploitation of the socioeconomically disadvantaged, and that recruitment to phase 1 trials is not consistent with any principle of fair selection of participants.^{21–25} Unless the exclusion argued for by the WHO working group is observed in relation to CHIs we should expect the phase 1 pattern of exploitative recruitment to be replicated in CHIs. This would make the projects *prima facie* unethical. We might, of course, say that because COVID-19 is a very significant and urgent problem we should accept this exploitative injustice. MacKay and Saylor, for instance, argue that we can in general allow exploitative recruitment if this imposes additional burdens on those who are already burdened (MacKay, p 14).²⁶ But they go on to argue that there is a distinction between burdens and risks and that exploitative recruitment is unethical when research participation leads to additional risks. COVID-19 CHI trials will expose participants to additional risk and will therefore, even following MacKay and Saylor's fairly liberal approach to the permissibility of exploitative recruitment, be unethical.

The requirement for fair selection of participants in medical research has been recognised in the literature for a number of years^{26–27} and aspects of fair selection have begun to appear in international declarations and guidelines.^{28–29} However, this has not in general led to the enforcement of an effective bar on potentially exploitative recruitment, or more specifically to a bar on potentially exploitative recruitment of healthy volunteers. Why should we expect CHI research to do better? The epidemiology of the COVID-19 outbreak in the UK and other countries already indicates that socioeconomically disadvantaged groups are more affected in terms of infection rates, morbidity and mortality.^{30–31} We thus already know that we are not 'all in this together' when it comes to COVID-19 and may suspect that we will not be in SARS-CoV-2 CHI trials 'all together' either.

There is a further, more internal problem for bioethics in relation to expecting fair selection of participants to be observed in CHI trials. The problem is that we have some reason to believe that the adherence to this criterion will be undermined by the arguments of some prominent bioethicists, including some who are coauthors of the papers arguing for the permissibility of CHI. A significant line of argument simply rejects the position that even severe exploitation in itself, without coercion, is sufficient to find an activity unethical; and also rejects the further implication that those who can be exploited in exploitative transactions should be protected by not allowing those transactions.^{32–34} This potentially undermines the long-term support for the kinds of conditions for fair participant selection proposed by the WHO working group and others.

CONCLUSION

Let us accept for the sake of argument that there is a possible world in which SARS-CoV-2 CHI trials can be conducted in an ethically acceptable way, because they fulfil all of the five conditions outlined at the beginning of this paper, including those conditions not discussed in detail in this paper. In that world there are robust and incorruptible regulatory and research ethics systems everywhere, and no corners are cut in the regulatory processes during a crisis. Fair selection of research participants is scrupulously observed. There is extensive scientific collaboration and coordination. Researchers, industry and state actors share

knowledge and intellectual property freely. Researchers and their institutions do not compete for glory or recognition but only in order to progress science. And, all actors are committed on a cosmopolitan basis to do whatever is necessary to ensure wide and equitable access to any vaccine or treatment that is developed, even to the extent of potentially funding access for their sworn enemies.

However, as I have argued in some detail above in relation to two of the conditions, this is not the world we live in. We live in an imperfect broken world, where it is highly unlikely that the conditions that are necessary for ethical CHI trials to take place will be fulfilled. Most, if not all, CHI trials will thus be well intentioned but unethical.

It might be counterargued that these five conditions are not necessary after all, but perhaps only ideal conditions that we should aspire to reach in our CHI trials. However, this argument cannot hold on the benefit side. If we know in advance that the social benefit is unlikely to be high, there is no benefit to counterbalance the known risks and harms generated by the research. High social value is a *sine qua non* for a CHI trial to be ethical because it is the only positive reason that can potentially justify the major deviation from traditional research ethics principles involved in CHI research without a rescue treatment.

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ORCID iD

Søren Holm <http://orcid.org/0000-0002-7200-5607>

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