Uncertainty, error and informed consent to challenge trials of COVID-19 vaccines: response to Steel *et al*

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ABSTRACT

In a recent article, Steel, Buchak and Eyal (SBE) argue that current levels of uncertainty do not present a good reason to bar controlled human infection (CHI) trials of COVID-19 vaccines from proceeding. We argue that their argumentation for this conclusion is flawed. SBE are mistaken about the effects which different forms of ignorance have on participants' ability to provide valid informed consent. Decision-makers considering whether to allow such trials, we argue, must ultimately consider the likelihood that consent to participation in such trials under current conditions would be valid, and whether this likelihood is high enough to permit such trials. This is a question that SBE completely ignore. We conclude that there indeed are valid concerns about conducting CHI trials given the current state of knowledge about COVID-19, concerns which SBE fail to address.

There is no doubt that quickly finding a safe and effective vaccine to COVID-19 would be of immense value. Controlled human infection (CHI) trails might significantly speed up the process of obtaining valuable evidence about the efficacy and safety of possible vaccines. Conducting such trials could save countless lives and prevent various forms of suffering. There are, therefore, strong ethical reasons to support CHI trials. But are there also strong ethical reasons against allowing them?

In light of unease expressed by several bioethicists about CHI trials, Steel, Buchak and Eyal (SBE) discuss possible concerns about conducting such trials, focusing on the current high levels of ignorance and uncertainty about the new disease, attempting to rebut several versions of these concerns.[1] They conclude that 'current levels of uncertainty do not present a good reason to bar S-CHIs from proceeding'.[1] However, their discussion, we claim, fails to support this conclusion. Whether or not CHI trials of COVID-19 vaccines should be permitted—a question that we shall not try to answer here—SBE's argumentation for their conclusion is flawed, and fails to address some valid concerns about conducting CHI trials given the current state of knowledge about the disease.

SBE discuss three main arguments against CHI trials: The first is based on the claim that participants in CHI trials would be subjected to levels of risk which exceed permissible risk levels; the second is based on the claim that the current state of ignorance and uncertainty makes it impossible to obtain valid informed consent to participation in CHI trials; the third, on the claim that proper caution prevents CHI trials from being ethically performed at present. Our response focuses on SBE's claims about the effect of current states of knowledge and uncertainty on volunteers' ability to provide valid informed consent to participation in CHI research. These claims lie at the heart of their responses to both the second and third arguments.

Against the possible claim that current states of ignorance and uncertainty about the new virus make it impossible to obtain valid informed consent, SBE claim that 'high uncertainty among experts is perfectly compatible with valid informed consent: consent can remain valid when researchers' understanding is highly incomplete, or even completely wrong'.[1] This claim then underlies their response to the possible claim that proper caution prevents CHI trials from being ethically performed. This possible claim is based on the idea that under certain conditions of 'deep' ignorance, the responsible ethical approach involves a pessimistic assessment of the risk of fatality, and that given such a pessimistic assessment, the estimated risk of fatality might exceed permissible risk levels.[i] SBE respond that while taking a pessimistic attitude to risk may be plausible, given that competent adults can provide valid informed consent to their participation, they should be allowed to determine for themselves how pessimistically or optimistically to make decisions in light of the uncertainty surrounding those risk.

At least three questions must be asked to determine if CHI trials should be barred on grounds pertaining to the validity of participants' consent: (1) Can valid informed consent to participation be obtained given very partial knowledge and high levels of uncertainty, of the kind we currently possess about COVID-19 and the risk involved in CHI trials? (2) Can valid consent be given on the basis of error and wrong understanding? (3) If CHI trials are allowed, how likely is it that consent to participation would be valid, and is the chance that consent would not be valid a reason to bar such trials? While SBE answer the first question correctly, they provide a wrong answer to the second question, and completely ignore the third question, which is ultimately the one that decision-makers must consider.

Can valid informed consent to participation in research be obtained given high levels of uncertainty? SBE answer the question in the positive, and we agree with their answer. They rightly point out, that by its very nature, research addresses areas where there are gaps in existing knowledge; and that accordingly, if a (near-) complete understanding were required, then valid informed consent for research would seldom be obtainable. Complete understanding of the options before us and the risks and benefits they involve is not required because we can be aware of the partiality of our understanding, and take our ignorance into account in our deliberations.[2] Indeed, we often make perfectly valid decisions, both in healthcare contexts and other contexts, just because we know that we lack relevant knowledge, and either want to obtain it, contribute to its obtainment, or limit the dangers to us and to others that emerge from our incomplete knowledge.

But can valid consent be given on the basis of error and wrong understanding? SBE claim that it can: 'consent can remain valid when researchers' understanding is highly incomplete, or even completely wrong' (2, our emphasis). Here SBE are mistaken, because they ignore the different effects which error and mere lack of knowledge have on our ability to provide valid informed consent. Incomplete knowledge and understanding differ from wrong understanding in their effect

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[i]The idea is that our uncertainty regarding certain outcomes should be represented by a range rather than a unique number, and that a pessimistic approach involves acting on the basis of the high end of the range of uncertainty.

on the validity of consent, because when we suffer from incomplete understanding, we can know that our understanding is incomplete, and take our lack of knowledge and understating into account in our decisions and deliberations. In contrast, when we suffer from a false belief, we cannot take the fact that our belief is false into account in our deliberations. One cannot hold a false belief while knowing that it is false.[2] Accordingly, making a decision based on a false belief undermines autonomous authorisation, and thus can often render one's consent invalid. If researchers provide volunteers with misleading descriptions of the research, and volunteers consent to participate just because they were provided with misleading descriptions, and would not have consented otherwise, their consent is not valid. It is true that if researchers provided the misleading descriptions because their own understanding is wrong, they might not be blameworthy. But that does not mean that consent was valid. Indeed, consent in such a case is not valid. If someone in charge learns that volunteers agreed to participate in research only because they were given a misleading description of the research, and if their participation has still not begun, then prima-facie, the person in charge should not allow their participation to go through, until they are alerted to the error, and valid consent is obtained from them.

Thus, even if researchers communicate to volunteers their best current understanding of relevant features of the study, this is insufficient to guarantee the validity of consent. Accordingly, decision-makers considering whether to approve CHI trials must ask themselves the third question presented above: What is the likelihood that consent to participation in CHI trials would be valid, and is this likelihood high enough to permit such trials? SBE completely ignore this question, but this is the question that decision-makers should ultimately consider. And the question is not settled by the fact that valid informed consent to participation in CHI trials can be obtained under current conditions. After all, the claim that valid consent to a certain consent-requiring transaction—for example, paid sexual encounters—can be obtained, does not settle the question whether such transactions should be allowed. For even if valid consent can be given, it may still be the case that if permitted, most transaction of this kind would go through without valid consent. To determine whether to permit COVID-19 CHI trials, decision-makers must consider what the chances are that consent obtained under current conditions of still emerging understanding be based on error in a way that undermines the validity of consent. This is a question that cannot be answered from the armchair. But one thing is clear: given the limited evidence on which our understanding of COVID-19 is based, chances that participants be provided with misleading descriptions of important features of COVID-19 CHI trials is much greater than the chances that participants be provided with misleading descriptions of trials involving better understood diseases. Therefore, concerns about the validity of consent to COVID-19 CHI trials are much more serious than concerns about the validity of consent to more standard medical experimentation.

Thus, there are real concerns about the validity of participants' consent to COVID-19 CHI trials under the current conditions of knowledge and understanding, which SBE's discussion fails to address. Whether these concerns are weighty enough to outweigh the very weighty ethical reasons to support CHI trials is a question we cannot answer here. But that is surely a question that decision-makers must seriously study before giving COVID-19 CHI trials the green light.

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REFERENCES

1 Steel R, Buchak L, Eyal N. Why continuing uncertainties are no reason to Postpone challenge trials for coronavirus vaccines. *J Med Ethics* 2020;46:808–12.
2 Keren A, Lev O. Informed consent, error and suspending ignorance: why very little knowledge is required for autonomous consent. *Unpublished manuscript*.