Ethical Guidelines for Deliberately Infecting Volunteers with COVID-19

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Abstract

Global fatalities related to COVID-19 are expected to be high in 2020-21. Developing and delivering a vaccine may be the most likely way to end the pandemic. If it were possible to shorten this development time by weeks or months, this may have a significant effect on reducing deaths. Phase 2 and Phase 3 trials could take less long to conduct if they used human challenge methods – that is, deliberately infecting participants with COVID-19 following inoculation.

This article analyses arguments for and against such methods and provides suggested broad guidelines for regulators, researchers and ethics committees when considering these matters. It concludes that it may be possible to maintain current ethical standards yet still permit human challenge trials in a context where delay is critical. The implications are that regulators and researchers need to work together now to design robust but short trials and streamline ethics approvals processes so that they are in place when applications for trials are made.

Introduction

The speed of threat that COVID-19 poses to global health is unprecedented in recent times. Current precise estimates for global fatalities in 2020-21, both directly related to COVID-19 and those related to societies' mitigation measures, are likely to be inaccurate but the number will be inevitably be high – particularly if there are a large number of infections in the developing world where availability and standards of healthcare are limited.[1] The three potential medium-term endings of the pandemic are; firstly the possibility of a period during which the basic reproduction number of the virus R_0 is below 1 simultaneously across the world eradicating the disease; secondly, widespread infection leading eventually to herd-immunity; and thirdly, the development and deployment of an effective vaccine or treatment. The chances of the first option occurring are unlikely given the degree of sustained international co-operation required, the second option will result in a very large number of deaths, and a response to the third option may be that vaccines are easier and more desirable to develop than effective treatments.

Although there is no guarantee that researchers can develop an effective vaccine in time to usefully bring the pandemic to an end, COVID-19 vaccine research is currently proceeding at a relatively fast rate.[2] However in the case of the current pandemic, time is crucial, and a

delay even of weeks or months may result in a very large number of deaths that could potentially have been prevented.

The Phase 2 and Phase 3 human trials of vaccine candidates may be the longest in time segments of vaccine development and delivery. Methods that can significantly shorten these phases can be considered desirable or even necessary if it is ethical to do so. The primary methodology which could shorten these phases currently identified could be by using human challenge experiments – i.e. deliberately infecting volunteers with COVID-19 after giving them the vaccine candidates. These experiments carry with them the obvious risk that some of those volunteers may develop serious illness or die as a result of the experiment.[3]

Moments of crisis are rarely good moments to develop ethics. They carry with them the possibility of self-interested bias due to the threat to everyone's health and welfare, and the speed at which decisions have to be made affords little opportunity for reflection. However, delay for sober contemplation and slow ethical guideline developments will, in this instance, come at significant human cost. As such, it is now incumbent on regulators, researchers and ethicists to work together quickly to consider whether or not it is ethically acceptable to conduct human challenge experiments with COVID-19, and if so then how best to do it.

Whilst there are currently no vaccine candidates ready for late stage human trials, this is exactly the time to develop these ethical protocols such that clear methodologies can be developed and potential participants recruited to avoid future delay. Not to consider these issues now, would be a dereliction of our moral responsibility to society.

This paper seeks to outline considerations for regulators, law makers, ethics committees and researchers when considering human challenge experiments with COVID-19.

<u>Arguments against human challenge experiments</u>

(i) There is a significant risk of serious harm and death to participants

Even if participants are recruited from relatively low-risk demographics, and quality medical care provided, it is likely given the numbers of participants needed for these studies, that some of them will become seriously ill and there is a non-negligible possibility that some of them will die. As well as the direct effects of COVID-19, there are the possibilities of adverse reactions to the vaccine candidates, and also a possibility that the vaccine may result in making an individual's response to COVID-19 more severe. It could be argued that conducting these experiments knowing these risks does not adequately respect a person's right to life and the sanctity of human life itself.

(ii) The experiments may not result in a useable vaccine

Whilst it is almost certain that some of the participants will experience harm during the experiments, it is far from certain that the research will yield a viable vaccine. As with all research, the results are unknown before the research is conducted and many medicine candidates do not successfully pass Phase 2 and Phase 3 testing.[4]

(iii) It may be impossible for an individual to truly give free and informed consent

A potential participant may experience psychological pressure as a result of their own fear or desire to make a social contribution, real or perceived pressure from friends, or a potential societal pressure to speed up vaccine development. It could be argued that this pressure may be to such an extent that it would preclude the possibility of an individual voluntarily giving their consent.

(iv) Conducting these experiments may damage the reputation of research and researchers more generally

History has many examples, particularly from the twentieth century, of human experiments that were conducted in ways that are currently regarded as seriously unethical.[5] It is possible that society, either now or in the future, may reflect negatively on any human challenge experiments conducted that have a significant human cost. This may lead to a long-lasting diminishing of public trust and confidence in research and researchers.

(v) These experiments may be the start of a slippery slope

Even in recent history, such as with the Zika virus, proposals for human challenge experiments have not been considered ethical.[6] If we allow such experiments now, it could make it easier in future situations with a less substantial risk to society to authorise potentially unethical experiments.

Counterarguments and Potential Mitigation Strategies

A utilitarian perspective would regard the potential benefits to large numbers of people from a quicker-developed vaccine to outweigh the likely harms caused to a smaller number of people.[7]

A Kantian perspective may regard vaccine challenge studies as violating the second formulation of the categorical imperative as it would involve using the humanity of a participant merely as a means to an end.[8] However it could be argued that this takes insufficient account of a participants' ability to voluntarily consent to use their humanity in a sacrificial self-determinative way. Indeed as Wertheimer argues, "one's choices may have moral value only if they are made autonomously, and so if we want people's lives to have positive moral value, we need to provide the space for them to make choices for themselves."[9] Elsewhere,[10] he expands on the idea that it may be morally praiseworthy for a person to participate in a study where the expected personal risks outweigh the expected personal benefits because of the anticipated benefits to others, and rejects the argument that such studies amount to a form of social conscripting and that slower scientific progress is always a morally necessary price to pay.

A virtue ethics approach whilst valuing the intent to do good, would become more complex when faced with the issue of whether conducting experiments with a non-negligible risk of serious harm or death to individuals denigrates the value of an individual, and harms humanity through the consequent moral failing. The philosophical objections raised by the intrinsic value of a human argument could potentially be mitigated by ensuring that consent

was truly obtained voluntarily, after appropriate disclosures by researchers, and by individuals with the capacity to so consent.

(i) Addressing the risk of harm to participants

As society we already permit individuals the freedom to make choices that pose significant risks to their health, for example smoking or riding a motorbike. We also permit them to voluntarily engage in occupations that carry with them a non-negligible risk of serious harm or death, such as astronauts or soldiers. It is not uncommon for a society to ask soldiers to go to war where there is significant likelihood of serious injury or death, and the outcome of their work is uncertain. Indeed, there have been many medical trials in recent years that have resulted in some harm to participants,[11] albeit the risks were generally smaller than they likely would be in a COVID-19 human challenge study.

(ii) Addressing the potential of no useable vaccine

Whilst it is true that any particular vaccine candidate studies may result in no viable vaccine, there is also a significant chance that it will result in one and consequently likely result in saving a very large number of lives.

(iii) Addressing the validity of consent

It is impossible for any human to be totally devoid of the effects of individual, interpersonal and societal pressures, both conscious and sub-conscious, when considering the voluntariness of any consent. It could be argued that it actually withdraws from a person's humanity and autonomy to deny them the opportunity to offer their consent to partake in research that could result in such a potentially large societal benefit. Whilst part of the roles of societies and the law may be to protect people from themselves, their roles are also to permit conditions where a person can freely live and express their autonomy. The negative effects of COVID-19 are widely understood by likely participants, at least in broad terms, due to the media they are likely to have already consumed. Research, particularly on any long-term effects of COVID-19 is necessarily at an early stage and so for a participant to be fully informed, can reasonably be interpreted as being made aware, in terms that they understand, of the currently-understood risks and benefits at the point of making a consent decision.

(iv) Addressing reputational risk

It is always possible that future humanity will look back on a decision to proceed with an experiment and reflect negatively on it. It is also possible that future humanity could reflect negatively on a decision to *not* conduct such experiments, or to *not* put sufficient efforts into assessing the possibilities of such experiments. Public confidence in researchers and the research process could be undermined if experiments with such great potential benefits were not undertaken, and ethics approvals processes not adapted to be conducted at great speed whilst remaining robust.

(v) Addressing the slippery slope

Slippery slope arguments in general have been extensively considered[12] and when applied in this context they rely on an assumption that it would be a change in ethical standards to permit COVID-19 human challenge experiments in the current context. It could however be argued that to allow such experiments would not be changing our ethical standards, merely

applying them to this new context. There are key differences in the contexts of, for example, Zika research and COVID-19 – particularly in the gravity of threat they pose to society. Shah et al.'s key question when ethically assessing proposed human challenge studies remains the same,[6] namely "are the risks reasonable, minimized, and justified by the potential social value of the trial?" – it may be that the answer to this question is different in this case.

The 'reasonableness' of a risk and the 'potential social value' of a study are ordinary English words and will require interpretation by those in authority.

Guidance for Regulators, Researchers and Ethics Committees

Below is a non-exhaustive list of considerations when designing and assessing the ethical implications of human challenge COVID-19 studies.

Has reasonable care been taken to maximise the potential benefits of the proposed study and minimise the risks of harm to participants?
A pragmatic approach needs to be taken when interpreting 'reasonable care'. Given the short timescales involved and the effect of delay it is likely that this should be interpreted as 'good enough care' rather than 'ideal care'. Very sensible proposals have already been brought forward by Eyal *et al.*[13] on how to do this (e.g. using participants with a high baseline risk of natural infection, sequential administration of vaccine candidates to small groups) and it is hoped that other researchers will build on these proposals in the near future – for example ensuring, if possible, guaranteed availability of ventilators for participants should they become necessary.

Is the informed consent process sufficiently robust?
Potential participants will need to be informed using the most up-to-date medical information, and in terms that they understand, of the known likely risks and benefits of participating. They should be afforded an appropriate reflection period before consenting, such as 3 days. They should be given the right to withdraw from the research at any point up until the end of the study and still be guaranteed the best available medical care. If relevant new information on risks and benefits are discovered during a trial, participants should be informed so that consent can continue to be considered on an ongoing basis. Any financial payment made to individuals must be only of a moderate nature, this is to guard against the possibility of undue financial inducement. However, it would be appropriate to promise to pay for treatment relating to any consequent medical complications and to promise to pay an appropriate level of compensation in the event of severe adverse health outcome or participant death. The participants must be of sufficient consistent cognitive capacity and not be suffering from a mental health condition that would be likely to affect their capacity – it may be that in many cases a suitable psychological assessment of potential participants may need to be performed.

What do we need to do now to amend our processes to speed up the consideration and approval processes for proposed COVID-19 vaccine candidate Phase 2 and Phase 3 trials?
Countries where vaccine trials are likely to take place need to act now to streamline their legal and regulatory experimental approval processes – such that they retain their rigor, but can deliver decisions, advice and approval in a very short time frame. It is possible that if

work commences immediately to do this, that such processes can be in place by the time they will be needed in the coming months to assess proposed trials.

Conclusion

Despite these extreme circumstances, robust ethical assessments of potential research experiments remain vital and our standards of ethics should not change. This article instead argues that current processes of assessment need to be streamlined and significantly speeded up, and that it is in fact ethical to permit fully-informed volunteers, who have the capacity to consent and do voluntarily consent, to participate in human challenge COVID-19 studies. A major factor in this, is the very significant cost of delay of vaccine development and the potential vast benefits to humanity of an effective vaccine.

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