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Challenge Trials: What Are the Ethical Problems?

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If, as is alleged, challenge trials of vaccines against COVID-19 are likely to save thousands of lives and vastly diminish the economic and social harms of the pandemic while subjecting volunteers to risks that are comparable to kidney donation, then it would seem that the only sensible objection to such trials would be to deny that they have low risks or can be expected to have immense benefits. This essay searches for a philosophical rationale for rejecting challenge trials while supposing that they have huge benefits and relatively low risks. Although it finds some force in objections to challenge trials grounded in the obligations of researchers to limit the harms imposed on some individuals for the benefit of others, it argues that there is no compelling objection to challenge trials of vaccines for COVID-19—if they have the benefits and risks that have been claimed.

Keywords: *challenge trials, COVID-19, human subjects, SARS-CoV-2, vaccine trials*

I. INTRODUCTION

It has been suggested that challenge trials that deliberately expose fully informed volunteers to the SARS-CoV-2 virus (1) will appreciably speed up the availability of effective vaccines (thereby saving thousands of lives and massive suffering), (2) will subject volunteers to about a 1 percent chance of hospitalization and a 0.03 percent (or less) chance of death (Salje et al., 2020, fig. 2), which (3) cannot be avoided or further diminished without losing the benefit. If these claims are true, then it might seem obvious that such trials are morally acceptable. A solid expectation of a truly gigantic benefit should

justify risks of this magnitude to a small group of volunteers. There is general acquiescence in many practices in which individuals take risks of a similar or greater magnitude when, for example, caregivers assist them in donating organs or soldiers fight our wars. The antecedent is controversial: Will such trials have huge benefits?[1] Are the risks as low as alleged? Is there any way to acquire the benefits while lessening the risk?

As crucial as these questions are, I shall pass over them. Suppose we grant that these trials have the virtues they are alleged to have. Are there still ethical objections to them? It seems that these trials should be permitted by the "common rule" governing research on human subjects, which states: "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." If the facts are as I am assuming, then challenge trials of vaccines for COVID-19 can meet this requirement. Not only is knowledge of vaccines for COVID-19 important, but in addition to the risks, there are some anticipated benefits to the subjects that are vaccinated.

However, even assuming that challenge trials can be expected to have huge benefits and low risks, some commentators are uneasy about subjecting participants in challenge trials to more than "minimal risk," where "minimal risk" is understood vaguely as the level of risk one encounters regularly in daily life (Hope and McMillan, 2004, 112). Why?

II. COMPONENT ANALYSIS

One argument in defense of prohibiting the imposition of the significant risks involved in challenge trials rests on "component analysis" and the determination that these trials count as therapeutic. Defenders of component analysis require that "procedures . . . administered with a therapeutic warrant . . . must pass the test of clinical equipoise," by which is meant that "study treatments—whether they be experimental or control treatments—must be consistent with this standard of care" (Weijer, 2000, 354). This condition is not satisfied by all the components of challenge trials because deliberately infecting the unvaccinated control group is hardly consistent with the standard of care. If challenge grants are considered as therapeutic in intent, then component analysis finds challenge trials to be impermissible.

Now why should one regard challenge trials of vaccines against COVID-19 as therapeutic in intent? The benefits to those vaccinated, which are not the purpose of the trial, are uncertain and members of the unvaccinated control group receive no therapeutic benefit. If one does not regard challenge trials as therapeutic in intent, then the question is whether the potential contribution to knowledge justifies the risks. Given the assumptions concerning risks and benefits, challenge trials of vaccines against COVID-19 would pass this test.

It is both dubious whether challenge trials are intended to be therapeutic and whether it is sensible to demand a prior determination of whether trials are therapeutic or nontherapeutic and then to apply different criteria to their assessment.[2] Doing so demands a sharper distinction between the purposes and consequences of trials than is typically available and poses difficulties in applying the conflicting standards. A more direct procedure is to set aside the often unanswerable question of whether trials are therapeutic or not. The evaluation of proposed research can begin by determining whether there is clinical equipoise, followed by a determination of whether risks have been minimized and whether the knowledge that is likely to result justifies the risks that are not balanced by benefits to the participants (Wendler and Miller, 2006). It seems plausible that if challenge trials were to save thousands of lives and sharply lessen the social and economic costs of the pandemic, then it would be permissible to subject a small group of people to a 0.03 percent chance of death.

III. PROHIBITIONS ON IMPOSING MORE THAN MINIMAL RISKS

Some commentators and ethical codes have argued for a general prohibition on exposing healthy experimental subjects to more than minimal risks, even if the subjects are well informed and consent to the risks (Evans and Evans, 1996). According to the Royal College of Physicians guidelines: "There are some situations, such as the treatment of serious disease, where it is ethical for research studies to involve more than minimal risk. These would never involve healthy volunteers" (1990, 11.14). If these guidelines were defensible, then challenge trials of vaccines for COVID-19 would be impermissible.

Is there a sound ethical basis for refusing to allow healthy volunteers to assume significant risks, when, as is here supposed, the expected benefits, even if only to others, are this large? If one takes this as an absolute prohibition, as opposed to a rule of thumb, then it cannot rest on consequentialist grounds. For it is obvious that there are some circumstances in which exposing healthy volunteers to significant risks has better consequences than protecting them from those risks. The challenge trials in question are, by assumption, such cases. A rule of thumb, prohibiting allowing subjects in nontherapeutic trials to encounter much more than minimal risk might have a consequentialist justification, and perhaps that is what the Royal College had in mind. If research subjects are badly injured or killed, that is not only tragic in itself, but it could undermine confidence in medical research and in medical caregivers. This is a serious concern (Hope and McMillan, 2004), especially when, as is sometimes the case, considerable portions of the populace regard the medical establishment with suspicion. However, whether or not there is a good consequentialist case for a general prohibition, challenge trails of vaccines against COVID-19 are, by assumption, cases where

the rule of thumb does not apply. The stakes are so large that the risk of undermining confidence in medical research is worth taking. Of course, the trial might turn out to be a fiasco—but that is true of every investigation. Although the consequentialist case for challenge trials is thus not as obvious as it might appear, I think that it is still strong.[3]

Alternatively, one can argue that rather than a rule of thumb advising against subjecting subjects to more than minimal risk, there is an absolute prohibition on intentionally inflicting harm and especially a significant risk of death on any innocent individual. The Nuremberg Code, in passages presumably intended to apply to largely nontherapeutic research, asserts:

> 5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects . . .
>
> 10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe . . . that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject. (Mitscherlich and Mielke, 1949, xxxiii–xxv)

One might invoke a general principle forbidding the intentional infliction of significant harm to any innocent person in order to ground this stringent prohibition on risking harm to participants in experiments. It is, for example, standard Catholic doctrine that there is an absolute, exceptionless prohibition on intentional killing of an innocent person. That prohibition might be extended to forbidding imposing a serious risk of death or serious harm on innocent individuals. More modestly, one might defend a prohibition on intentional harming like the Nuremberg Code that applies only to medical caregivers and researchers.

Despite the appeal of such principles, a prohibition on intentionally harming individuals faces obvious counterexamples, whether it applies generally or only to medical personnel. Removing a kidney from a healthy donor intentionally harms the donor and imposes on the donor a small risk of death, yet, under the proper circumstances, removing a healthy kidney appears to be morally permissible.[4]

Rather than give up the prohibition on intentionally imposing serious harm or risk of harm on innocent individuals, philosophers have resorted to fancy footwork to defend it from apparent counter examples. Defenders of the "doctrine of double effect" maintain that harm counts as *intentional* if and only if it is a goal of the action or a means to a goal (McIntyre, 2018). If it is instead a side effect, then the prohibition does not apply, and, if there is sufficient justification, it may be permissible to cause harm or a significant risk of death as a side effect. So, a defender of a prohibition on intentional harming might argue (implausibly, in my opinion) that the harm done to the kidney donor is only a side effect of an action undertaken to improve the health of another person rather than a means to accomplish that end.

Notably, it is hard to see how removing a kidney from a healthy donor could fail to count as a means to improving the health of the kidney's recipient. Those who would condemn challenge trials on the ground that they intentionally inflict harm as a means to achieving a good need to explain why their principles do not condemn innocent procedures such as kidney donation. Those who would, on the other hand, defend challenge trials and other risky research must either show that the risks to which experimental subjects are exposed are side effects, rather than means to the expected benefits of the research, or, more simply, they can reject the prohibition on the intentional infliction of harms or risks.[5]

IV. LIMITATIONS ON RESEARCHERS

A different argument in defense of refusing to impose large risks on experimental subjects, even if they have freely volunteered and the expected benefits are also large, lies in shifting the question from "Is it acceptable for subjects to face such risks?" to "Is it acceptable for research to impose such risks on subjects?" Although the risks of participating in a COVID-19 vaccine challenge trial are not substantially different from the risks of donating a kidney, no researcher is asking for your kidney. An experiment in which individuals were asked to donate kidneys for the purposes of research would raise different moral questions than assisting individuals who choose to donate a kidney for transplantation, even if the benefits were of a similar magnitude. What is rational or morally justified for individuals to choose is a different question from what is morally permissible for researchers to do to them. Even though medical research is driven by decidedly mixed motives, in asking some individuals to undergo risks for the benefit of others, it encounters ethical limits. In a liberal society, there are limits on what can be done to some individuals in order to benefit the populace as a whole. Although we allow self-sacrifice, as in the case of organ donation, we may refuse to allow individuals to take similar risks for the sake of overall social welfare, except in circumstances in which such sacrifice is necessary, as in war. Allowing research that has a large risk of death or injury takes unacceptable advantage of individuals for social benefits. Imposing risks on experimental subjects is more analogous to the imposition of risks on fire fighters or police. Additionally, the costs of doing without police and fire fighters is far higher than the typical costs of avoiding research that imposes comparable risks.[6]

One way to assess the risks and benefits of an experiment is from the perspective of the experimental subjects—what are the expected costs to them in relationship to the objectives they hope to achieve? From this perspective, one way to impose fewer additional risks on participants in challenge trials would be to seek out individuals whose occupations or living arrangements

put them at high risk already. For example, if volunteers could be recruited from among workers in meat packing plants, there may be little additional risk attached to joining the trial and possibly a very significant benefit.

Notice that the probability of death or serious illness facing any participant can be made as low as one likes, simply by adding individuals to the trial who are not exposed to the virus. For example, suppose one thought that the greatest risk of dying that it is tolerable to impose on experimental subjects is 1/10,000 and that imposing a 1/3,000 risk in a challenge trial is thus unacceptable. The problem is easily fixed. Instead of recruiting 100 individuals and (oversimplifying here) vaccinating half and exposing all 100 to the virus, 400 individuals could be recruited with 100 treated as before and 300 neither vaccinated nor exposed to the virus. In this way, experimenters can, with certainty, lower the risks to subjects of joining a challenge trial.[7] Doing so would, of course, contribute nothing to the scientific merits of the study, but it would lessen the expected harm of participating in the trial. Under double-blind procedures, where neither the subjects nor the experimenters interacting with subjects know who is vaccinated or who is exposed, each volunteer would then have a 1/12,000 probability of dying from the trial, and the trial would no longer involve excessive risk. (If experimenters wanted to expose individuals to no more than a 1/100,000 risk of death, they would need to recruit more than 3,000 volunteers, but with enough subjects, experimenters can make the risk as low as is wanted.)

The point of this strange hypothetical is not to propose recruiting additional individuals in order to lower the chance that any particular volunteer will be exposed to the virus (which would have no effect on the outcome of the trial). The point is to make it obvious that the perspective of those assessing the merits of the experiment differs from the perspective of the participants. The relevant metric for those assessing the experiment is not the risk of entering the trial (which could be reduced to a negligible number), but the risks caused by exposure to the virus and the risks of the vaccination. Adding an additional 300 participants, who are not exposed to the virus, lowers the risks participants face, but it has no effect on the expected harm the experiment may do. For example, an experiment devoted to a study of the physiological changes immediately after death that required giving a few fatal injections could be low risk to participants if 100,000 were recruited and under double-blind conditions and only a handful were injected with poison rather than with a harmless saline solution. The problem with such a study lies in what the harms the researchers deliberately inflict on a few of the subjects; it does not lie in the level of risk each experimental subject faces. In challenge trials, the ex ante probabilities of serious illness and death individual participants face reflect our ignorance of the detailed biological stories that determine vastly different individual reactions to the SARS-CoV-2 virus. Expectations of benefits and harm are relevant to the participants, and the accuracy of their expectations is crucial to their informed consent. But

the experimenter's ethical concern should focus on the outcomes medical researchers will have imposed on participants.

Although there is a place for a retrospective appraisal of the benefits and harms of an experiment, which will depend on the actual outcomes, they are, of course, unknown when the experiment is under consideration, and hence decisions about whether to approve an experiment must rely on expectations concerning the benefits and harms that will result from the study. This appraisal of anticipated outcomes is not independent of the expectations of participants, but it is not the same. For example, if the chances of death faced by individual participants exposed to the virus were independent of one another (which they are not, of course), the risks to individuals would be just the same, while the odds of there being multiple deaths would be infinitesimal. One cannot estimate the probability of hospitalizations or deaths the research causes just from the odds facing individuals who join the study.

Although germane to the choices of individuals, the risks to individuals from participating in a challenge trial are not the relevant variables for the ethical choice of whether to carry out the trial. The spectrum of outcomes among those exposed to the virus is just the same, whether or not volunteers would face high risks of infection if not in the trial. Similarly, although the expected probability that a volunteer will get sick diminishes if individuals who are not exposed to the virus are added to the study, whether the risk of participation is deemed sufficiently low and whether it is acceptable to the participants are not the relevant criteria to answer the question. The germane questions are whether it is permissible to impose the risks of exposure to the virus on individuals who agree to undergo them and whether the participants are chosen fairly from among the volunteers.[8] The relevant criteria in terms of which to judge whether it is permissible to impose such risks on participants call for social determination rather than individual preferences of participants. The actual harms may of course be more or less than expected, and the variance in the possible outcomes and not just the mean matters to the assessment of the trial.

How then should the social choice be made of whether to inflict a risk of serious harm on individuals (who, to be sure, have volunteered) for the sake of a large expected benefit to others? The relevant ethical question for the researcher is whether the potential benefits are significant enough to justify medical research that may cause deaths and serious illness, not whether volunteering is a good bet for an individual. How much can medical research reasonably ask of individuals? We do not and should not let that decision be made by what risks informed participants are willing to incur, because the decision depends on what harms researchers can inflict, rather than on what risks subjects are willing to undergo. In my view, if the benefits of challenge trials for COVID-19 are as great as some have claimed, then it is permissible for researchers likely to cause a few serious illnesses and

to impose a small risk of death. In defense of this assertion, I appeal to the expected net benefits.

V. CONCLUSION

Whether challenge trials of vaccines against COVID-19 can be beneficial is questionable. The United States and some other countries are doing such an awful job of containing the pandemic that regular phase III vaccine trials may yield results rapidly. The question in this article is hypothetical: *if* the benefits of challenge trials can be expected to be enormous and their risks are relatively low (and the consent of the subjects is fully voluntary and informed), are challenge trials still morally objectionable? I have argued that general prohibitions on subjects incurring more than minimal risks are unjustified, but that there are significant questions about what risks and harms researchers should be allowed to impose on experimental subjects. It is dangerous for medical research to sanction not just allowing harm to some to benefit others, but intentionally inflicting harm on some for that purpose, and I cannot refute those who find those dangers so serious that they oppose challenge trials. However, when the stakes are as high as they may be in the case of COVID-19, I think that moral qualms about inflicting a small number of harms, few of which are likely to be serious, should give way to the massive good the trials are by hypothesis assumed to do.

NOTES

1. In addition to expediting the development of vaccines, challenge trials could be valuable in determining correlates of protection and in understanding the early stages in the development of the disease and in the immunological response to it.

2. "A rigorous separation of the moral calculi for therapeutic and non-therapeutic procedures protects research subjects better than any other approach. This separation prevents the justification of risky non-therapeutic procedures by the benefits that may flow from therapeutic procedures" (Weijer, 2000, 352).

3. As a referee pointed out, the selection of volunteers is of great importance to popular perception of challenge trials. Even though members of especially vulnerable groups might benefit most from the recruitment of volunteers from those groups, and could complain at being excluded, the perception that the disadvantaged are being used as guinea pigs has lasting harmful consequences that would be greatly magnified if challenge trials resulted in many serious illnesses and deaths.

4. The case of kidney donation is intended as a counterexample to the general principle prohibiting the intentional infliction of harm on innocent individuals. It thus aims to undermine possible grounds for a rule prohibiting the infliction of harm on healthy research subjects. Kidney donation is not research and thus violates no rules governing research.

5. In debates about abortion and euthanasia, in which what is at issue is killing rather than harming, there may be more to be said for the doctrine of double effect. This is not the place to resolve those controversies.

6. Police and firefighters are also paid. What about participants in challenge trials? With literally thousands of volunteers for challenge trials, paying participants can hardly be regarded as undue inducement, threatening the force of their consent. Whether the subjects in challenge trials should be paid is not relevant to this essay.

7. I am not, of course, alleging that experimenters expand the number of participants for this purpose, or that they would welcome this possibility. The point concerns how to think about risk. To clarify, in the odd hypothetical case I am considering, 50 subjects are vaccinated and exposed to the virus, 50 are unvaccinated and exposed to the virus, and 300 are neither vaccinated nor exposed to the virus. Although there is uncertainty about the efficacy of the vaccine and even about whether it might make the disease more dangerous, experimenters might not only lower the risks but also enhance the personal advantages of participating by vaccinating the additional 300 recruits and not exposing them to the virus.

8. There might also be questions about who is volunteering.

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