

# Why Challenge Trials of SARS-CoV-2 Vaccines Could Be Ethical Despite Risk of Severe Adverse Events

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**ABSTRACT** Human challenge trials to test the efficacy of vaccine candidates against SARS-CoV-2, the novel coronavirus behind Covid-19, could save considerable time and many lives. But they may initially seem unethical because they expose healthy volunteers to a live virus that is killing many people and for which no cure exists. This article argues that this is not the correct test of their ethics. The correct test is comparative. And in the special circumstances of the Covid-19 pandemic, human challenge trials meet the correct test better than standard efficacy testing would.

**KEYWORDS** coronavirus, Covid-19, vaccines, human challenge studies, randomized controlled trials, risk taking, research ethics

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The deep health, economic, and social crisis the world is in as a result of the Covid-19 pandemic cannot be sustainably resolved without a proven vaccine against the novel coronavirus.<sup>1</sup> As experts consider ideas for accelerated testing of vaccine candidates,<sup>2</sup> one approach is to replace conventional phase III testing, the longest and most expensive phase of clinical research, with human challenge trials (also known as *controlled human infection trials*). Challenge trials could replace conventional efficacy testing either completely<sup>3</sup> or, by weeding out unpromising vaccine candidates before conventional testing, in part. Either way, challenge trials could make testing—in multi-arm adaptive platform trials,<sup>4</sup> for instance—faster and more manageable.

In a human challenge trial, healthy participants are intentionally exposed to a pathogen. This helps researchers find out fast whether participants earlier randomized to the vaccine under investigation are protected more than the participants in the control group (who will have typically received a placebo). Results come much faster than in conventional phase III testing, in

which significant differences between the group that received the vaccine and the control group start surfacing only months later, as participants (who typically try to avoid exposure as much as they can, for example, by donning protective gear) get exposed to the pathogen. If an outbreak moves elsewhere before many participants are exposed, conventional phase III testing fails to complete—which normally cannot happen in challenge trials.

Human challenge trials are regularly done for seasonal flu, typhoid, and malaria,<sup>5</sup> with the typical justification that “carefully controlled experiments involving intentional infection often pose only minor risks,”<sup>6</sup> because, for example, the disease is mild or therapies are available. That justification probably fails for a live SARS-CoV-2 challenge since there are deadly risks (although participant selection could make death unlikely enough to respect commonly assumed limits on tolerable risk in consensual clinical studies)<sup>7</sup> and, at this point, no proven cure.<sup>8</sup> While there are also technical questions about how much challenge trials could accelerate testing for the novel coronavirus,<sup>9</sup> this article de-

fends the ethics of coronavirus challenge studies on the assumption that, technically, they could substantially accelerate testing—and widespread rollout.

### THE RIGHT QUESTION

Fair and beneficent treatment of participants in a challenge trial depends not simply on reducing the likelihood of severe clinical outcomes (such as fatality) in the study, for participants might have experienced similar or worse events anyhow, and it makes no sense to hold such outcomes against the protocol. The trial should reduce (for each participant and for the entire cohort) how much that likelihood exceeds that of commensurate bad outcomes for the same people under two alternative scenarios delineated below, which do not involve participation in that particular study.

The idea is straightforward. Doctors offer patients surgeries and toxic drugs that may result in severe clinical outcomes, or they experiment with new interventions, all the time. These approaches are perfectly justified when the doctors thereby save these same patients from greater likelihood of similar bad events without the treatment or the experiment. One thing that is worse than getting your belly cut for an indicated operation is not undergoing that indicated operation because, say, you are uninsured. The operation injures you and puts you at risk, but it usually brings a net benefit. To move from the fact that an injured belly would, in itself, be a harm and a source of risk to the conclusion that being uninsured is a blessing would be fallacious. In assessing the risks and the benefits to study participants, research ethics heeds not simply the risks of study participation. It also heeds the balance of incremental risks and incremental benefits from participation, which matters much more.<sup>10</sup>

This calculus applies to human challenge trials as well. What matters in assessing the offer that researchers make to candidate participants is not simply the so-called absolute risk,<sup>11</sup> better described as the *raw* or *contributing risk*, that comes with the challenge—whether viral exposure poses only minor or controllable risks or, alternatively, more serious ones—but the *net* risk: the risk from participating in that trial *minus the risk that the same person would face otherwise*. In other words, what matters is the full balance of personal risk and benefit. The evaluation of a challenge trial ought to look

at the difference the trial would make to the participant's health (or life). An institutional review board, for example, should heed the change in risk exposure that would apply to the participant because she would be in the trial and not in some alternative scenario.

For judging the ethics of a SARS-CoV-2 challenge trial, two alternative scenarios to participation in the challenge trial are especially pertinent. In one, a person declines to participate in any SARS-CoV-2 vaccine efficacy test. That scenario helps identify how trial participation may affect that person overall, for good and for ill. In another, the same person participates in the competing form of trial, namely, a standard efficacy trial

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for the same vaccine. The latter would result in delay, but it may be tempting to argue that it is kinder to study participants and hence more ethical. To compare personal risks between the two studies, we shall look at the participant's (average) counterpart in the efficacy study, whether or not the participant of the challenge trial can herself join a standard efficacy study.

### THE ANSWER

It turns out that, compared to either of these two alternative scenarios, both for each individual and for the cohort, the net risk from participating in a SARS-CoV-2 vaccine challenge would be negative, small, or unclear. The net risk could not be clearly very large. Differently put, a SARS-CoV-2 challenge trial may turn out to constitute indirectly beneficial research for study participants—so that they would be medically disadvantaged if ultimately excluded from it or if they were

admitted to a standard efficacy trial instead. Properly done, a challenge trial certainly would not expose participants to a known far higher prospect of net harm than would either of these alternatives.

How might introducing a sometimes deadly and incurable pathogen into the body of a perfectly healthy person improve that person's health and welfare prospects? The explanation lies in the peculiarities of the current pandemic, which features a highly transmissible virus and overwhelms health systems worldwide. For any individual, the probability of incurring death or disability from an infection is  $a \times b$ , where  $a$  stands for the probability of getting infected, and  $b$  stands for the probability of either dying from or developing a long-term disability as a result of the infection. What is  $a \times b$  if an individual participates in a challenge trial? What is it if she declines? What is it if she participates instead in a standard efficacy trial? Is the probability largest in the first case, and by enough to justify blocking willing and decisionally capacitated adults from enabling highly valuable trials? To gauge the magnitude of  $a \times b$  in a challenge trial versus outside any trial versus in a standard efficacy trial, let us look separately at  $a$  and at  $b$  in each of these three scenarios.

When people assume that challenge trials are very dangerous to participate in, they usually focus on  $a$  (the probability of getting infected under these three scenarios). For any candidate participant, the likelihood of getting infected is clearly greater with the challenge trial's artificial challenge than if the person either declines to participate in any trial or participates in a standard efficacy trial. However, in the SARS-CoV-2 case, the research team can and should select participants for whom the probability of infection is *least* larger in a challenge trial. Recent models predict widespread worldwide exposure to this coronavirus. Some areas are likely to experience infection rates of greater than 50%,<sup>12</sup> and the proposal is to recruit only from areas with ongoing or expected high transmission rates.<sup>13</sup> Since the world is a large and variegated place, and candidate selection can be careful and targeted, there should be many outlier areas, among which to choose, where the probability of getting infected later would be very high at the time of candidate selection. Because expedited vaccine trials could shorten the current global economic recession and prevent many deaths worldwide, it would make

perfect sense to invest in carefully selecting and then safely transporting a few hundred healthy candidate participants from high-transmission areas to the isolated research centers—even across international borders. In light of the public health emergency, related red tape should be removed. If participants are selected in that way, the challenge trial is much likelier to hasten participants' exposure than to impose an exposure that they would have otherwise avoided. In the rare event that exposure kills a participant, the earlier exposure could mean that the individual dies a few months sooner than if exposed to the virus outside the trial design, but this temporal factor seems less significant than the substantial effect trial participation could have on how likely the person is to die.

With appropriate trial procedures and smart participant selection,  $b$  (the probability of dying or developing disability if infected) would be smaller in a challenge trial. It may be much smaller. First, the proposed trial design includes frequent monitoring that may catch disease and enable participants to receive supportive care and any therapeutics proven by that point very early, probably before any complications develop.<sup>14</sup> Outside the challenge trials, by contrast, testing could be scarce, and many carriers could remain asymptomatic, which impedes a "test-and-treat" approach that may be deemed promising for some patients. Any therapeutics proven by then might not be universally available yet. It would be only prudent and fair toward trial participants to prioritize them for any novel therapeutics.<sup>15</sup> Challenge trials for a SARS-Cov-2 vaccine should also offer guaranteed access to standard-of-care life-sustaining treatments, including immediate assistance during cardiac arrest. As life-support services reach capacity in many parts of the developed world over the coming months, patients from high-transmission areas who develop severe disease will often die outside trials. It is true that, according to reports published so far, most Covid patients who rely on critical care do not survive,<sup>16</sup> but, crucially here, younger Covid patients who need critical care tend to survive.<sup>17</sup> In the United Kingdom, for example, of the Covid patients aged 16 to 39 whose critical care outcomes were reported by May 15, 2020, 81.9% had been released from critical care.<sup>18</sup> It is also true that a period in intensive care for Covid-19 treatment may leave patients physically or psychologically disabled.<sup>19</sup>

But the option of receiving critical care, which significantly helps prevent the very worst outcome of short-term fatality, is clearly a substantial medical benefit. Because, for young patients with severe Covid-19, the absence of life-sustaining interventions makes a big difference between likely survival and no chance at all, the probability of averting death in the event of infection would be substantially better inside a challenge trial than outside any trial. And this probability would be somewhat larger than in a standard efficacy trial, which would find it somewhat harder to provide that full guarantee of support to its thousands of participants.

In short, if researchers conducting challenge trials act as recommended, admittedly, the probability of getting infected would remain larger inside a challenge trial than either outside any trial or in a standard efficacy trial; but the probability of death or disability is likely to be much smaller inside a challenge trial than in these alternative scenarios. Overall,  $a \times b$  could be smaller for any individual inside the challenge trial than either outside any trial or in a standard efficacy trial. What the individual would lose in the probability of averting infection (with that probability rising) she could gain in better protection from death.

Even if, eventually, with more data and calculations,  $a \times b$  turns out to be equal under these alternative scenarios, or slightly better under them, here is what is unlikely to be the case, dynamic and uncertain data notwithstanding: that  $a \times b$  is much, much smaller if a properly selected and treated individual does not participate in any trial or if she partakes in a standard efficacy trial instead. This matters. In espousing a limit on how risky participating in a trial may justifiably be, contemporary research ethicists usually describe what exceeds that limit in terms of *extremely high net* risk to the participant; the limit is surpassed only when the overall balance of prospective medical harms and medical benefits to the participant is highly adverse.<sup>20</sup>

There is another important welfare or borderline-medical benefit from participation. Some potential challenge participants simply could not extinguish risk of getting exposed, say, because they have to leave home for essential work. They could not extinguish it either by declining to participate in any trial or by participating in a standard efficacy trial instead. Among them, those who live with others would understandably worry about

infecting household members, including, in some cases, old or frail relatives. They would know that *if* reinfection is rare or impossible (something that scientists are still examining), they would not infect them as long as their own infection and infectious period take place in isolation. Putting at least a temporary end to the risk of infecting others would help keep their loved ones alive—surely a substantial benefit.<sup>21</sup> By contrast, if they do not join any study or if they participate in a standard efficacy study, the probability of infecting those dearest to them could remain substantial.

All in all, so long as challenge participants are selected and supported as recommended above, the prospective harms, properly understood as the incremental harms, are unlikely to far exceed the benefits for individual participants. They could actually be smaller.

To sum up so far, the answer to the right question, about the appreciation in net risk, is that, on balance, challenge trial participation could be either prospectively beneficial or neutral or slightly prospectively harmful—certainly not highly prospectively harmful. Therefore, it cannot justify paternalistic protection when adults with the requisite decision-making capacity wish to help researchers do enormous good.

## OBJECTIONS ANSWERED

Consider five potential objections to the argument I have laid out.

**Exploitation.** One objection is that my argument compares participation in a challenge trial to the wrong scenarios. The correct comparison, it could be objected, is to idealized circumstances—of greater justice. Otherwise, a vaccine producer might exploit unjust background strife of candidate participants to offer them less safety than it should.<sup>22</sup>

To exploit someone is, roughly, to use their unjust disadvantage to one's unfair advantage, leaving them with less than they should have.<sup>23</sup> For example, a sweatshop owner makes to potential workers a worse offer than she should (the pay is unfairly low, and the degree of safety is not what it should be), exploiting their alternatives, which are, unfairly, even worse—starvation, for instance. The fundamental problem here may have to do with the distributive consequences, say, that the owner winds up with too much, and the workers too little; or with the workers' effective inability to decline

the offer; or simply with the perverse relation in which the owner stands to them. Whatever the fundamental problem may be, we usually consider this problematic. And inasmuch as widespread infections and lack of access to critical care flow from injustices, one could claim that recruiters for human challenge trials or the societies they serve are likewise exploiting an unjust disadvantage. Instead, one could argue, the appropriate comparator of participating in a challenge trial is living in a world free of these injustices or their disadvantageous sequelae. Indeed, two senior French doctors were recently condemned for having proposed testing coronavirus vaccines in African patients, based on assumptions about African nations' financial inability to fight the virus effectively.<sup>24</sup> While the backlash probably had more to do with unsympathetic, and somewhat racist, suggestions that these doctors made on the occasion, the potential exploitation of background economic injustices may also have been a concern.

The challenge trials I discuss here would probably take place in leading research centers in the richest countries. But inside these countries, transmission rates and the need for unavailable critical care services may typically end up being worst in impoverished, minority, and undocumented migrant neighborhoods, among the uninsured and underinsured, and among other victims of societal injustice. Some unethical historical challenge trials were done on such participants, improving these participants' overall risk exposure compared to their unjust alternatives.<sup>25</sup> While these historical comparisons are obviously inappropriate (given that these abuses also involved violations of consent, of independent review, and so forth),<sup>26</sup> their unethical nature may also have involved the exploitation of background injustices.<sup>27</sup> Does the potential for that kind of exploitation undermine my case for testing SARS-CoV-2 vaccines through the challenge trial design?

There is a simple answer to the concern about exploitation. To avoid preying on victims of injustice likely to live in certain areas, all research teams need to do is recruit elsewhere. The world is a big place, and, unfortunately, there will be plenty of areas with ongoing and expected high transmission, as well as devastating demand for critical care services, even absent grossly unjust background poverty, disparities, lack of insurance, and the like. Some locales are experiencing or can ex-

pect a surge in Covid-19 cases for reasons other than preexisting systemic injustice—simply because of bad luck or even warranted choices that panned out poorly (for example, governments may not have invested a great portion of health care funds in intensive care units and supplies in the years before the pandemic, in favor of investing in cost-effective interventions that, over time, promote population health and longevity more). Researchers could always focus recruitment on such locales. Indeed, although researchers should recruit from high-transmission areas, those need not be areas of the very highest transmission rates if the latter locales correlate closely with background injustices. Some other areas that are generally better-off would do. Of course, it is impossible to project which locales will have become high-transmission areas when it is time to test the efficacy of each candidate vaccine. For illustrative purposes, however, consider middle-class areas of Stockholm, if social democratic Sweden's recent choices to avoid social distancing turn out to have been epidemiologically mistaken (not quite the same thing as unjust).<sup>28</sup> Again, transporting a few hundred candidate participants from afar, even across borders, to the research center is a rational financial and administrative investment toward alleviating a deep recession.

A second answer is that, in this instance, research teams may be able to recruit volunteers driven not solely by promoting their own health but also by altruism. The nonprofit 1Day Sooner is collating contact details of potential volunteers for live SARS-CoV-2 challenge trials and reports over 21,000 applications at the time of this writing.<sup>29</sup> Many potential volunteers study or teach at elite academic institutions. Many are self-identified "effective altruists" who recount past altruistic acts. While self-reports ought to be taken with caution, it may turn out that enough participants would volunteer with full comprehension of the medical risks, perhaps out of altruism and not because of misunderstanding—and not because they have suffered systemic injustice that makes them vulnerable to exploitation. Avoiding financial incentives for participation would further help select volunteers with the best motives.<sup>30</sup> The causal route to their participation would not exploitatively rely on offering benefits to thwart major injustices toward them.

A third answer is that the ethics around nonexploitation is complex. Avoiding exploitation, as defined



above, would mean that some victims of injustice are denied any benefits of trial participation and that many people like them, of the same racial minority, for example, or as undernourished as they are, are denied the benefit of the vaccine's having been tested in people like them. The upshot of showing that an action would be exploitative is therefore unclear. Sometimes, it is much better to be exploited than not to be exploited.

Finally, even if exploiting unjust strife were unavoidable in challenge trials of SARS-CoV-2 vaccines, concerns about exploitation would not be strong enough to unseat the otherwise very strong case for these trials. It is true that, even with a study volunteer's willing consent and even given the need to thwart a public health disaster, some research ethicists (not all)<sup>31</sup> would consider high likelihood of grave harm to a volunteer to remain forbidden.<sup>32</sup> But no one I know seriously argues that worries about beneficial, perfectly consensual research that is marred merely by an exploitative route to benefit and consent is enough to ban a study that can be expected to save an inordinate number of lives. Remember that the challenge trial design could cut several months in the wait for vaccine rollout, translating into thousands or millions of lives spared from exponential growth in direct Covid deaths.<sup>33</sup> True, only a third to one half of all vaccine efficacy trials lead to vaccine approval,<sup>34</sup> and there is some chance that none of the over 100 extant vaccine candidates will work or that an approved vaccine will not be rolled out widely. But even a portion of the potential lives that might be spared, thanks to SARS-CoV-2 vaccine challenge trials, from Covid death, from death or serious harm from other diseases that are neglected during the pandemic, and from famines and halted economic development during months of delay could be a very large number of lives spared.

Put more dramatically, the main factor resting on one side of the moral scale is a significant chance at averting a great number of deaths—probably vastly more than in the 2014-2016 Ebola outbreak (with 11,315 deaths) or even the 2004 Indian Ocean tsunami (with around 250,000 deaths). What stands on the other side is not averting serious net harm to an individual, which is the consideration that some research ethicists count more. The complaint on that side is that, while, admittedly, challenge trial participation could benefit that individual on balance and she could rationally and

autonomously choose to enroll, the causal roots of that benefit are impure. This is not a balance that would stop any serious research ethicist from approving a crucial trial.

For all these reasons, the concern about exploitation, even if applicable and cogent, cannot unseat the initial case for conducting challenge trials. This is not to say that researchers should ignore that concern. It may affect how best to conduct the trials—say, by recruiting from areas with high transmission rates but no blatant injustices. Still, some form of challenge trial remains permissible and, to accelerate vaccine rollout, highly recommended ethically.

**Inability to decline.** Challenge trials should enroll individuals only with their fully free and informed consent.<sup>35</sup> But with some medical trials, just or unjust background circumstances are so dire that they leave candidate participants no reasonable option except to enroll. Perhaps that is what troubles ethicists who consider challenge trials and warn about dire background injustices. It may also be part of what worries some about the quality of consent in trials of novel cancer therapeutics, which give terminal patients a last hope to fight off a cancer that is irresponsive to approved treatments.<sup>36</sup> In a sense, these desperate patients cannot (because they cannot afford to) say no and are “forced” to participate. In English, when one chooses the less bad of two bad options, one is often said to have been “forced” or “compelled” to make that choice.<sup>37</sup> All this may seem to invalidate any consent that people in dire circumstances may give to trial participation and may make their inclusion in the trial unfree and, one could argue, wrongful. And, given the effects of the current pandemic, anyone joining a challenge trial for a vaccine for the novel coronavirus may be said to be “forced” to participate.

This argument that bad alternatives to trial participation invalidate consent to participate cannot work. It would forbid many ordinary participant selection procedures for cancer therapy research. It could even, absurdly, invalidate consent to advanced cancer care, on the parallel ground that the patient cannot afford to say no. But the argument is even more questionable when applied to vaccine research. The risk profile of someone who knows that she has advanced cancer is very different from that of someone who—like vaccine trial recruits—has not been infected and is therefore at far

less dramatic risk. Especially if research teams recruit only young and healthy individuals, for whom even infection is highly unlikely to translate into severe disease, recruits should not feel desperate or compelled to participate in the trial for their own health's sakes. What I argued above is only that there are health benefits from participation, not that recruits should feel desperate for them. If some persistently do, they should be excluded in the consent process for misunderstanding relevant facts, or on psychiatric grounds. In that respect, since we should permit these cancer studies, we should also permit human challenge studies of novel coronavirus vaccines.

**Vaccine safety.** Some vaccine candidates may turn out only in efficacy testing to be toxic.<sup>38</sup> Some may turn out only during efficacy testing to enhance Covid-19 severity, manifold.<sup>39</sup> The greater the chance for vaccine safety issues, the better in that respect for individuals to decline to participate in trials.<sup>40</sup> This may suggest that participating in the challenge trial is prospectively harmful, after all.

Let me offer four responses. First, challenge trial participants would prospectively benefit in other ways and so may still prospectively benefit overall—this risk notwithstanding. Second, that chance for vaccine safety issues is as likely per person to arise in standard efficacy trials. Assuming that some form of efficacy testing of vaccines is legitimate in this crisis, this factor should not weigh against challenge trials. Third, in standard efficacy trials, toxicity and severe disease are much less safe for participants because they erupt in the field, not in a controlled medical environment with frequent monitoring and guaranteed medical help.<sup>41</sup> Therefore, vaccine unsafety is far more dangerous to a participant in a standard efficacy trial than to one in a challenge trial. Fourth, in standard efficacy trials, any risk of toxicity or enhanced severity accrues to 10 to 50 times as many participants, for the simple reason that such trials require 10 to 50 times as many participants. In short, appropriate concern about enhanced severity cannot constitute an advantage of standard efficacy trials over a human challenge trial. Quite the contrary. It only strengthens the ethical case for challenge trials to replace standard efficacy testing of vaccines against the novel coronavirus.

**Indirect benefits.** I have argued that if challenge trials are done right, the incremental risk from participation in them may be smaller than the incremental benefit from it. The main benefit invoked was priority access to critical care and therapeutics in the event of severe Covid-19. However, that benefit may seem irrelevant or tertiary to some, either because harm allegedly matters more than benefits or because this particular benefit is indirect.

Contempt for “mere” benefits merits only a short response. Researchers, as well as clinicians, appropriately offer countermeasures known to be riskier when the expected benefits exceed the expected risks. While some benefits (such as mere enhancement and mere financial benefit) might be less important than a trial's primary benefit to the participant, others are clearly as important. The benefits discussed here are in terms of avoiding Covid-19 fatality—the main risk under consideration; indeed, it is not even clear what counts as reduction in incremental risk and what as increase in incremental benefit.<sup>42</sup>

What is worth further discussion is the worry that these life-saving benefits are nevertheless merely indirect because they would not “aris[e] from receiving the intervention being studied.”<sup>43</sup> Nor is treatment for Covid-19 among “the clinical benefits of the procedures that are scientifically necessary to test the experimental intervention under study.”<sup>44</sup> An anonymous reviewer of an earlier version of this article thought that indirect benefits should not count toward the assessment of study participants' balance of personal risks and personal benefits, lest researchers “address” any major risk with financial compensation or still other indirect benefits.

However, for the purposes of this article, we can set aside the question whether money can ever adequately compensate for acute medical risk. Again, priority access to Covid-19-related critical care is a medical, not a financial, benefit. It directly addresses the main risk of challenge participation, namely, premature Covid-19-related mortality. How can such an indirect benefit not count?

In addition, some benefits from participation in a Covid-19 challenge trial would be direct benefits. Consider potentially better protection for one's family (if infection provides long-term immunity) and a safer

environment for episodes of enhanced disease severity, compared to the environment for standard efficacy trial participants. These benefits emanate directly from the best scientific way to hold the study.

Furthermore, scholars who have looked at indirect benefits usually propose including them in institutional review boards' risk-benefit calculations<sup>45</sup> or even on informed consent forms.<sup>46</sup> In fact, the (questionable, in my view) regulatory block on invoking indirect benefits pertains in the United States only to research on people who cannot provide informed consent, such as children,<sup>47</sup> and is irrelevant to the present case of challenge trials on decisionally capacitated adults.<sup>48</sup>

Even the benefit of better access to critical care and therapeutics in a challenge trial than in one's high-transmission area is borderline direct. While not strictly speaking "scientifically necessary to test the experimental intervention under study," this care would be part of trial safety. It is not ancillary care or retroactive compensation for a trial that risks Covid-19 fatality. Instead, it preempts high risk of Covid fatality resulting from the viral exposure in the study.

Access to critical care is also ethically owed to study participants, per most accounts of research ethics, anyhow. Critical care is not experimental treatment that, as such, might not be owed. Nor is it in rich countries so exquisitely rare that, despite participants' especially strong claim to it, they should be denied it. Not to offer critical care would be preposterous in a challenge trial for a deadly disease that critical care helps treat. Far from an afterthought to appease those protesting an unfair risk-benefit ratio, critical care is owed in the first place.

**Personal risk factors.** What if a candidate participant who hails from a high-transmission area actually has low risk of getting infected for a reason that sets her apart from her neighbors, such as being personally willing and able to isolate herself extraordinarily well? Then there is an important sense in which trial participation could harm that individual greatly. In the trial, exposure would be certain, whereas outside the trial, it would remain unlikely.<sup>49</sup>

Researchers should go some way toward identifying and excluding such individuals (for example, by asking about candidate participants' work and household arrangements or even surveying them on risk behavior).

Perhaps informed consent forms should exhort candidate participants to consider personal risk factors and avoid participation if they are highly unlikely to get exposed naturally. However, just as some participants would have less risk of natural exposure than researchers could know, others would have greater risk of natural exposure than researchers could know. Researchers should ascribe to candidates the average risk level for the risk category package they investigate. By sticking with the average, non-omniscient researchers are as likely to introduce more net harm than expected as they are to introduce less net harm than expected. It should all balance out. And the risk exposure that researchers are ethically responsible for is arguably the one that they know (or could with reasonable effort find out) about, not the objective one discussed here.

## TWO PRACTICAL IMPLICATIONS

As I have argued, the right ethical question about human challenge trials for SARS-CoV-2 vaccines is *not* the commonly raised one, about their likelihood of leading to deaths and other severe adverse events, given the disease's seriousness and the current lack of proven therapeutics. The right question is whether challenge trials would increase study participants' likelihood of similar bad outcomes, compared to two alternative scenarios: nonparticipation in any trial and participation in standard efficacy trials for the same vaccines. As shown, surprisingly, compared to these two alternatives, human challenge studies would, on balance, probably benefit or at least not dramatically harm study participants. Challenge trials could also reduce the overall prospect of harm in the participant cohort.

With respect to SARS-CoV-2, ethicists should not advocate a ban on a trial design that may accelerate a proven vaccine's rollout by months just because risks were calculated the wrong way. Let us not miss our chance to quash the current global crisis earlier through perfectly permissible research.

A further conclusion follows. Based on the ethical requirement to give participants a fair balance of risks and benefits, it need not be important to recruit individuals or a cohort who would be at low risk of bad outcomes in the trial. The balance of risks and benefits may turn out to be similar for participants who would be at



low risk in the trial (such as young and healthy individuals) and for ones who would be at high risk (such as older people and individuals who have relevant underlying health problems). It may turn out that, compared to these alternative scenarios, challenge trial participation is prospectively beneficial (or not very harmful) for all potential recruits, including high-risk ones.

If and when that is indeed the case, it would seem compatible with sensibly calculated risk-benefit requirements to recruit for a challenge trial not only young and healthy people,<sup>50</sup> for whom both risks and benefits are low. It would also seem permissible to recruit old people and people who live with health conditions that make them especially vulnerable to Covid-19, people for whom both risks and benefits are high. All could benefit, or at least not lose a lot in their prospects, compared to if they do not participate and compared to if they participate in a standard efficacy trial.

Recruiting an ample number of participants from several such vulnerable populations may allow us to skip further testing for vaccine safety,<sup>51</sup> or efficacy, in populations earlier excluded from the efficacy study, and move straight to conditional approval and, alongside further rigorous testing in broader populations, wide rollout. Additional months would be saved in the race to a universal vaccine rollout.

Other ethical considerations may be thought to weigh against recruiting older patients and patients with conditions that increase risk from infection. One is that their recruitment could increase the risk that some patients would die from trial procedures, undermining public trust. Another is that for these higher-risk populations, the benefit of guaranteed access to therapeutics and life-sustaining interventions in the event of severe infection might be crucial enough to “force” them to participate, in the sense expounded above. Whether these two considerations are sensible and weighty enough to forgo cutting additional months from the process is a question that I shall leave for another day. ♦

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42. It is therefore odd that writing on SARS-CoV-2 vaccine challenge trials either demotes promoting benefits to a less important consideration than minimizing risk (WHO Working Group for Guidance on Human Challenge Studies in COVID-19, *Key Criteria for the Ethical Acceptability of Covid-19 Human Challenge Studies*) or calculates the maximal allowable risk with no consideration for any balancing benefits. As an example of the latter approach, take Shah et al., “Ethics of Controlled Human Infection to Study COVID-19.” Shah and colleagues assess whether these trials would be excessively risky to participants with no consideration of their potential indirect benefits to these same participants. But surely any limits on risk to participants must remain sensitive to those benefits. It is only the balance for these participants that must not be overly adverse. Shah seemed to assume as much in earlier work. In writing on very risky HIV-cure-related studies that transplant stem cells from other people, an intervention that is several orders riskier to participants than SARS-CoV-2

challenge trials are and that has far greater than 1% risk of killing participants, she seemed to permit these riskier studies in adults. The reason was surely that participants of those cure-related studies could gain a side benefit, namely, a cure for their terminal cancers (Shah, S. K., “When to Start Paediatric Testing of the Adult HIV Cure Research Agenda?,” *Journal of Medical Ethics* 43 [2017]: 82-86). I agree with the earlier Shah that large benefits to participants can license large risks, including risks that, considered alone, would violate any limits on trial risk to participants. The later Shah should have applied the same standard to SARS-CoV-2 challenge trials.

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