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THE CHALLENGE FOR CORONAVIRUS VACCINE TESTING

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FROM the early days of the COVID-19 pandemic, vaccines were considered the safest and most sustainable way out of the health and economic crisis of the pandemic. Researchers, policymakers, and bioethicists debated ways in which vaccine development could be expedited. One suggestion was human challenge trials in which volunteers are infected with the pathogen after having received either the candidate vaccine or a placebo or alternative control treatment.[1] The idea behind challenge trials is that because researchers do not need to wait for participants to be naturally infected (if ever), challenge trials promise faster results.[2] In a pandemic that induced much suffering, even small gains in time can be highly beneficial. Decision makers hesitated and opted for field trials first. When challenge trials started belatedly in the United Kingdom, safe and efficacious vaccines had already been developed. Was this hesitation justified?

The question is not only of retrospective interest. Pandemic preparedness has received renewed attention due to the salience and visibility of COVID-19, but also due to advances in biotechnology that some fear make pandemics more likely.[3] The question of the permissibility of challenge trials is then also a question of pandemic preparedness in our ethical frameworks and regulations. My argument, which focuses on COVID-19, has, therefore, lessons for future pandemics, too.

One key concern about accelerated testing was the risks to participants. I argue that challenge trials can be justified even on a framework for research ethics that is strongly protective of research subjects. Philosophical arguments for challenge trials have been made both on broadly consequentialist and anti-paternalistic grounds. These arguments were often critical of research

1 Eyal, Lipsitch, and Smith, "Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure"; and Plotkin and Caplan, "Extraordinary Diseases Require Extraordinary Solutions."

2 Some scientists were less optimistic about the time advantage, pointing to the need to develop a strain of the virus that is not needed in field experiments. See Kahn et al., "For Now, It's Unethical to Use Human Challenge Studies for SARS-COV-2 Vaccine Development."

3 Pannu et al., "Strengthen Oversight of Risky Research on Pathogens."

ethics practice.[4] My argument develops a somewhat more sympathetic line of research ethics that not only permits challenge trials but also points to new options in vaccine research that could be useful, especially in pandemics with pathogens more dangerous to individuals than COVID-19. The argument also shows how nonconsequentialist and broadly contractualist moral theory can be an appealing way of thinking about the regulation of risk in medical research. Last, it highlights the connections between the risks to study participants, risks to study cohorts, and the benefits to nonparticipants.

In section 1, I start by discussing and developing ethical standards for clinical research risks. Applying these standards in sections 2 and 3, I argue that challenge trials can meet these standards. I also explain how a low-dosage challenge can render challenge trials permissible that initially appear too risky.[5] Section 4 turns to the question of post-challenge safety testing. I argue that a proposal for accelerated post-challenge safety testing is no more problematic than the established testing procedure.[6] Sections 5 and 6 discuss how and when benefits to nonparticipants can justify risks to participants of clinical research.

1. WHEN ARE RISKS JUSTIFIABLE TO STUDY PARTICIPANTS?

The key concern about challenge studies is that they are overly risky for research subjects.[7] To take an extreme example, it would clearly be impermissible to subject willing volunteers to very high risks of death to find a cure for a minor cosmetic condition that affects only a few people worldwide. Research ethics expresses this idea with the requirement of a favorable risk–benefit ratio.[8] A favorable risk–benefit ratio is a necessary condition that must be met if clinical research is to be permissible. Clinical research is justified if the favorable risk–benefit ratio is satisfied alongside various non-risk-related conditions

4 Savulescu and Wilkinson, "Extreme Altruism in a Pandemic," focuses on anti-paternalism. Eyal, "Is There an Upper Limit on Risks to Study Participants?" focuses on a broadly consequentialist approach highlighting large stakes. Other arguments like Chappell, "Pandemic Ethics and Status Quo Risk," are not necessarily consequentialist but challenge the distinction between harms arising from research and harms arising from the pandemic.

5 See Steuwer, Jamroziak, and Eyal, "Prioritizing Second-Generation SARS-CoV-2 Vaccines through Low-Dosage Challenge Studies."

6 See Eyal, Gerhard, and Strom, "Strengthening and Accelerating SARS-CoV-2 Vaccine Safety Surveillance."

7 Deming et al., "Accelerating Development of SARS-CoV-2 Vaccines"; and Shah et al., "Ethics of Controlled Human Infection to Address COVID-19."

8 Emanuel, Wendler, and Grady, "What Makes Clinical Research Ethical?" 2705–6; Rid and Wendler, "A Framework for Risk-Benefit Evaluations in Biomedical Research."

(informed consent, fair participant selection, etc.). I assume the latter conditions are satisfied in order to focus on the question of research risks.

However, the idea of a favorable risk–benefit ratio is in need of further details. When do benefits outweigh the risks? Which benefits should we take into consideration? How much priority should we give to reducing the risk to participants at the expense of forgoing benefits to nonparticipants? I now argue for three standards that fulfill the favorable risk–benefit ratio.

At times, the favorable risk–benefit ratio is interpreted as a requirement to provide favorable prospects to the participants of clinical research.[9] In other words, research is permissible only when undergoing the research is in the rational self-interest of the participants. It is highly controversial whether research must meet such a high bar, but it is easy to see why clinical research that meets this standard would be permissible. Researchers would be acting no differently from physicians who recommend to patients what they believe is in the best interest of the patient.[10] There can be little doubt about the ability of individuals to give informed consent to such research, just as there can be little doubt about the ability of individuals to give informed consent to medical procedures. Once the participants understand that the gamble is in their self-interest, they will typically consent to it. This is the *favorable prospect standard*.[11]

To see if any less demanding standard is justified, consider the role of informed consent in the aforementioned argument. Informed consent both licenses the risks associated with the research and licenses the necessary intrusions into one's body and privacy. Vaccines require access to a person's body; monitoring requires at least access to medical records. A second interpretation of the risk–benefit ratio limits the role of consent to this latter role. It asks, "Would the risk imposition be permissible if it could be done without invading the person's body and privacy?" Since informed consent means that individuals

9 For a good discussion on both the presence of this idea and how it conflicts with important parts of research practice, see Wikler, "Must Research Benefit Human Subjects If It Is to Be Permissible?"

10 This corresponds to what Rid and Wendler call the "informed clinician test" ("A Framework for Risk-Benefit Evaluations in Biomedical Research," 158–59). Rid and Wendler also point out that the right comparison is whether the testing is beneficial as compared to already existing interventions and not as compared to no intervention (157–59). This distinction raises interesting questions about the correct comparator. What about citizens of developing countries without access because other countries are hoarding vaccine supply? Unfortunately, I need to sidestep this question here.

11 A related idea is "clinical equipoise," which refers to the situation in which the researcher-clinician does not judge either option (participating/nonparticipating) to be better than the other. While the prospects are not favorable in such a case, they are not disfavorable either. See Weijer, "The Ethical Analysis of Risk."

waive their moral objection against these intrusions, we should ask whether the risk imposition by itself is justifiable. If the risk is such that we could have imposed it without consent, then there can be no objection against risks of this kind involved in research. This standard is not equivalent to the favorable prospect standard. Avoiding at all times all net risks of harm to individuals is an impossibly stringent requirement that would lead to paralysis. Many daily activities impose risks on others without any compensating benefit. In many of these activities, risks for some can be justified by benefits to others. For example, when we call an ambulance for an injured person, risks to bystanders potentially hurt by a car accident with the ambulance can be justified by benefits to the injured person.[12] But, of course, there are limits to the extent to which some can be put at risk of harm in order to provide benefits to others.

Therefore, we should focus on the question whether the risk of harm would wrong any individual participating in the research. The focus on wronging individuals also explains why the risking of active harm counts more heavily than the failure to prevent harm due to the COVID-19 pandemic. We need to take care not to wrong anyone. But as long as no individual is wronged by the risk imposition, we are permitted to impose risks with the aim of benefiting others.

The point can also be expressed in the language of rights. Any rights violation necessarily wrongs an individual. I am less certain whether every act of wronging an individual also constitutes a rights violation. In the case of risks, however, it does seem plausible that there is a right against the imposition of some risks.[13] If put in the language of rights, the earlier point is even clearer. Rights act as side constraints to our actions in pursuit of the social good, but if the side constraints are respected, we are free to pursue important social aims.

To ensure that our act of risking harm does not wrong any individual or violate their rights, we must ensure that our action can be justifiable to each of

12 The ambulance example does not involve net risks if we allow for so-called intrapersonal aggregation. That is, we would consider the costs and benefits of living with a principle that generally licenses an act or risk imposition. This renders more actions beneficial for all. T. M. Scanlon appeals to intrapersonal aggregation of this sort (*What We Owe to Each Other*, 197–202, and "Contractualism and Justification," 24–25, 38–40). Moral theory would be understood as "legalist" in the sense that moral principles are seen as the equivalent of laws that generally govern human behavior. Liam Murphy discusses how contractualism ties up with legalist moral theory in "Nonlegislative Justification." The question that the favorable prospect standard asks is, however, different. It asks whether, in this particular instance, the risk imposition is in the interest of the agent. This standard of not allowing net risks at any point in time surely leads to paralysis. I thank a reviewer for pressing me to highlight the distinction between net risks of principles allowing risky activities and net risks of individual risky actions.

13 This is argued for by John Oberdiek in *Imposing Risk*, ch. 4. It is also supported by Stephen Perry, "Harm, History, and Counterfactuals," 1306–9.

them separately. If no single person can raise a valid complaint against the risk imposition, then we have ensured that the risk imposition is justifiable to each and every one. Consequently, the risk imposition does not wrong any single individual.[14] I call this the *justifiable risk standard*. Importantly, the justifiable risk standard requires the presence of benefits to nonparticipants in order to justify the research risks. This sets it apart from the favorable prospect standard and will become important in sections 4 and 5.

The connection to rights against being subjected to risks suggests a third way for clinical research to be ethical. This third way, as the justifiable risk standard, relies on the benefits to nonparticipants to justify research risks, but it does so in a different manner. If individuals can waive their rights to bodily integrity and privacy for the purposes of research, then why can they not waive their right against being subjected to risk, too? Individuals who participate in studies justified under the justifiable risk requirement do so for reasons other than their self-interest. Participants in research, in fact, often report being motivated by considerations other than their self-interest. Participants might be motivated by the desire to help others, to do their part in fighting a disease, or to do something meaningful with their lives. The motives of participants are important here not to evaluate the participants' conduct but rather because of the different justifications that researchers are able to give to individuals depending on whether or not the research is in the participant's clinical interests. If individuals are permitted to waive some rights in pursuit of altruistic motivations, then why should clinical research prevent them from waiving their rights against being subjected to risk in pursuit of them? Indeed, health care systems already accept the idea that individuals can waive their rights against being subjected to (substantial) risk. Around the world, health care systems accepted volunteers during the COVID-19 pandemic, knowing that volunteering to help exposed these individuals to additional risks they would not otherwise face. A good example is volunteers in emergency medical services who, in rural areas, are often exposed for a substantial time to the risk of infection while transporting suspected cases. These health care systems allowed volunteers to be exposed to risks that were only justifiable because individuals consented to these risks. There is no good reason, in principle, why research subjects should

14 This account of the wrongfulness of risk imposition resonates well with contractualist ideas of justifiability. See Scanlon, *What We Owe to Each Other*. Frances Kamm has argued that contractualism is intimately connected with the question of whether our actions wrong individuals. See Kamm, *Intricate Ethics*, 456–68. Oberdiek, who argued in favor of a right against the imposition of risk, refers to contractualism as an answer for how to specify the scope of such a right (*Imposing Risk*, ch. 5).

be treated differently. We should accept a parity between putting consenting individuals at risk outside and inside the research context.[15]

Even when individuals are allowed to waive their right not to be put at risk, that does not imply that all risks are permissible. Critics of research ethics frameworks sometimes suggest that risk-benefit protections for willing and consenting volunteers are motivated by paternalism. They analogize medical research to risky activities like free climbing El Capitan. In the case of free climbing El Capitan, the only plausible justification for restricting autonomous agents from doing so is paternalism.[16]

But medical research is not like free climbing El Capitan. The question is not whether we should prevent individuals from doing something they otherwise would and could do on their own. The question is whether we are permitted to solicit and encourage people to let us do something on them that they otherwise would and could not do on their own. Let me unpack two of these differences.

First, researchers solicit, encourage, and induce volunteers to take part in the study. In studies that cannot be justified under the favorable prospect standard, they need to appeal to the volunteer's altruistic motivations. If researchers ask volunteers to take on additional risks, they need to ensure that they can justify asking for these sacrifices. This means that the risks must be necessary for the proposed research. Recruiting additional volunteers without expecting any scientific benefit could not be justifiable to them. The researchers could not appeal to the altruistic motivations of these subjects. The presence of these additional subjects would not help anyone. Their contributions would be pointless sacrifices. A similar observation holds for cases in which the social benefits are sufficiently trivial that we cannot justify encouraging individuals to take up great risks.

Second, researchers facilitate the risks, and their facilitation is done to serve ends other than those of the risk-taker. Facilitation is different from nonintervention. Anti-paternalism can ask for nonintervention. In the case of El Capitan, that is all that is needed. But in the case of research risks, we

15 See Chappell and Singer, "Pandemic Ethics." Similar comparisons with nonresearch contexts are made by Alex London (see "Reasonable Risks in Clinical Research" and "Clinical Research in a Public Health Crisis"). One reason to treat research risks differently is possible externalities to nonparticipants. The most discussed externality is distrust in vaccines. Vaccine hesitancy arguments raise a variety of complicated empirical and moral questions, so I will largely sidestep these. See, however, the discussion in note 28 below.

16 In the context of COVID-19, see Savulescu and Wilkinson, "Extreme Altruism in a Pandemic." More generally, see Miller and Wertheimer, "Facing Up to Paternalism in Research Ethics"; and Shaw, "The Right to Participate in High-Risk Research."

go beyond nonintervention. Without the research trial, the risk would not exist. The researcher facilitates, in the sense of making possible the risk to the research subject.

This becomes important in cases of excessive heroism. Consider the following case. There is a burning building, perhaps a skyscraper, with very many people inside. There is a small possibility of putting out the fire in the basement and saving these lives if someone runs into the building. The person running into the building would risk almost certain death. No one inside the building can reach the basement. Even if, in this case, we believe it impermissibly paternalistic to prevent a person from running into the building, it is quite another matter for us to facilitate this and give the person the means to do so. Clinical trials with excessive risks do not simply fail to prevent individuals from signing up out of a sense of faint heroism; they actively make this faint heroism possible. The example suggests a kind of proportionality condition that rules out facilitating excessive sacrifices.

The third standard then holds that clinical research is permissible if the additional risks taken up by the participants are neither excessive nor pointless. It rules out extreme acts of altruism and self-sacrifice. I call this the *moderate sacrifice standard*.

To summarize my argument so far, I have argued that morally permissible clinical research must meet one of the three standards I have set out. An important distinction exists between the favorable prospect standard and the other two standards. According to the favorable prospect standard, we can justify research without invoking social benefits. The research is justified the same way as clinical interventions are—purely by reference to the participants' self-interest. The latter two standards—the justifiable risk and moderate sacrifice standards—require, in different ways, social benefits to justify the research.

2. ARE CHALLENGE TRIALS EXCESSIVELY RISKY?

As mentioned earlier, challenge trials involve deliberately exposing consenting volunteers to the SARS-CoV-2 virus to observe whether the vaccine protects against infection. Importantly, this means that even volunteers in the control arm need to be infected. Opponents of challenge trials believe that the risk is too high. In terms of my framework, these opponents believe that challenge trials do not meet the moderate sacrifice standard and qualify as excessive risks.

Some challenge trials can fend off this challenge. Proposals for human challenge trials typically rely on selecting participants already at low risk from the virus. For young and healthy volunteers, participating is a moderate sacrifice. Proponents of challenge trials have often invoked comparisons with live kidney

donations.[17] The risks involved in kidney donations are clearly proportional to the aim of extending a kidney recipient's life. They also are proportional to the gains that challenge trials could bring.

More difficult are cases in which the mortality risk is high.[18] Consider the risk the virus poses to an octogenarian with multiple preexisting conditions and a weakened immune system. Can this be justified? For this, we need to have a closer look at the benefits of challenge trials. There is a chance that challenge trials will not yield any benefits at all. This might be, first, because the tested vaccine is a dead end. Second, this might be because challenge trials with younger and healthier volunteers would have been similarly informative. Third, field trials might have yielded a similarly fast resolution. Field trials were much faster than proponents of challenge trials feared, and the development of an artificial strain of the virus takes time. The expected value of challenge trials is, then, to some extent, driven by the fact that there is a smaller chance of very large gains. For *if* challenge trials with high-risk participants are not subject to any of the three limitations, then many harms due to the pandemic can be averted.

If the proportionality condition, which determines which risks count as excessive, is read purely in terms of expected value, then this could provide an endorsement even for challenge trials with high-risk participants. But this seems too extreme. Suppose researchers believed that if they experimented on a live lung that is removed from a patient, they might find the resolution to the pandemic immediately. They admit the chance is very, very small, and they admit the patient is almost certain to die. The potential benefits are enormous, so the expected value may appear to be proportional. But we should not succumb to such fanaticism. The moderate sacrifice standard should not be read as simply comparing the prospect of the patient with the expected value. High risks to a patient are excessive if there are only small chances of benefit from the research. This connects with the burning building analogy that I used earlier. What seems objectionable about the example is not the expected value—after all, very many people could be saved. What seems objectionable is the small chance of survival for those entering.

While this argument rejects challenge trials on high-risk patients, the earlier point stands that the risks to healthy and young volunteers are within the margin of moderate sacrifices.

17 Eyal, Lipsitch, and Smith, "Response to Cioffi"; and Jayaram, Sparks, and Callies, "Justifying the Risks of COVID-19 Challenge Trials."

18 This more radical proposal is raised by Savulescu and Wilkinson, "Extreme Altruism in a Pandemic."

3. LOW- VERSUS HIGH-DOSAGE CHALLENGES

Things might be different in the next pandemic. In the following, I specify a way for challenge trials to be adopted even if the risk appears initially as too high. Challenge trials are preceded by a dose escalation study that determines how much of a pathogen—what dosage—should be used to infect the participants. A low-dosage challenge trial is a challenge trial that uses a lower dosage than is conventionally used for such challenge trials. For example, consider a trial that uses a dosage corresponding to half of the conventional infection risk. Halving the risk of infection would already reduce the risk of serious harms by half. Without infection, no disease and no harm. But there is a second factor at play. For some diseases, the amount of virus that one is infected with has an impact on the severity of the ensuing disease. There is some evidence that SARS-CoV-2 is among these viruses, although the matter is still subject to scientific dispute.[19] Even if we discount for the provisional nature of this evidence, we should discount the risk by a factor of a little bit more than what is achieved through reductions in the infection risk alone. In the example used, the risk is then reduced by a bit more than half. But the low-dosage challenge could be run at an even lower dosage. In principle, we could reduce the risk as much as is needed to ensure that the moderate sacrifice standard is met.

The low-dosage challenge trial reduces the risk to participants by relying on an exposure that is less likely to infect individual participants. To yield statistically meaningful results, the low-dosage challenge trial needs a larger number of participants. Because a lower proportion of people will be infected in the control arm, researchers need a larger number of people in the control arm (and therefore also in the treatment arm). Nevertheless, this means that each participant faces a lower risk in the trial.

The low-dosage challenge trial should be distinguished from a volunteer lottery in which researchers randomize among volunteers before regular dosage exposure and take the odds prior to randomization as relevant.[20] Such a lottery can trivially reduce risks judged from the standpoint before participant selection. The key difference consists in the way the risk reduction is tied to the exercise of the researcher's agency. In a volunteer lottery, the researcher is performing an equally risky action at the time of exposure. The dice of the previous lottery have already been rolled, and the volunteers who are being exposed

19 For discussion, see Spinelli et al., "Importance of Non-Pharmaceutical Interventions in Lowering the Viral Inoculum"; Trunfio et al., "Lowering SARS-CoV-2 Viral Load Might Affect Transmission but Not Disease Severity in Secondary Cases," as well as Spinelli, Rutherford, and Gandhi, "Authors' Reply."

20 Steel, "Risk Dilution."

receive no safety benefit from the earlier lottery. However, in a low-dosage challenge, researchers perform a less risky action at the time of exposure. The intervention of the researcher is less risky. Exposure is the dice roll, and every volunteer stands a better chance of avoiding harm in the trial.

A volunteer lottery could be designed in order to select and expose at the same time.[21] The trial could be selecting participants at the same time as delivering the vial. But transforming a volunteer lottery into a simultaneous process serves no purpose other than to avoid moral liability. Joining the two processes runs together the risks from infection upon exposure and the risk of being selected for exposure. One risk, which is inherent to the treatment, is joined with another risk that is artificially created by the agent.[22] The low-dosage challenge is different. Exposure to the virus is inherently a chancy process. The only factor explaining the risk in the low-dosage challenge is the exposure to the virus. In other words, in the case of the volunteer lottery, we run a lottery to determine who receives a very risky treatment. By contrast, in a low-dosage challenge, we give a much less risky treatment to more people.

Reflections on the low-dosage challenge thus reveal two points. First, the low-dosage challenge is easier to justify than a regular challenge trial. Second, some form of challenge trial, a suitably low-dosage one, can be justified on grounds of the moderate sacrifice standard.

The risk reduction comes, however, at some price. In order to infer comparably good information from the trial, the number of infections needs to remain more or less constant.[23] With infections being commensurate to a high-dosage challenge, what might matter is the likelihood that there will be harms in the trial cohort. This depends on the exact increase in the number of volunteers and on the extent to which the risk of harm is decreased by a lesser exposure

21 I owe this challenge to a reviewer who pressed me to clarify how a low-dosage challenge differs from a volunteer lottery.

22 Johann Frick similarly argues for the decomposition test according to which what matters are the odds at each stage of agential intervention. He also highlights that artificially running together different stages by using a surrogate for agential intervention is a way to undermine the test, not to meet it. See Frick, "Contractualism and Social Risk," 210–12. See also Kamm, *Morality, Mortality*, 2:303.

23 Does this show that the low-dosage challenge serves no purpose after all? No. Each individual has been subjected to a much lower risk than they would have been in a high-dosage challenge. The comparison between the two is like a scenario in which a harm has to be distributed. A high-dosage challenge concentrates the risk of harm in few individuals; a low-dosage challenge disperses the risk of harm across more individuals. This makes the distribution of risks fairer. See Broome, "Fairness"; and Daniels, "Can There Be Moral Force to Favoring an Identified over a Statistical Life?" It can also be seen as a risky analog to Larry Temkin's "Disperse Additional Burdens View" (*Rethinking the Good*, ch. 3).

dosage. In a pessimistic scenario, a low-dosage challenge does little (if anything) to reduce overall harm. In the next section, I will look at a more extreme version of such a trade-off in which reducing the risk to individuals comes at the cost of increasing the risk that there will be harm in the cohort. If my arguments in favor of a restricted rollout are sound, then they also respond to any concern about the increased cohort size in a low-dosage challenge.

4. FROM SAFETY TESTING TO RESTRICTED ROLLOUT

At whichever level of dosage the challenge trial is performed, I endorsed the (near) consensus that challenge trials should be performed only with low-risk participants. However, if the vaccine is not tested on members of high-risk demographics, we have incomplete information about vaccine safety and need a bridge safety study. The problem is how to generalize from our test population to our target populations. There is no clear rule for how to deal with this generalization. For example, some countries like India insist that trials have to be performed on the local population before being released. For most other countries, the trial data from, for example, Brazil was deemed sufficient. Given that the effects of COVID-19 were quite different in different age groups, it is reasonable that testing on older people was needed to solidify our evidence of vaccine safety. A common and uncontroversial protocol for such bridge safety testing is the following:

> *Safety Testing*: A vaccine that has proven to be efficacious in a challenge study will be tested on persons from previously excluded groups under close safety monitoring. Assume testing will include approximately three thousand elderly persons. If the tests are successful, the vaccine will be rolled out universally.

Safety Testing requires the informed consent of all participants. No one doubts that Safety Testing, an established procedure for establishing that vaccines are safe before release, is permissible. But which standard does it meet? This question is important, as we shall see, because it determines whether social benefits are necessary in justifying the procedure. Can Safety Testing be justified on grounds of the favorable prospect standard, or, as in the case of challenge trials, do we need to appeal to social benefits? Safety Testing includes risks of harm to the individuals participating in the study. These are harms caused by either vaccine toxicity, increased exposure to SARS-CoV-2, or SARS-CoV-2 exposure with the background of a faulty vaccine that enhances disease severity. However, given that the test candidate has already been shown safe and efficacious in human studies, these risks are reduced. Moreover, participants would face increased risks of a SARS-CoV-2 infection in the absence of the test vaccine. The individual

benefits of the test vaccine are the possibility of longer protection from SARS-CoV-2. One might, therefore, believe that Safety Testing meets the favorable prospect standard and is in the rational self-interest of elderly volunteers.

However, this judgment is disputable. The risks are still partially uncertain, and the vaccine is still experimental. Safety information has not been gathered yet for older persons. Given these concerns about the still experimental vaccine, I will proceed on the assumption that the justification for Safety Testing needs to appeal to the social benefits to nonparticipants. In other words, Safety Testing meets the moderate sacrifice standard or the justifiable risk standard. Later, in section 5, I will explain how my argument changes if we do not need to appeal to social benefits to justify Safety Testing because Safety Testing meets the favorable prospect standard. The social benefits at stake include the eventual protection of large populations from the virus. The earlier the vaccine is ready and can reduce transmission rates, the greater the social benefits from the trial. The social benefits of the test vaccine, if successful and properly distributed, thus include thousands of saved lives.

A controversial alternative to Safety Testing that would cut time in the release of the vaccine is the following protocol:

> *Restricted Rollout*: A vaccine that has proven to be efficacious in a challenge study will be released to a restricted, yet large group of consenting persons under conditions of registration and close monitoring. The restricted rollout includes previously excluded groups. Assume a rollout to one million persons with approximately three hundred thousand elderly persons. If the monitoring is successful in that large group, the vaccine will be rolled out universally.

Restricted Rollout would make the vaccine available to a large population by declaring the vaccine "conditionally approved." Comparisons can be drawn with data from population-wide health care providers like the National Health Service or via samples from the nonvaccinated population.[24]

I now turn to my argument for the moral equivalence between Safety Testing and Restricted Rollout. In terms of the risks and benefits to individual participants, Restricted Rollout imposes the same or almost the same individual risks of harm on participants as Safety Testing. The vaccine itself is neither more nor less dangerous to individuals in either of the two protocols. The only relevant risk factors that may change are that Safety Testing provides for a better opportunity to teach participants about minimizing risks and that Safety Testing provides for

24 Eyal, Gerhard, and Strom, "Strengthening and Accelerating SARS-CoV-2 Vaccine Safety Surveillance," 3456.

better monitoring and timely detection of adverse effects of the vaccine. Monitoring means that adverse effects are more likely to be detected in participants, and possible interventions can be taken. These interventions can range from the suspension of follow-up vaccine shots to hospitalization. This reduces the risks to participants. Close monitoring is easily feasible in Safety Testing, given the small number of individuals involved. Operationally, monitoring the larger participant group is more difficult in Restricted Rollout than in Safety Testing.

However, Restricted Rollout fares *better* than Safety Testing in another respect that is relevant for the timely detection of adverse effects. Because of its larger size, Restricted Rollout generates better safety information than Safety Testing, and that information can be used to intervene in the trial when necessary. The larger trial size allows researchers to detect rare vaccine side effects. Writing about drug safety, Brian Strom points out that traditional drug safety protocols typically do not detect adverse effects that occur in frequencies of 1 in 1,000. Even larger trials like Safety Testing would struggle to detect adverse outcomes that have frequencies of less than 1 in 3,333.[25] Such adverse side effects are not uncommon for drugs or vaccines. For comparison, the high-profile example of blood clots following coronavirus vaccinations that have paused vaccinations in various countries has been estimated at the time at a frequency of 1 in 100,000.[26]

So, while Restricted Rollout has less individual monitoring, it also has the capacity to detect a greater variety of adverse effects that can allow researchers to intervene and minimize the risk to participants. On balance, it is therefore not clear that Restricted Rollout produces greater risks to participants than Safety Testing. A reasonable estimate on which I will proceed is that the two ways in which Safety Testing and Restricted Rollout reduce risks even out. It is straightforward that Restricted Rollout also provides the same individual benefits to each participant as Safety Testing does. In the case of an efficacious and safe vaccine, both protocols offer earlier added protection from SARS-CoV-2 to each participant.

The two protocols differ, however, in the social benefits to nonparticipants as well as in the number of participants. The social benefits are larger in Restricted Rollout for two reasons. The first is related to the earlier point about the increased power to detect rare adverse effects. The vaccine, when tested in Restricted Rollout, will, therefore, be safer upon eventual release than a vaccine tested by means of Safety Testing. In addition, just as researchers are better equipped to observe

25 Strom, "How the US Drug Safety System Should Be Changed," 2072. The second calculations are based on Eyal, Gerhard, and Strom, "Strengthening and Accelerating SARS-CoV-2 Vaccine Safety Surveillance," 3455.

26 Cines and Bussel, "SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia," 2255.

rare side effects, they are better equipped to gain information about the effects of the vaccine on more fine-grained demographics. The increased abilities for such fine-grained observations can make the vaccine safer in the long run by providing more detailed safety information. In addition, Restricted Rollout produces larger social benefits by cutting short the pandemic and preventing loss of life and misery from the direct and indirect effects of the pandemic.

In Safety Testing, the benefits are jointly produced by the efforts of a smaller group. In Restricted Rollout, larger benefits are jointly produced by the efforts of a larger group. The right comparison for the benefits to nonparticipants is the *marginal* social benefit—that is, the benefits that are possible due to increased participation in the testing process. This is in line with what the moderate sacrifice standard demands. To assess whether we can justify exposing additional volunteers to the risk, we need to know whether including more volunteers will also lead to sufficient benefits or whether their contribution would be superfluous or an instance of faint heroism. We could not appeal to altruistic reasons to justify the inclusion of additional test candidates if we could achieve the same (or almost the same) altruistic benefit without these test candidates. A similar argument holds for the justifiable risk standard. An individual could raise a complaint against a risk imposition if that risk imposition does not produce enough marginal benefits to nonparticipants. In such a case, the complaint against the additional risk imposition could outweigh any possible complaint against the withholding of benefits to nonparticipants. In other words, individuals may be required to bear the burden of a risk imposition for the sake of greater benefits to nonparticipants, but without such benefits to nonparticipants, there is no consideration that justifies the risk imposition.

Even if we focus only on the marginal social benefits of the wider release in Restricted Rollout as opposed to Safety Testing, the marginal social benefits will be very substantial in Restricted Rollout. The increased size of the testing population produces, if the vaccine is safe and efficacious, greater benefits in terms of earlier reduction of transmission rates and delivers more fine-grained information about adverse effects from vaccine usage. We need additional participants to produce these benefits. The protocol of Restricted Rollout can make a large impact on transmission rates and generate better safety information only because it releases the vaccine to a large group. Even though estimating the social benefits is difficult, it is reasonable to assume that the benefits produced by the added test population meet the moderate sacrifice standard or perhaps the justifiable risk standard.

The real difference between the two protocols is then neither the individual effects on participants nor the marginal benefits to nonparticipants. The real difference is simply the scale of the risk imposition (and, thus, the scale of *total*

social benefits to nonparticipants). Safety Testing subjects a smaller number to the risk; Restricted Rollout subjects a larger number to the risk. Should this difference matter?

I believe it should not. We can give the following argument why the scale of the risk imposition does not matter in itself. The risk imposition on one group of three thousand volunteers is justifiable to each of them. The risks are outweighed by benefits to themselves and by benefits to nonparticipants. Either this means that the risk imposition itself is not morally problematic and justifiable to them, or this means that we can permissibly appeal to their altruistic motivations. In either case, no one person in the group of three thousand volunteers would be wronged by the risk imposition. Now, take a second group of three thousand volunteers. Here, too, the risk imposition is justifiable to them either in virtue of their self-interest or our appeal to their altruistic motivations. The risks are independent; testing both the first and second groups creates no adverse effect on any one person. The argument repeats until we reach all three hundred thousand volunteers.

If the risk imposition to the first three thousand volunteers was justifiable to each one of them and wronged none of them, then it has to be justifiable to all other persons who are affected in the very same way. If no one would be wronged if the risk was only imposed on their group of three thousand, then who is wronged in the larger group? Individual objections to the risk imposition cannot depend on the fact that the decision-maker is doing something to *other* people, which is perfectly permissible.

This argument can be generalized. In its essence, it holds that the permissibility of risks in clinical research is invariant to scale. As long as scaling up produces the same individual risks, individual benefits, and marginal social benefits, it is permissible to perform the research on the larger group as well. I will call this the *scale invariance argument*. The scale invariance argument can also explain why the cohort effect for low-dosage challenges is not problematic. Scale invariance means that the number of participants can be increased as long as the marginal social benefits are sufficiently high. This is the case for a low-dosage challenge trial.

5. Risks and Benefits to Participants and Nonparticipants

It is helpful to compare my argument to a similar argument made by Johann Frick, among others.[27] According to this argument, risks that are in an

27 Frick, "Contractualism and Social Risk," 186–88; Dougherty, "Aggregation, Beneficence, and Chance," 8–11; Hare, "Should We Wish Well to All?" 455–67.

individual's self-interest can permissibly be scaled up. If the risk is in the rational self-interest of various persons and it would be permissible to impose the risk on each person taken separately, then it should also be permissible to impose the risk on all persons taken together. My scale invariance argument is structurally similar but differs insofar as it does not require that the risks are in the rational self-interest of each individual. Instead, my argument holds that if the individual risk is justifiable because of considerations of self-interest *and* marginal social benefits taken together, then it is justifiable to impose the risks all at once. The difference between the two arguments is important for two reasons. First, it more satisfactorily explains why we permit the risks of experimental vaccines in controlled testing environments. The fact that we regard the vaccines as experimental indicates that we are not convinced there is a large-scale self-interested argument in favor of the vaccines. Second, and relatedly, the combination of self-interest and marginal social benefit can explain why my argument need not necessarily imply an even more radical option that dispenses with the post-challenge safety study.

> *Unrestricted Rollout*: A vaccine that has proven to be efficacious in a challenge study will be released to any person who wishes to be vaccinated.

Restricted Rollout already achieves very large social benefits in terms of shortening the COVID-19 pandemic by several months. The proposed protocol contemplates a universal rollout once short-term outcomes have been analyzed. Unrestricted Rollout, or skipping the safety bridge study, makes safety monitoring very difficult. This could have additional benefits if everything goes well, but it also comes with corresponding risks. This shows that my revised argument that relies on marginal social benefits is sensitive to the scale of the risk imposition in one sense. The argument is sensitive to considerations regarding the necessity of imposing these risks. Scaling up the risk does not guarantee that social benefits will be scaled up at the same rate. Only when scaling up the risk means that all relevant factors can be scaled up is it permissible to proceed with the risk imposition for the larger group.

What if, contrary to my assumption so far, such benefits are not, in fact, necessary? Perhaps it is the case that the individual benefits outweigh the individual risks. In future pandemics, there might be some vaccines or medicines for which this is the case. These trials would meet what I described as the favorable prospect standard. Does my scale invariance argument, together with the assumption that the favorable prospect standard is met, entail that Unrestricted Rollout is morally permissible (or even required) for such trials?

Meeting the favorable prospect standard means that taking the vaccine is in the rational self-interest of those who wish to take it. Unrestricted Rollout

means that everyone for whom this is the case is allowed to access the vaccine. Therefore, provided the favorable prospect standard is met, any objection to Unrestricted Rollout cannot rest on paternalism. Any objection to Unrestricted Rollout would have to be based on effects on nonparticipants. There are two such pertinent considerations. Both of these are empirical, and their strength will depend on the details of the vaccine in question.

The first consideration is possible effects that such a policy can have on public trust in vaccines. Dispensing with a safety bridge study, as Unrestricted Rollout effectively does, deviates markedly from our ordinary process of vaccine certification. It is possible that this is acceptable to the public, given the unusual conditions of a pandemic. But there is also a danger that this undermines trust in vaccine and drug certification. If the latter is the case, then Unrestricted Rollout would be causing long-term harm for short-term gains.[28] The second effect on nonparticipants is the possible risk of increased pathogen exposure. Some vaccine candidates have the reverse effect of increasing exposure to the pathogen. The protocol of Restricted Rollout registers participants and monitors. It also makes it easier to isolate those participating in the rollout as much as possible from the rest of society. Unrestricted Rollout does not and can, therefore, create additional risks for nonparticipants due to an increased spread of pathogens.

Again, whether these effects are actually present in the case of any given candidate vaccine depends on circumstances and difficult empirical questions. (The same holds, as I outlined earlier, for similar concerns about Restricted Rollout.) For some candidate vaccines, these considerations will be weighty enough. For others, they will not. If neither of these adverse effects is weighty enough and if the vaccine meets the favorable prospect standard, then my argument entails that the more radical option of Unrestricted Rollout is permissible. But in such a case, it is also hard to see what would be wrong with this implication. This would be a vaccine that is in the rational self-interest of many persons and does not create negative externalities for nonparticipants. What possible reason could we have for depriving some individuals of taking a medical intervention that is in their best interest without harming third parties?

28 Richard Yetter Chappell doubts this argument on grounds that trust considerations would mean refraining from aiding innocent people now for the sake of protecting others—namely, those who distrust vaccines—from self-inflicted harm ("Pandemic Ethics and Status Quo Risk," 69–70). However, as I put it in the main text, the crux of the argument is that decline in trust in vaccines has long-term consequences. Trust in vaccines often stems from a trust in regulatory mechanisms and institutions. If trust in vaccines and the medical establishment generally declines, then everyone loses out because infectious diseases can spread more easily.

6. SCALE INVARIANCE AND COHORT RISKS

One further aspect changes with the scale of the risk imposition. It becomes more likely that there will be harm *ex post* the risk imposition in the proposed protocol. Although the risk to each individual is the same whether she is in the smaller or larger protocol, in the smaller protocol, there is a lower likelihood that a participant will be harmed. Some critics of challenge studies appear to be concerned mainly with the risk to the trial cohort.[29] Does this constitute an objection to my argument that the permissibility of risk impositions should be invariant to mere scaling up?

A critic might argue that my argument has only established that no individual would be wronged by either the low-dosage challenge or Restricted Rollout. But this critic would go on to argue that whether an action wrongs any one individual is not sufficient to establish that the action is not wrong. Actions can be wrong without wronging any single individual. One way to spell this out is by embracing pluralism about moral rightness. The argument that I have given so far captures one important wrong-making feature of an act. My argument has shown that this wrong-making feature is not present in the cases I discussed. But loss of aggregate well-being could be another wrong-making feature of an act. The low-dosage challenge or Restricted Rollout might be wrong for this reason. Promoting aggregate well-being, under this understanding, is a *pro tanto* reason in favor of an action.[30]

A second way to spell this out gives a less prominent role to aggregative and impersonal considerations. According to this way, in almost all cases of interpersonal morality, the question whether or not an action is justifiable to each person determines the moral permissibility of the action. Interpersonal morality can be defined as governing those cases in which only the effects on persons are morally relevant. Only in some cases of interpersonal morality can this be overridden by exceptional circumstances. A great loss of life could be such an exceptional circumstance.[31] This objection would most naturally focus on the fact that the risks in the low-dosage challenge and Restricted Rollout appear to be positively correlated. In the unlikely scenario of great toxicity, this

29 See Corey et al., "A Strategic Approach to COVID-19 Vaccine R&D"; Deming et al., "Accelerating Development of SARS-CoV-2 Vaccines."

30 This way of spelling out pluralism is broadly in line with Johann Frick's pluralism about rightness. Frick does not use the language of "wronging." However, he makes clear that both wrong-making features are parts of "interpersonal morality," which deals with our duties to other persons; see Frick, "Contractualism and Social Risk," 218–23.

31 This is the view that I tentatively favor. For an excellent discussion of the tension between personal and impersonal considerations, see Nagel, *Mortal Questions*, ch. 5.

would affect a great number of individuals at once. The worst-case scenario is worse if we adopt these protocols.

But to move from the fact that in these protocols there is a higher likelihood that volunteers will be harmed to the conclusion that these protocols are wrong (even if not wronging any one) is too quick. The reason is that both the low-dosage challenge and Restricted Rollout save the lives of many nonparticipants compared to the slower, established protocols. The quicker release of the vaccine means that the COVID-19 pandemic will be shortened, and many lives will be saved. The net effect is going to be one of more statistical lives saved rather than lost. The moral catastrophe of a large number of persons dying is already happening in an ongoing pandemic, putting concerns about prioritizing the worst-case scenario in perspective.

The objection to the proposed protocols would have to be that it is more likely that lives of *participants* will be lost. It is not unusual in research ethics to be especially concerned with the risk to trial participants, largely because this risk is actively caused by the researchers. This is particularly evident in the case of challenge trials in which researchers deliberately infect, but this is also the case in field trials in which there is the risk that the vaccine administered by researchers enhances the severity of the existing disease.

There are indeed good grounds for special concern with research subjects. The most natural concern is that the risk imposition wrongs an individual or violates their rights. If we can save a larger number only by violating the rights of a smaller number of people, then we may not do so. This explains why active harm caused by researchers is prioritized heavily over harm researchers passively allow. But my whole argument rejects the view that any single person is wronged. I have not made the simple consequentialist argument that challenge trials avert more harm than they cause. Rather, I argued that the risk impositions inherent in the low-dosage challenge and the Restricted Rollout do not wrong any individual, nor do they violate any of their rights. The objection currently under consideration is different. It relies on the idea that individualized and interpersonal morality does not capture everything of relevance. The objection pushes us to consider collectivized and impersonal morality. Our concern may be, for example, the loss of aggregate well-being. But if *this* is our concern, then we do not have any good reason to ignore the effects on nonparticipants. There cannot be an objection that, for example, Restricted Rollout compromises aggregate well-being when it, in fact, saves more lives than Safety Testing would.

The central point of my argument is not limited to the COVID-19 pandemic. It also applies to other health emergencies or future pandemics in which faster testing protocols would avert great harms to public health. There are ways to

avert such harm and save many lives without compromising the value of each individual or sacrificing some for the sake of the greater good. It is one of the cases in which deontological and consequentialist considerations do not pull in opposite directions.[32]

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