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Justifying the risks of COVID-19 challenge trials: The analogy with organ donation

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Abstract

In the beginning of the COVID pandemic, researchers and bioethicists called for human challenge trials to hasten the development of a vaccine for COVID. However, the fact that we lacked a specific, highly effective treatment for COVID led many to argue that a COVID challenge trial would be unethical and we ought to pursue traditional phase III testing instead. These ethical objections to challenge trials may have slowed the progress of a COVID vaccine, so it is important to evaluate their merit. One common way of doing so is to make an analogy to other social practices that are relevantly similar and which we currently sanction. We submit that non-directed live organ donation (NDLOD) is a promising analogy. After arguing that the risks to volunteers for each activity appear similar, we explore potential disanalogies that would undermine the comparison. We note that there are differences in both the kind and certainty of benefit secured by NDLOD compared to challenge trials. We conclude these differences are insufficient to make NDLOD permissible and challenge trials impermissible. Ultimately, if we think the risks associated with NDLOD are ethically permissible, then we should think the same of the risks associated with COVID challenge trials.

KEYWORDS
clinical trials, COVID-19, human challenge trials, organ donation, research ethics

1 | INTRODUCTION

Human challenge trials—where research participants are deliberately exposed to pathogens so that researchers can study the progression of a disease—have played an essential role in the development of interventions to prevent and treat smallpox, peptic ulcers, cholera, yellow fever, and a host of other diseases. In the beginning of the current pandemic, researchers and bioethicists called for human challenge trials to hasten the development of a COVID vaccine.[1] Over 38,000 people volunteered for such trials, where they would be exposed to the novel coronavirus after receiving either an experimental vaccine or a placebo.[2] Advocates claimed that COVID human challenge trials could help researchers show the effectiveness of candidate vaccines more quickly and with smaller numbers of human subjects than traditional phase III studies.

However, the fact that we lacked (and still lack) a highly effective treatment[3] for COVID led many prominent physicians and

[1]Eyal, N., Lipsitch, M., & Smith, P. G. (2020). Human challenge studies to accelerate coronavirus vaccine licensure. *The Journal of Infectious Diseases*, *221*(11), 1752–1756. https://doi.org/10.1093/infdis/jiaa152; Plotkin, S. A., & Caplan, A. (2020). Extraordinary diseases require extraordinary solutions. *Vaccine*, *38*(24), 3987–3988. https://doi.org/10.1016/j.vaccine.2020.04.039; Chappell, R.Y. & Singer, P. (2020, 27 April). Opinion | Pandemic ethics: The case for experiments on human volunteers. The Washington Post. https://www.washingtonpost.com/opinions/2020/04/27/pandemic-ethics-case-experiments-humanvolunteers/ (accessed July 4, 2020)

[2]1 Day Sooner. (n.d.). https://1daysooner.org (accessed December 12, 2020).

[3]As of November 2020, there are some treatments for COVID. The FDA approved the antiviral medication remdesivir and granted emergency use authorization to two monoclonal antibodies treatments. Patients are also treated with oxygen support and steroids. But none of these treatments is as effective as treatments we have for volunteers in other challenge trials, such as those for malaria, so the question remains as to whether challenge trials are permissible in the absence of a specific, highly effective treatment.

bioethicists to argue that a COVID challenge trial would be unethical.[4] They argued that our norms do not allow researchers to expose participants to diseases that threaten their lives or long-term health interests.[5] Such risks were considered too high, even if subjects volunteered to accept them. After roughly a year of delay, the first challenge trial began in the UK in late February 2021. It is hard to say for sure whether an earlier and more widespread embrace of challenge trials would have sped up the development of a COVID vaccine. But, we can easily imagine a case where challenge trials would hasten vaccine development: one where, for instance, the vaccines' phase III trials did not coincide with a spike in infections. So, it is important to evaluate the objections to COVID challenge trials and to see whether we can make a case for the permissibility of deliberately exposing research subjects to the novel coronavirus in order to hasten vaccine development.

In discussions about risk in biomedical research, it is common to make analogies to other social practices where individuals are permitted to assume high levels of risk. Advocates for challenge trials suggest that the risks and benefits of COVID challenge trials compare favorably to the risks and benefits of skydiving, volunteer firefighting, serving in the military, or donating an organ.[6] If we permit individuals to take on risk in these cases, they argue, we should be willing to let them take on similar risks in biomedical research.

This argumentative strategy has the benefit of grounding the discussion in broadly empirical issues.[7] If we can find an activity with a similar structure to challenge trials, where individuals take on similar risks to secure similar benefits for others, and where that activity is generally considered morally acceptable, that will constitute a good prima facie case for the permissibility of COVID challenge trials.[8] Of course, there are other considerations besides risk levels that determine the permissibility of any particular challenge trial: Are the participants sufficiently informed about the risks? Are the participants selected in a way that avoids exploitation?[9] Will the trial provide adequate medical care for participants? Is the study well designed and based on an appropriately representative sample? Satisfactory answers to these questions would be required before a challenge trial would be permissible, all things considered.[10] Here we focus narrowly on whether the tolerability of the risks justifies the research community in conducting human challenge trials.

As with all analogical reasoning, the crux is finding a good analogy—in this case, an activity that is sufficiently like proposed COVID challenge trials to ground an argument about the propriety of such trials. We submit that non-directed live organ donation[11] (NDLOD) is the most promising since it brings similar risks and benefits and is structurally similar to participation in a challenge trial. Both are voluntary and, unlike skydiving, altruistic—that is, both donors participating in NDLOD and COVID challenge trial participants are, generally, taking on risk for altruistic reasons. Unlike firefighting or military service, both organ donation and participation in a challenge trial take place in a medical context, where there is a knowledge asymmetry between the person imposing the risk and the person assuming it. In both cases, participants do not have control throughout the risky activity, as they do while firefighting or serving in the military.[12]

There are, of course, several potential disanalogies between NDLOD and COVID challenge trials. This article will focus on two in particular—the "kind" and "certainty" of the benefits—but there are two others that we briefly address here. First, one may argue that, while there are other ways to test effective COVID vaccines without deliberately exposing participants to risk—namely, non-challenge phase III trials—there is no other way to get the benefits of organ transplants without the risks of organ donation. We should, therefore, sanction a higher level of risk in NDLOD than in challenge trials. This seems initially plausible, but a closer look reestablishes the analogy. It is true that there are other ways to test COVID vaccines, but the benefit of challenge trials is not just testing the vaccine; it is testing the vaccine faster. Non-challenge phase III trials would not

[4]Rosenblatt, M. (2020, June 23). Challenge trials aren't the answer to a speedy Covid-19 vaccine. *STAT*. https://www.statnews.com/2020/06/23/challenge-trials-live-coronavirus-speedy-covid-19-vaccine/ (accessed July 1, 2020); Macklin, R. (2020, June 15). Human challenge studies for Covid-19 vaccine: Questions about benefits and risks. *The Hastings Center*. https://www.thehastingscenter.org/human-challenge-studies-for-covid-19-vaccine-questions-about-benefits-and-risks/ (accessed July 1, 2020); Branswell, H. (2020, May 1). Infect volunteers with Covid-19? A proposal lays bare a minefield of issues. *STAT*. https://www.statnews.com/2020/05/01/infect-volunteers-with-covid-19-in-the-name-of-research-a-proposal-lays-bare-a-minefield-of-issues/ (accessed May 27, 2020); Nam, R. (2020, April 24). Controversial idea to speed coronavirus vaccine gains ground. *The Hill*. https://thehill.com/policy/healthcare/494417-controversial-idea-to-speed-coronavirus-vaccine-gains-ground (accessed July 1, 2020).

[5]It is not entirely clear whether current norms, in fact, make it impermissible to expose participants to life-threatening diseases. Some argue that intentional infection may be permissible, as long as certain conditions are met. See: Selgelid, M., & Jamrozik, E. (2018). Ethical challenges posed by human infection challenge studies in endemic settings. *Indian Journal of Medical Ethics, III*(4), 274–278.

[6]Eyal et al., op. cit. note 1; Miller, F. G., & Joffe, S. (2009). Limits to research risks. *Journal of Medical Ethics*, *35*(7), 445–449. https://doi.org/10.1136/jme.2008.026062; London, A. J. (2006). Reasonable risks in clinical research: A critique and a proposal for the Integrative Approach. *Statistics in Medicine, 25*(17), 2869–2885. https://doi.org/10.1002/sim.2634

[7]This kind of reasoning is common in bioethics. While there are differences, this analogical reasoning is very similar to casuistry. Beauchamp, T. L. (2003). Methods and principles in biomedical ethics. *Journal of Medical Ethics*, *29*(5), 269–274. https://doi.org/10.1136/jme.29.5.269

[8]London, op. cit. note 6.

[9]For instance, if challenge trial participants were paid, we might worry that people are participating out of need, rather than altruism. To maintain the analogy with NDLOD, we assume here that challenge trial participants, like NDLOD volunteers, are not paid for participating.

[10]For additional recommendations about how to design morally acceptable challenge studies, see Binik, A. (2020). What risks should be permissible in controlled human infection model studies? *Bioethics*, *34*(4), 420–430.

[11]Non-directed live organ donation occurs when a donor, who is still living, donates an organ to someone they do not know, on the basis of need and compatibility alone. According to the US Department of Health and Human Services, only ~1–3% of living organ donations (predominantly kidney and liver) are non-directed. While NDLOD of kidneys is fairly well accepted within the medical community, some are less accepting of NDLOD of livers because of the increased risk to donors. Still, non-directed live organ donation of both kidney and liver tissue is accepted in the medical community. U.S. Department of Health and Human Services. (n.d.). Ethics - Living non-directed organ donation - OPTN. https://optn.transplant.hrsa.gov/resources/ethics/living-non-directed-organ-donation/ (accessed July 9, 2020).

[12]London, op. cit. note 6.

provide that degree of benefit. Similarly, we can say that, while there are other ways to get some degree of the benefits of organ donation—we can treat kidney or liver problems with dialysis or drugs instead of transplants—there is no other way to get the same degree of benefits. In both cases, then, there are alternatives that would not expose participants to risk but would also result in more deaths—either from less effective treatment or a slower vaccine delivery. In neither case can we get the *same* benefits without exposing participants to risk.

Second, one might worry that, if any challenge trial volunteer suffered adverse effects, the public would attribute those effects to the vaccine, rather than to COVID. Given the importance of vaccine confidence to public health, we might therefore worry more about the risks of challenge trials than of organ donation. We agree that this is a potential concern, but without empirical data on public perception of challenge trials, it is hard to know whether it requires us to sanction different levels of risk. It is worth further study: to what extent would the public associate the effects of the virus with the effects of vaccines in challenge trials?[13]

In the remainder of the paper, we argue that there is a strong analogy between COVID challenge trials and NDLOD. In Section 2, we point out that the risks of performing live organ donation and of conducting a COVID challenge trial are similar. In Sections 3 and 4, we consider two potential disanalogies involving the kind of benefit involved in each activity and the confidence we have in securing that benefit. We argue that these disanalogies are not sufficient to make NDLOD permissible and COVID challenge trials impermissible. We, therefore, conclude that, if the medical community is willing to participate in activities with risks and benefits similar to those of NDLOD, they should be willing to participate in activities—like COVID challenge trials—that carry similar risk/benefit profiles.

2 | RISKS OF LIVE ORGAN DONATION VS. CHALLENGE TRIALS

Despite the widespread death and suffering caused by COVID, advocates for challenge trials argue that the risks to participants would be comparable to the risks of live organ donation.[14] This is, in large part, because challenge trials would only recruit volunteers who were at the lowest risk of death or severe complications from COVID—people in their twenties with no other health problems—and provide them with the best possible medical care. Among this group and under those conditions, the risks of the two activities seem to be similar.

While the overall COVID infection fatality rate (IFR) across all populations is around 0.68%,[15] the IFR is considerably lower for younger people. Recent meta-analyses and models put the number between 0.01% and 0.04% for 25–29 year olds.[16] This fatality rate is comparable to the fatality rate from kidney donation of 0.01%,[17] and considerably lower than the fatality rate for liver donation, which a systematic review estimates at 0.2%.[18] It is harder to compare the potential complications from COVID and organ donation, both because they are different in kind and because there are fewer systematic studies. But, a few studies suggest that the rate of hospitalization from COVID for people 20–29 is between 0.6–1.0%,[19] while "major" complications affect a higher percentage of organ donors: 3–6% of kidney and 1.1% of liver donors.[20]

Moreover, the risks to challenge trial volunteers are likely to be lower than these studies suggest. The studies do not exclude young people with comorbidities, as challenge trials would, nor do they factor in the benefits of having continuous health monitoring and on-site care.[21]

Opponents may still worry that we do not know enough about the long-term risk from COVID. Perhaps young people who recover now will still suffer long-term consequences. That is certainly a concern, but the situation is not much better with live organ donation. There are few studies on the long-term health and quality of life of kidney and liver donors.[22] However, some studies suggest serious

[13]We thank an anonymous reviewer for these two potential disanalogies.

[14]Eyal, N., Lipsitch, M., & Smith, P. G. (2020). Response to Cioffi. *The Journal of Infectious Diseases*, *222*(1), 169–170. https://doi.org/10.1093/infdis/jiaa217

[15]Meyerowitz-Katz, G., & Merone, L. (2020). A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *International Journal of Infectious Diseases*, *101*, 138–148. https://doi.org/10.1016/j.ijid.2020.09.1464

[16]Brazeau, N., Verity, R., Jenks, S., Fu, H., Whittaker, C., Winskill,P., Dorigatti, I., Walker, P., Riley, S., Schnekenberg, R. P., Heltgebaum, H., Mellan,T., Mishra, S., Unwin, H., Watson, O., Cucunuba Perez, Z., Baguelin, M., Whittles, L., Bhatt, S., … Okell, L. (2020). Report 34: COVID-19 infection fatality ratio: Estimates from seroprevalence. *Imperial College London*. https://doi.org/10.25561/83545; O'Driscoll, M., RibeiroDos Santos, G., Wang, L., Cummings, D. A. T., Azman, A. S., Paireau, J., Fontanet, A., Cauchemez, S., & Salje, H. (2021). Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature*, *590*, 140-145. https://doi.org/10.1038/s41586-020-2918-0; Levin, A. T., Hanage, W. P., Owusu-Boaitey, N., Cochran, K. B., Walsh, S. P., & Meyerowitz-Katz, G. (2020). Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. *European Journalof Epidemiology*, *35*(12), 1123-1138. https://doi.org/10.1007/s10654-020-00698-1. PMID: 33289900; PMCID: PMC7721859.

[17]Kortram, K., Ijzermans, J. N. M., & Dor, F. J. M. F. (2016). Perioperative events and complications in minimally invasive live donor nephrectomy: A systematic review and meta-analysis. *Transplantation*, *100*(11), 2264–2275. https://doi.org/10.1097/TP.0000000000001327

[18]Middleton, P.F., Duffield,M., Lynch, S.V., Padbury, R.T.A., House, T., Stanton, P., Verran, D., Maddern,G. (2006). Living donor liver transplantation—Adult donor outcomes: A systematic review. *Liver Transplantation*, *12*(1), 24–30. https://doi.org/10.1002/lt.20663

[19]Jamrozik, E., & Selgelid, M. J. (2020). COVID-19 human challenge studies: Ethical issues. *The Lancet Infectious Diseases*, *20*(8), E198-E20. https://doi.org/10.1016/S1473-3099(20)30438-2

[20]Kim, P. T. W., & Testa, G. (2016). Living donor liver transplantation in the USA. *Hepatobiliary Surgery and Nutrition*, *5*(2), 133–140. https://doi.org/10.3978/j.issn.2304-3881.2015.06.01; Lentine, K. L., & Patel, A. (2012). Risks and outcomes of living donation. *Advances in Chronic Kidney Disease*, *19*(4), 220–228. https://doi.org/10.1053/j.ackd.2011.09.005

[21]Eyal et al., op. cit. note 1.

[22]Sterkenburg, A., Kulu, Y., Mieth, M., Sommerer, C., Zeier, M., Mehrabi, A., Büchler, M., & Hoffmann, K. (2020). Long-term surgical outcome and risk factors in living kidney donors. *Transplantation Proceedings*, *52*(3), 722–730. https://doi.org/10.1016/j.transproceed.2019.12.044; Poggio, E. D., & Reese, P. P. (2018). The quest to define individual risk after living kidney donation. *Annals of Internal Medicine*, *168*(4), 296–297. https://doi.org/10.7326/M17-3249; Dew, M. A., Butt, Z., Humar, A., & DiMartini, A. F. (2017). Long-term medical and psychosocial outcomes in living liver donors. *American Journal of Transplantation*, *17*(4), 880–892. https://doi.org/10.1111/ajt.14111; Humphreville, V. R., Radosevich, D. M., Humar, A., Payne, W. D., Kandaswamy, R., Lake, J. R., Matas, A. J.,Pruett, T. L., & Chinnakotla, S. (2016). Longterm health-related quality of life after living liver donation. *Liver Transplantation*, *22*(1), 53–62. https://doi.org/10.1002/lt.24304

long-term consequences: 8.4% of kidney donors suffer serious complications and 1.1% of liver donors end up with lasting disability.[23] Of course, the fact that we allow organ donation under these circumstances does not necessarily mean we should allow COVID challenge trials—perhaps we should reject both. But, if we are willing to tolerate the risks and uncertainty of organ donation, then we have a prima facie case for tolerating the risks of COVID challenge trials.

While the risks appear similar, there are two potentially relevant differences between NDLOD and COVID challenge trials. In the following section, we compare the kind of benefit each activity is expected to secure. In the next, we compare the certainty we have in securing that benefit.

3 | THE KIND OF BENEFIT

Consider first the *kind* of benefit potentially conferred by challenge trials compared to non-directed live organ donation. While organ donors potentially provide a great benefit to one individual (the organ recipient), challenge trial volunteers have the potential to help eliminate a small risk of infection to a larger population. Because of this difference, one may argue, we should permit volunteers to take on more risk in NDLOD than in COVID challenge trials.

From a purely consequentialist perspective, this difference would not be significant. A strict consequentialist relying upon an expected utility calculation would see no difference between certainly saving one person's life and eliminating a 1% risk of death for 100 people. Both courses of action can be expected to save one life, and so both courses of action are equally valuable from the consequentialist point of view.

However, for some non-consequentialists, the difference between NDLOD and challenge trials raises concerns. According to what we can call the "competing claims" theory of morality, morality requires us to recognize the competing claims of individual moral agents rather than aggregating the claims of many.[24] On this view, it is unethical to aggregate the trivial claims of many in such a way that they swamp the vitally important claims of the few. For instance, some consequentialists think that if we can choose only between curing a large group of people of their minor headaches, on the one hand, and saving a person's life, on the other hand, there is some number of headaches such that we should cure the group rather than save the one life.[25] It is exactly this kind of interpersonal aggregation that is rejected according to the competing claims model. Saving a group from minor headaches and saving an individual's life are simply different *kinds* of benefit and are thus not comparable—numbers notwithstanding.[26]

Proponents of the competing claims model might argue that, while we can justify organ donors taking on a particular amount of risk by pointing to the recipient who is likely to benefit greatly, we can't justify the same amount of risk for challenge trial volunteers. Rather, it would appear impermissible on the competing claims model to allow challenge trial volunteers to take on significant risk in order to slightly reduce the risk of morbidity for a much larger group.

The competing claims model captures something important about morality. But whatever the difference between the benefits produced by NDLOD and challenge trials, it is not the same as the difference between curing headaches and saving lives. Both NDLOD and challenge trials can be expected to significantly reduce the risk of death or serious injury—the former can be expected to significantly reduce a nearly certain risk of death to one individual and the latter can be expected to significantly reduce a lower risk of death to many individuals. These are different, to be sure, but they aren't fundamentally different *kinds* of benefits. Both kinds of benefits are providing a reduction in risk of death, and both can be reliably predicted to save lives (as we argue in the next section).

Challenge trials boil down to subjecting individuals to the infection fatality risk in order to save the global population from the population fatality risk. Advocates of the competing claims model might balk at allowing individuals to take on a 0.03% risk of death in order to eliminate a 0.003% risk of death for 10 others. They might even balk at allowing an individual to take on a 0.03% risk of death in order to eliminate a 0.003% risk to 100 others. But while the strength of individual claims certainly matters from a moral point of view, so too does human well-being. And, of course, if the challenge trials are successful, we eliminate a significant risk to the entire global population, sooner than we otherwise would have. The widespread reduction in risk of death that could be generated by accelerating vaccine development should be enough to outweigh worries about allowing a small group of volunteers to take on significant risks, even for supporters of the competing claims model of morality.

Moreover, if we imagine things from some future perspective, where the risks to challenge trial participants and to the general population have resolved (or failed to resolve) into actual harms, we can see that the kind of benefit secured by NDLOD and challenge trials are the same: a reduction in death and morbidity. It's easy to identify the beneficiaries in NDLOD and more challenging to find the particular individuals who benefitted from accelerated vaccine development. But nevertheless, in both cases, some particular individuals who would have experienced death or illness are spared. From this future perspective, the kind of benefit is the same.[27]

[23]Sterkenburg et al., op. cit. note 22.

[24]Scanlon, T. (1998). *What we owe to each other.* Belknap Press of Harvard University Press.

[25]Norcross, A. (1997). Comparing harms: Headaches and human lives. *Philosophy & Public Affairs*, *26*(2), 135–167. https://doi.org/10.1111/j.1088-4963.1997.tb00079.x

[26]Dorsey, D. (2009). Headaches, lives and value. *Utilitas*. *21*(1), 36–58. https://doi.org/10.1017/S095382080800335X

[27]Even if one believes that there is still some significant difference in the kind of benefit produced by NDLOD and participation in a challenge trial, respect for autonomy should push us towards allowing volunteers/donors to decide whether they want to take on a particular amount of risk to secure a larger benefit to one individual or a great number of smaller benefits for many people.

Thus, we maintain that the risk imposed on individual challenge trial volunteers is morally permissible if the risks from NDLOD are. This judgement, however, is predicated upon our confidence that challenge trials would actually produce a benefit, an issue we turn to in the next section.

4 | THE CERTAINTY OF THE BENEFIT

How does our confidence that COVID challenge trials would hasten the development of a viable vaccine compare to our confidence of success in organ transplantation? Miller and Joffe have argued that they do not compare favorably.[28] They write:

> The most important ethically relevant distinction … is the substantially greater likelihood of or confidence in preventing grave harm and producing benefit in the transplantation case, compared with clinical research. In transplantation, known probabilities of substantial benefit to the recipient are balanced against the risks to the donor of organ extraction. In contrast, in research there is an inherent and unquantifiable uncertainty that any given study will produce social benefit.[29]

Miller and Joffe say that we can have far greater confidence in the benefit of NDLOD than challenge trials because NDLOD has "known probabilities" of success and "in research there is an inherent and unquantifiable uncertainty." There are two ways we can read Miller and Joffe: as making a point about our relative confidence of success or as making a point about the relative precision of that confidence.

Confidence of success, in this context, refers to the probability we assign to the proposition that we will develop a successful vaccine in a significantly shorter timeline given that we use challenge trials. Precision refers to the way we are able to characterize this confidence. Were we able to say that the probability of success was .82, we would have a fairly high degree of precision. Our precision would be less if we could only give an interval to characterize our confidence; for example, perhaps the best we can say is that the probability of success is somewhere between .68 and .96. Even less precise would be a qualitative characterization; for example, our confidence of success is "pretty high."

First, suppose Miller and Joffe are making a claim about the comparative *precision* of our confidence in producing a benefit. They are right to assert that, because of our track record with organ transplantation, we can estimate the likelihood of success with a fairly high degree of precision. Whatever our confidence in producing a benefit with a challenge trial, the precision with which we can estimate the likelihood of that benefit is comparably low, since we don't have a sufficiently long track record of producing vaccines for coronaviruses using challenge trials, and since the benefits of research are—as Miller and Joffe suggest—inherently uncertain.

However, it is possible to have a high degree of confidence in some outcome, even when it is impossible to specify that confidence precisely. Enrico Fermi, when he activated the Chicago Pile, was highly confident that there would not be an uncontrollable chain reaction, even though he could not estimate the likelihood of avoiding such a reaction with any precision. We might prefer to have precise estimates of the likelihood of success with a challenge trial, just as Fermi might have preferred to have a more precise estimate about the likelihood of avoiding catastrophe in Chicago. But when we are deciding whether to take on some risk, it is sufficient to have a high level of confidence in our success; we do not need to be able to precisely estimate that confidence.[30]

That is not to say that precision doesn't matter *at all*. Betting on an outcome with a probability of .7 is different than betting on an outcome with a probability somewhere between .5 and .9. And it's certainly possible to be overconfident or to otherwise make mistakes in estimating the probability of success. The present point, however, only requires the claim that a lack of precision in our estimate of the probability of success with a challenge trial does not *on its own* make the risk of a challenge trial unacceptable.[31]

Instead, Miller and Joffe may be making a different claim: that our *confidence* in producing a benefit is higher in the case of NDLOD. If this were so, and if the magnitude of the benefits were similar, this would justify allowing larger risks for NDLOD than for challenge trials.

Miller and Joffe are right that we cannot be certain that any particular challenge trial will yield a benefit. One study claims that vaccine candidates entering phase III trials have historically had a 50% probability of success, while another put the number at 85%.[32] In contrast, every NDLOD is very likely to help someone.[33] So, if we

[28]Miller & Joffe, op. cit. note 6.

[29]We should note that Miller and Joffe agree that arguments by analogy are useful in debates about risk in biomedical research and that organ donation is a leading comparator activity. But, they argue, because the benefits of research are fundamentally uncertain, the acceptable levels of risk are lower.

[30]At this point, a reader may be wondering why we compare the precise benefits of NDLOD with the imprecise benefits of challenge trials, when we could offer a more direct analogy. We could compare live organ donation *for research purposes* with challenge trials. Since both require risks in exchange for imprecise benefits, we can therefore compare apples to apples. If we would not allow live organ donation for research purposes, then we should not allow a similar risk for challenge trials. We thank an anonymous reviewer for this objection. However, we do not think that the more direct analogy is helpful here. Our intention is to start with the widely accepted practice of NDLOD and show that the same risks are justified for challenge trials. It would not help our case to start with a practice like organ donation for research, which we have no clear social judgment on. It is possible that organ donation for research would be widely accepted if the potential benefits were as significant as those of challenge trials. But, that would be a conclusion of our argument, not its starting point.

[31]These points and the ones that follow could also apply, mutatis mutandis, to our estimation of the risks to challenge trial participants. If the probabilities we assign to adverse outcomes are sufficiently low, a lack of precision in estimating those risks would not make challenge trials unacceptable. Thanks to an anonymous reviewer for noting this parallel.

[32]Wong, C. H., Siah, K. W., & Lo, A. W. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics*, *20*(2), 273–286. https://doi.org/10.1093/biostatistics/kxx069; Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature Biotechnology*, *32*(1), 40–51. https://doi.org/10.1038/nbt.2786

[33]Rana, A., & Godfrey, E. L. (2019). Outcomes in solid-organ transplantation: Success and stagnation. *Texas Heart Institute journal*, *46*(1), 75–76. https://doi.org/10.14503/THIJ-18-6749

understand research subjects as participating in some particular challenge trial, we might not be able to justify the risks.

However, as Alex John London and Jonathan Kimmelman have argued, when we are evaluating the ethics of a research trial, we should not view it in isolation, but as part of "trial portfolios — series of trials that are interrelated by a common set of objectives."[34] This is in part because seeing a research trial as part of a portfolio changes the expected risk to benefit ratio. And indeed, if we pursued a portfolio of challenge trials, it would have been quite reasonable to expect them to produce a significant benefit.

In early July, there were 179 COVID-19 vaccine candidates at various stages of development, and 10 of them were in, or had completed, phase II human trials.[35] The 179 candidates represented at least eight different strategies for combating the virus, which increased the chances that one would work.[36] Moreover, COVID seemed to be the kind of disease that would be susceptible to a vaccine. Those who get it develop antibodies, so we knew that an immune defense was possible. And the COVID virus mutates slowly, which made a vaccine more likely to remain effective.[37] Even at that time, Anthony Fauci said that, based on early results and the resources being poured into development, it was a question of "when, not if" we got a vaccine.[38]

Of course, there are no guarantees in research. Until November, we had never produced a vaccine for any coronavirus. But, the previous, short-lived, efforts for SARS and MERS did not have the urgency, funding, or duration that COVID does. Based on the number and diversity of approaches, as well as what we knew about the virus when we were considering challenge trials, it was reasonable to expect the portfolio to deliver an effective vaccine, at some point.

This is especially true if, as London and Kimmelman further argue, and the WHO strongly recommended,[39] the challenge trials were well coordinated. When research trials are coordinated, even a "failed" trial provides a significant benefit. In addition to adding to our scientific knowledge, a negative result contributes to the eventual development of a vaccine by directing researchers toward more promising vaccine strategies. And, for the COVID vaccines, there was an unprecedented amount of global coordination. Organizations like the WHO, NIH, CEPI, and GAVI were working with labs around the world to share data, diversify vaccine strategies, ensure regulatory compliance, and prepare for eventual manufacturing and distribution. The same level of coordination in challenge trials would have justified us in thinking of volunteers as engaged in a joint, global project, which we could expect to produce a vaccine.

However, while there was general confidence that a coordinated effort would produce a vaccine, there was considerable debate about whether challenge trials would have sped up the research process. Proponents argued that challenge trials would speed up the timeline by several months, which would have saved tens of thousands or even hundreds of thousands of lives, both from COVID and the consequences of reduced economic activity.[40] Critics disputed that, arguing that challenge trial protocols would take just as much time as traditional phase III trials that require more participants. They also worried that data from the smaller numbers and younger people involved in challenge trials would not have given us enough confidence in the safety and efficacy of a vaccine for all populations. If so, then we would have needed a non-challenge phase III trial with all populations represented, negating some of the time saved by challenge trials.[41]

Given the vast potential benefits, however, it was worth doing all we could to prepare for challenge trials until we knew whether they would, in fact, speed up vaccine delivery. Even a slight acceleration in a vaccine's timeline would have produced an enormous benefit and justified the risks to volunteers. And, if we had determined that challenge trial protocols were taking too long, or the demographics would have made the results unhelpful, then we would have known that before the trials started and before we subjected anyone to their risks.

Once we gain that level of confidence that challenge trials will produce a benefit, we no longer have to worry that there is too much uncertainty to subject anyone to risk. At that point, one may still argue that uncertainty is a factor in calculating the benefit. One may insist that challenge trial benefits occur in the future, while the benefits of organ donation are immediate, so we ought to place a greater value on the latter. We could do so by discounting the benefits of challenge trials by some reasonable amount to account for the inherent uncertainty in future benefits. Even if we did so, however, the sheer number of lives that could be saved by faster vaccine development means that the benefits of challenge trials are still likely to be comparable to NDLOD, if not significantly greater.

5 | CONCLUSION

We have argued that, if we can tolerate the risks of non-directed live organ donation, then we could have tolerated the risks of COVID challenge trials. We have not established that COVID challenge trials would be morally acceptable, all things considered.

Perhaps because the world was watching, the medical community generally chose to exercise caution. Death or severe illness as a result of COVID challenge trials could have diminished medicine's standing

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[38]Neergaard, L., & Alonso-Zaldivar, R. (June 23, 2020). Fauci says 'it will be when not if' for a COVID-19 vaccine. *ABC News*. https://abcnews.go.com/Health/wireStory/fauci-testify-fraught-time-us-pandemic-response-71396585 (accessed July 7, 2020).

[39]WHO. (2020, March). A coordinated global research roadmap: 2019 novel coronavirus. https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap (accessed December 10, 2020).

[40]Eyal et al., op. cit. note 1.

[41]Even if phase III trials with all demographics are ultimately necessary, however, challenge trials may still save time and reduce the total number of participants in trials by identifying the most promising candidates for phase III testing.

and impeded further progress in biomedical research. But the fact that the world was watching cuts both ways. Failure to, for example, perform organ transplants when there are reliable techniques, willing donors, and many in need could also damage medicine's reputation. And the same could be true for failing to use morally acceptable means for developing a vaccine as quickly as possible.

It is nearly certain that there will be another pandemic in the not-too-distant future, perhaps again requiring the rapid development of a vaccine. The kind of analogical reasoning used in this paper, analyzing the risks and benefits of comparator activities, could and should be used in determining the appropriateness of relying on challenge trials during a future pandemic. But we may not even need to look too far into the future. The novel coronavirus has already demonstrated its ability to mutate and produce variants, and it is not entirely clear the extent to which our current vaccines will be effective against these new variants.[42] In the event that new vaccines are required with haste, challenge trials could aid in the production of those new vaccines. As we've argued, if we think NDLOD is morally acceptable, we should not rule out COVID challenge trials, at least not on the grounds that the risks to research subjects are too great.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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