



Research Ethics and Covid-19

Pandemic ethics: the case for risky research

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Abstract

There is too much that we do not know about COVID-19. The longer we take to find it out, the more lives will be lost. In this paper, we will defend a principle of *risk parity*: if it is permissible to expose some members of society (e.g. health workers or the economically vulnerable) to a certain level of *ex ante* risk in order to minimize overall harm from the virus, then it is permissible to expose fully informed volunteers to a comparable level of risk in the context of promising research into the virus. We apply this principle to three examples of risky research: skipping animal trials for promising treatments, human challenge trials to speed up vaccine development, and low-dose controlled infection or “variolation.” We conclude that if volunteers, fully informed about the risks, are willing to help fight the pandemic by aiding promising research, there are strong moral reasons to gratefully accept their help. To refuse it would implicitly subject others to still graver risks.

Keywords

Research ethics, clinical trials, COVID-19, human challenge trials

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The COVID-19 pandemic has upset ordinary moral assumptions. Restrictions on freedom of movement and association, to an extent previously unthinkable in liberal democracies, are now widely accepted as necessary. This is a significant revision to the ethics that guide our everyday lives. Few, in contrast, have shown such willingness to rethink the moral assumptions that guide our research into possible solutions to the pandemic. When so much is at stake, complacency and moral inertia cost lives.

In this paper, we will defend a principle of *risk parity*: if it is permissible to expose some members of society (e.g. health workers or the economically vulnerable) to a certain level of *ex ante* risk in order to minimize overall harm from the virus, then it is permissible to expose fully informed volunteers to a comparable level of risk in the context of promising research into the virus. We then apply this principle to three examples of risky research: skipping animal trials for promising treatments, human challenge trials to speed up vaccine development, and low-dose controlled infection or “variolaion.”

The principle of risk parity

Research ethics normally prohibits exposing human research participants to significant risks. The overriding aim is to prevent exploitation by researchers whose interests may not coincide with the interests of individual patients or volunteers. Article 8 of the Declaration of Helsinki (World Medical Association, 2013) reads:

While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

We agree that participants’ rights must not be violated but suggest that participants’ “interests” must be understood broadly to include any altruistic interest they may have in helping society to fight the pandemic.

In a pandemic, we all face heightened risks. As a result, restrictions on promising research (beyond the basic requirement of informed consent, confirmed via ethics committee approval) could easily prove counterproductive. The overriding aim must be to avoid a potentially catastrophic toll.

When grave risks are widespread, care is required to ensure that in protecting individuals against the risk of exploitation by researchers, we do not implicitly condemn everyone—including those we are protecting—to the far greater risks that would result from the pandemic continuing to spread, unchecked by the knowledge we could have gained from research using informed volunteers.

We are not suggesting any weakening of the basic requirement that medical researchers must scrupulously obtain the informed consent of their research participants. Requiring informed consent goes a long way to prevent or mitigate the greatest risks of unethical, exploitative research. Requiring informed consent

would have sufficed to prevent the great atrocities of 20th-century medical research, including those performed by Nazi and Japanese researchers on prisoners, the Tuskegee syphilis study in the United States, and the “Unfortunate Experiment” in New Zealand (Paul and Brooks, 2015). The scrutiny of a research ethics committee may provide additional oversight. But such committees should bear in mind the immense risk to innocent people of blocking promising pandemic research, in contrast to the swiftly diminishing moral returns to further risk-mitigating requirements beyond that of informed consent. In a pandemic, only the weightiest of moral reasons can justify preventing or delaying research that promises to help society to mitigate the catastrophic toll.

Many altruistic and public-spirited individuals want to play their part in overcoming the pandemic or at least reducing the huge toll it is taking on our society. This also became apparent during the Ebola crisis. Within minutes of an announcement from a Canadian Health Centre, “the phones started ringing and e-mails began arriving from people who wanted to . . . be injected with an experimental vaccine that might cause aches and fever – but could protect against the Ebola virus” (Tangwa et al., 2018). Altruism and public spirit were particularly apparent as there was no risk of contracting the virus in Canada.

To do their part in the fight against COVID-19, some serve as health workers or other essential workers, with a high risk of exposure to the virus as a result. Others stay at home, suffering social and economic costs in order to slow the pandemic’s spread. When considering these various risks and costs, it is also important to note that they are not all freely chosen. Many people paying these costs do so unwillingly, coerced by their employer or by the state, in a way that compounds the total moral cost of the situation.

Compare this to the situation in which fully informed volunteers help to fight the pandemic by participating in promising (but risky) research. Often such research is blocked on the grounds that it “raises ethical questions.” It does, of course, raise ethical questions. But so does slowing promising research, which extends the expected moral costs of the pandemic to everyone. The longer it takes to find an effective means of preventing the virus from killing people or making them seriously ill, the more deaths there will be, the more people there will be who are forced into dire poverty, and the more coerced individuals will suffer costs to which *they* never consented. Should we instead allow research participants to *voluntarily* undertake a comparable level of *ex ante*¹ risk in order to help relieve vast numbers of others of their burdens? Even non-utilitarians ought to answer this question in the affirmative.

The (theory-neutral) principle of risk parity tells us that risks incurred in the course of medical research are not intrinsically more morally problematic than risks arising in other contexts. There is no rational basis for allowing health workers and others to be exposed to high risk and then refusing to allow research

participants to voluntarily take on comparable levels of risk (for comparable or greater benefit). The cogency of defending research risks by comparing them to non-research activities is also suggested by Miller and Joffe (2009) as well as London (2006).

Given the immense and ongoing global harm caused by the pandemic, speeding promising research has immense expected value. And since the costs borne by informed volunteers are consensual, in contrast to many of the costs imposed on others in society, important non-utilitarian values such as *respect for autonomy* (Macklin, 2003) are also better served by permitting (indeed, encouraging) such research.

Much of the public discourse surrounding pandemic research ethics reveals an implicit failure to appreciate this principle of risk parity. For example, Paul Duprex, Director of the Center for Vaccine Research at the University of Pittsburgh, has cautioned against risky research in the present context, insisting that we must “be absolutely certain that we don’t do something for the greater good which is highly detrimental for that individual [volunteer research participant]” (Morning Ireland, 2020 at 32:15). The comment was made in an interview for Irish National Radio. Regrettably, the interviewer did not press him on why we shouldn’t be similarly concerned about other individuals, for whom delayed research in the context of the pandemic would prove even more detrimental.

When thousands of individuals are dying every day and millions more are suffering ongoing social and economic harm, any delay to promising research is clearly disastrous. We hope that defenders of conventional research ethics will rise to address this challenge. To reiterate, this is not about premeditatedly sacrificing some individuals for the greater good of the many. It is not a crude utilitarian trade-off that neglects or violates anyone’s rights. This is about allowing competent adults to choose to act altruistically within the context of medical research to address the pandemic, just as we allow (or worse: require) others to act altruistically in non-research contexts while the pandemic is ongoing.

One interesting argument that Duprex (Morning Ireland, 2020 at 31:47) does offer involves a kind of skepticism regarding whether informed consent is even possible given how little we know about COVID-19: “Are [research participants] fully informed, whenever we really only have a small amount of the information?” The implicit assumption seems to be that you cannot give informed consent to taking a risk without knowing exactly what the risk is (ideally, perhaps, knowing the *objective chances* of each possible outcome). But this assumption is far-fetched. What more plausibly matters for informed consent is that participants understand and accept whatever known *and unknown* risks apply *in light of our current epistemic situation*.² When the researchers themselves are highly uncertain about the outcome of a procedure and what hidden vulnerabilities might result in a seemingly healthy participant suffering unexpected harm, they need to

clearly communicate this uncertainty. Most candidates, facing such uncertain risks, would reasonably choose to refrain from participating in the trial, and that decision must certainly be respected. But others may reasonably choose to go ahead, accepting the risks (both known and unknown), in order to help fight the pandemic. This choice, too, should be respected.

Applying the principle of risk parity to COVID-19 research—three examples

While it is ultimately up to medical researchers to identify the most promising lines of research, we can here indicate three broad avenues within which greater tolerance for risky research (in line with the principle of risk parity) could plausibly save lives during the pandemic.

(1) Conventional standards require that new drugs be tested on animals before clinical trials with humans are permitted. For COVID-19, we suggest that sufficiently promising treatments (and vaccine candidates) should jump to human clinical trials as soon as is reasonably possible, bypassing the usual lengthy period of animal testing. This measure has already been taken in a vaccine trial in Seattle, which attracted considerable criticism from research ethicists.

A clinical trial for an experimental coronavirus vaccine has begun recruiting participants in Seattle, but researchers did not first show that the vaccine triggered an immune response in animals, as is normally required. (Lanese, 2020)

There is a precedent for such a move. In 1986, when azidothymidine (AZT) first showed promising results in the treatment of AIDS, patients demanded that the drug be made available without going through animal testing (Park, 2017). The Food and Drug Administration licensed it, saving many lives. AIDS had a much higher fatality rate than COVID-19, but even so, if we fully inform COVID-19 patients about the risks of taking part in an experimental treatment trial, they may reasonably choose to take that risk. When we consider the broader humanitarian benefits of confirming a treatment's (or vaccine's) effectiveness much sooner than would otherwise be possible, not to mention the reduced animal suffering involved, there is a strong moral case for allowing volunteers to make that choice.

(2) Similar arguments support allowing human challenge trials to speed development of a vaccine (Eyal et al., 2020). According to the World Health Organization (World Health Organization, 2016):

Human challenge trials are trials in which participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism

may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner.

Ordinarily, testing a candidate vaccine means waiting months to see whether injected research participants are less prone to infection. Deliberately exposing vaccinated volunteers to the virus could produce results much more quickly. Strikingly, there is no shortage of volunteers willing to undergo such a trial. More than 14,000 volunteers from more than 100 countries have already signed up to do so (Ramgopal, 2020).

(3) Finally, consider research into low-dose controlled voluntary infection, or “variola,” widely used to inoculate against smallpox before the discovery of vaccination (Boylston, 2012). Princeton University researchers Joshua Rabinowitz and Caroline Bartman (2020) have emphasized the importance of viral dose: people who receive a low dose of a virus are more likely to recover than those who receive a high dose, and this holds for coronaviruses too. Robin Hanson (2020) notes that, historically, variolation has reduced infection mortality by factors ranging from 3 to 30. All this seems to suggest a strong *prima facie* case for exploratory research into SARS-CoV-2 variolation as a possible vaccine substitute.

Some may object that it would be unethical to deliberately expose volunteers to a potentially lethal virus. But does this assumption really make sense in our current context? The seriousness of the coronavirus pandemic cuts both ways: more risk from the initial low-dose infection but greater benefits if it does protect the volunteers. For instance, if we can gain solid evidence that receiving a low dose of the virus (variola) leads to a mild case of COVID-19 and that such mild cases then bring immunity to further exposure to the virus, we would have found a means of saving a considerable number of lives—and millions of livelihoods—in the absence of a vaccine. Even the most optimistic scientists assume that COVID-19 vaccine development will take at least 12 months (Deutsch, 2020) and there is no guarantee that such optimism will be vindicated. It therefore seems both prudent and ethical to investigate alternatives by inviting healthy young adults to volunteer to receive a low dose of the virus, followed by quarantine and medical observation.

In fact, some individuals have already sought deliberately to infect themselves via uncontrolled “coronavirus parties,” despite medical experts urging them not to do so (Bauer, 2020). It would be better for everyone if such individuals were instead to have the opportunity to volunteer to receive a low dose of the virus as part of a carefully monitored trial. That would be safer for the participants than an uncontrolled infection, and the knowledge that we would gain from such a trial could guide us toward an earlier end to the pandemic.

There is too much that we do not know about COVID-19. The longer we take to find it out, the more lives will be lost. If volunteers, fully informed about the risks, are willing to help fight the pandemic by aiding promising research, there are strong moral reasons to gratefully accept their help. To refuse it would implicitly subject others to still graver risks.

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Notes

1. Based on forecasts rather than actual results.
2. It is also worth noting that case fatality rates for COVID-19 vary roughly between “0.2% in Germany to 7.7% in Italy” (Roser et al., 2020). Hence, one might argue that the risks taken by volunteers from being infected with the virus are at least *broadly* specifiable.

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