

Research ethics and public trust in vaccines: the case of COVID-19 challenge trials

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Received 13 December 2021
Accepted 7 May 2022

ABSTRACT

Despite their clearly demonstrated safety and effectiveness, approved vaccines against COVID-19 are commonly mistrusted. Nations should find and implement effective ways to boost vaccine confidence. But the implications for ethical vaccine development are less straightforward than some have assumed. Opponents of COVID-19 vaccine challenge trials, in particular, made speculative or empirically implausible warnings on this matter, some of which, if applied consistently, would have ruled out most COVID-19 vaccine trials and many non-pharmaceutical responses.

Around the turn of the millennium, it became common in bioethics to defend research ethics oversight as a matter of protecting public trust—trust in investigational products, in investigators, in clinicians and in health officials, as well as in the research, clinical and public health enterprises themselves.^{1–5} In the recent debate on testing COVID-19 vaccine efficacy through human challenge trials (HCTs), one argument against HCTs was that HCTs would exacerbate public mistrust of COVID-19 vaccines and of pandemic response efforts, or even research and vaccination campaigns in general.

This article argues against anchoring research ethics, and especially the ethics of COVID-19 vaccine testing, in the (very real) need to protect public trust. It uses COVID-19 HCTs as a case study. The next section explains what COVID-19 HCTs are and introduces the mistrust argument against them. The following section identifies the strongest version of the mistrust argument. The consequent sections address with greater detail the argument in that version. Another section addresses variations on that version. A final section concludes.

THE VACCINE-MISTRUST ARGUMENT AGAINST COVID-19 CHALLENGE TRIALS

The UK has completed COVID-19 challenge trials and starting others.^{6–7} In standard COVID-19 vaccine HCTs, consenting adult volunteers are randomised to receive either that vaccine at the dose and regimen being investigated, or control. The control can be another vaccine, the same vaccine at a different dose or regimen (eg, half dose, spaced out, with a booster, a mix of different vaccines), a placebo or a prior infection. Participants are then exposed to live SARS-CoV-2. Comparisons of later rates of infection (based on quantitative PCR) and of infectiousness (based on nasal titre) between active and control participants reveal the degree to which that vaccine

(at that dose and regimen) blocks infections, compared with no intervention (with or without natural antibodies), to other vaccines, or to other doses and regimens. Trialists can also characterise the duration and correlates of vaccine protection, and much else.⁸ All HCT volunteers are young and healthy, a population in whom the chance of severe COVID-19 outcomes is small.⁹ All remain isolated while infectious.

In 2020, a worldwide debate on HCTs in COVID-19 vaccine development, to replace or complement conventional field trials (my term for the much larger randomised controlled trials eventually used) asked among other things whether HCTs are safe enough for volunteers, compatible with their truly informed consent, and informative enough for public health purposes.^{10–18} Advocates pointed out that the risks to young and healthy volunteers could remain far lower than those of some widely accepted live organ donations, that the risk for a severe adverse event in the cohort may be lower than in widely accepted field trials of vaccine efficacy, that volunteers could be selected and further trained so that their comprehension levels are high, that the information gathered from COVID-19 HCTs was and remains important for reducing the enormous global COVID-19 burden, that vaccine safety could be established separately and other points.^{13–15–18–24} But what concerned some opponents was that HCTs would exacerbate ‘mistrust’.

These opponents warned, for example, that ‘undertaking an [HCT] in the context of this pandemic risks fueling and potentially worsening levels of public mistrust’.¹⁰ Other opponents explained: ‘Mistrust of research and of vaccines in particular is rampant; conspiracy theories, misinformation, and anti-science attitudes are spreading. Bad outcomes in a SARS-CoV-2 human challenge study could be devastating...’²⁵ In the eloquent words of some, “There is a finite amount of credibility that the scientific and the medical establishment have with the general public, and we want to be very concerned about not wasting that credibility.”²⁶ Still others provided stark reminders of the tragic case of Jesse Gelsinger,^{25–27} which we discuss later. A WHO Advisory Group tasked to consider establishing a COVID-19 challenge trial summarised it by focusing on what might happen following an accident under a challenge design: ‘The public trust needed to achieve high vaccination coverage with COVID-19 vaccines could be undermined if there was a highly publicised serious adverse event in a challenged volunteer’.²⁸ Many similar warnings are quoted below.



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To cite: Eyal N. *J Med Ethics* Epub ahead of print: [please include Day Month Year]. doi:10.1136/medethics-2021-108086

I shall call such warnings the ‘mistrust argument’ against conducting HCTs. Let me begin by distinguishing forms of that argument that, for reasons that I shall explain, are nonstarters that require only minimal discussion, from others that merit our painstaking attention.

WHAT IS THE STRONGEST VERSION OF THE MISTRUST ARGUMENT?

The warnings about potential ‘mistrust’ seem to argue that COVID-19 HCTs would undermine confidence in something. But what is that something? On different potential readings of the argument, confidence would decline in the COVID-19 vaccine’s efficacy or safety; or in the efficacy or safety of other vaccines; or in the competence of trialists? Their moral decency; or in those of public health officials; or in those of clinicians. Nor is it always clear in those warnings whose trust is in jeopardy: should we read this as referring to the trust of a majority of the general public? That of a considerable, vocal or powerful segment thereof? That of public health officials and ethicists themselves (a viable reading of some statements, as we see below)? I shall try to respond to the argument all of these readings.

Proponents of the mistrust argument sometimes sounded as though they are saying the following: COVID-19 HCTs would (or might) exacerbate public mistrust because COVID-19 HCTs are unethical independently, and unethical science makes people mistrust scientists and doctors. That seems to have underlay the warning that HCTs ‘that do not meet basic principles of research ethics [would undermine] public trust’.¹⁰ It may have also informed the warning that HCTs would undermine trust and cause delay because they are ‘violations of public trust’,²⁵ and because any severe adverse event would be ‘unconscionable’.²⁹

Literally interpreted, such assertions begged the question against defenders of COVID-19 HCTs. The latter, recall, claimed precisely that this design *can* meet basic principles of research ethics, remain faithful to public trust and remain perfectly conscionable. For if HCTs are independently unethical, that alone will be reason enough to oppose them. If that truly is the case, it will not matter whether they exacerbate public mistrust or not, as they should be prohibited due to their independent impermissibility alone.ⁱ

Accordingly, the current article will focus on a stronger way to put the mistrust argument, which does *not* assume that HCTs are otherwise unethical.ⁱⁱ To operationalise this comparatively

strong version of the argument, the article will take as a premise that HCTs *are* otherwise ethically permissible and ask whether issues of trust should render them unethical overall.

On that comparatively strong form of the mistrust argument, HCTs might exacerbate public mistrust, not because HCTs are anyhow unethical (they may or may not involve independent ethical problems) but for other reasons. In particular, this argument imagines that HCTs may exacerbate mistrust because the relevant stakeholders might perceive them as unethical (although they might not be independently unethical, or they might be unethical in ways other than the one that makes them be so perceived). Alternatively, the comparatively strong mistrust argument may imagine that HCTs would create the perception that the vaccines on trial are unsafe.

Few if any writers openly put forth this comparatively strong version of the argument, although I suspect it was on the minds of many. One potentially pure case were ethicists who pioneeringly supported COVID-19 HCTs but who later raised concerns about their potential impact on public trust; inasmuch as they considered these concerns reason enough to avoid HCTs, they were advancing what I shall treat as the strongest mistrust argument against HCTs.^{32 33}

This comparatively strong form of the argument avoids the above question begging. If successful, it would capture a factor that makes HCTs unethical, instead of assuming that they are. In fact, we use similarly structured arguments all the time: there may be nothing inherently wrong about frequently altering public health recommendations to reflect evolving evidence on an emerging disease. Yet inasmuch as mercurial recommendations exacerbate public mistrust, they should be avoided. Even if financial ties between drug companies and academic scientists could through regulation become a pure benefit, *perceived* conflicts of interest could still harm public trust, a serious concern in its own right³⁴; as the NIH Director said, on forbidding some industry relations, “The public trust in [biomedical research] is just essential, and we cannot afford to take any chances with the integrity of the research process”.³⁵ Nevertheless, we now criticise this comparatively strong version mistrust argument, on various readings distinguished in the next section.

MISTRUST IN WHAT?

The comparatively strong mistrust argument varies depending on the contribution to public health that it considers to be at risk:

Impact on vaccination rates (among the public one is hoping to convince to get vaccinated, or at least among a large or crucial segment thereof). In this vein, some warned: “if [HCTs] feed distrust among the public, they could exacerbate challenges in

ⁱThere is an additional problem with such assertions. Violations of basic ethics principles that undermine vaccine investigators’ *moral trustworthiness* would not necessarily translate into widespread *mistrust of vaccines*. Historically, the wider public as not always sensitive to research ethics considerations or to their application to all human beings. Unfortunately, researcher abuses of enslaved and incarcerated people, for instance, did not always undermine public trust in and utilisation of medical products. A hypothetical study that unnecessarily exposed participants to highly carcinogenic material would be unethical but the difficulty of reliably attributing cancers that result decades later to the study would usually shelter public trust. More generally, ‘trust is generally a three-part relation: A trusts B to do *x* (or with respect to *x*)’.^{30 31} Mistrust of investigators in one respect (ethics) need not undermine trust in them and in the products that they investigate in other respects (scientific and technical competency, product quality).

ⁱⁱ(Liza Dawson) suggested to me that concerns about spreading mistrust count against using HCTs in vaccine development given the sheer disagreement among influential ethicists about the permissibility of HCTs. An HCT would enable antivaccine demagogues who cherry-pick their experts to point out that

‘even expert ethicists’ consider the trial unethical. To preserve public trust, medical research should be ethical and be seen to be ethical; clinical trials that are independently ethical but not very clearly and uniformly seen as ethical, at least by ethics experts, fail this (epistemologically demanding) standard. My response is that for nearly every other trial design and public health measure that we have used, appropriately, in COVID-19 and elsewhere, some influential ethics experts protested it. If, as I believe, HCTs are *ethical* although they are not *evidently ethical*, and not *agreed to be ethical by all influential ethicists*, and that demagogues will therefore call them *unethical*, then we should point out the falsity of the demagogues’ representations, instead of assuming that the public is too dumb to recognise it. In a pluralistic society, the cost of taking no chance of offending this or that faction is paralysis, and specifically, the impossibility of hardly any medical research and of any initially controversial but necessary pandemic measure.

vaccine roll-out... and delay uptake of an effective vaccine".³⁶ Others added: 'With vaccines already a target of widespread misinformation campaigns, the death of a single [HCT] volunteer would likely cause even greater damage. From a public health perspective, it would be especially disastrous if it ... fueled the anti-vaccination movement'.²⁷ One account of how the HCT would do so is that, while there might be nothing intrinsically wrong with an HCT, it would be perceived, spontaneously or with antivaccine propaganda, as highly unethical, reducing vaccination rates. A very different possibility is that the HCT, which provides no safety data, would be seen as insufficiently assuring on product safety, reducing vaccination rates.

Impact on trial participation and later clinical care (of potential volunteers who might be dissuaded from joining either the HCT or other trials, now or in the future). In this vein, some wrote that 'When study volunteers die or suffer serious harm at the hands of researchers, [that is] potentially undermining the stakeholders' confidence in the research enterprise. One very bad outcome not only harms the individual volunteer, it harms the whole research process ... and public trust is likely to plummet'.²⁵ A cite then follows regarding public mistrust's stifling effects on recruiting wide populations to research.³⁷

Impact on smooth vaccine development without regulator-imposed bans (by ethicists or by other health-sector decision-makers). The authors of the above quote also cite the Gelsinger case, in which, following the death of a healthy young volunteer and research ethics violations at the University of Pennsylvania, regulators stopped a study, and halted the entire field of gene therapy research.²⁵ Others concur:

...what if one of the first volunteers dies, either due to the play of chance, a problem with the vaccine, or the individual's genetic makeup? This is unlikely to happen, but it can, and did, in another setting with consequences that stretched far beyond the single tragic death.

In 1999, Jesse Gelsinger volunteered for one of the first gene therapy trials. ...he was basically healthy ... and died as a result [which] set the field of gene therapy back by at least two decades.²⁷

Presumably that was also the upshot of ominous statements like 'A single death or severe illness in an otherwise healthy volunteer... would halt progress'.²⁹

FOOD FOR THOUGHT: SOME RIDICULOUS PROPOSALS

Before examining separately the success of the mistrust argument in explaining how each of these respective contributions to public health are at risk from challenge trials, ponder a few ridiculous mistrust arguments against other COVID-19 measures, and what may have gone wrong with each:

We discovered a rare COVID-19 vaccine side effect in a certain subpopulation. Let's permanently stop using this product in anyone, lest we risk worse public mistrust which may affect utilization of any vaccine and harm other pandemic- and non-pandemic trials, clinical care, and public health measures.

mRNA technology is a miracle. Unfortunately, many misunderstand it and worry that it changes their DNA. Let's therefore deploy only adenovirus and not mRNA.

32% of the US public falsely believes that a certain public health leader and valiant champion of vaccines supposedly has financial stakes in vaccines.^{38 39} He is excellent at his job but to protect crucial public trust let us fire him.

In summer 2020, there were demonstrations in South Africa against the conventional field trials for COVID-19 vaccines planned there at the time.⁴⁰ To avoid any risk of spreading mistrust, these trials

should have never taken place there (and, to err on the safe side, anywhere).

While infections and deaths are highest among disenfranchised populations, the tribulations of social elites command greater media and public attention and affect public trust more. To maximize public trust in public health interventions, let's therefore prioritize elite neighborhoods for vaccinations and other public health interventions.

Out of sheer ignorance, many deny that masks reduce infections. To build trust in our recommendations, let's stop recommending masking indoors.

As predicted, many Americans mistook the speed with which vaccines were tested in 2020 to substantiate mistrust in these vaccines. While testing was very thorough, to preempt that misplaced mistrust, we should have artificially dragged the testing for another year.

These proposals are utterly ridiculous, far more ridiculous than any arguments I am considering. But some of the factors that make these ridiculous proposals ridiculous, I shall point out below, are present in small doses in the type of mistrust argument against HCTs that we are considering.

IMPACT ON VACCINATION RATES?

The claim that, for reasons other than the HCTs independently being unethical, they may still spread mistrust that reduces public willingness to get vaccinated will be my main target. As mentioned, I can see two pathways through which HCTs might be thought to do all that and *not* in virtue of independently being unethical: (a) HCTs might be perceived as unethical and (b) HCTs might be insufficiently reassuring on product safety. As I now argue, hard questions arise for either of these pathways.

The perceived-as-unethical pathway

How likely are HCTs to be perceived as unethical, and how likely is such a perception to reduce vaccination rates?

Note that these questions are both empirical and complex. Vaccine hesitancy is elusive. Interventions like informing and reasoning, which might initially be expected to reduce hesitancy, could conceivably turn out to increase it.³¹ Organisational determinants are also complex. Succumbing to sceptics' pressures in order to appease them may in fact embolden them, or encourage their funders to pay them more. Philosophers and doctors should not imagine that they possess the professional expertise to pronounce about the likelihood of anything being perceived in this or in that way and the likelihood that such perceptions would reduce public trust. On pain of speculation,⁴¹ that discussion should largely be left to social scientists and communication experts.

Admittedly, it would be consistent with current scholarship on risk perception⁴² if the active and intentional nature of the viral infection in an HCT, by human agents in the healing professions, made resulting harm outrageous in the eyes of many. But live organ harvesting for transplantation purposes has all these characteristics and resulting harm does not lead to wide mistrust in medicine and public health; so do toxicity trials in healthy human volunteers (imagine if organ harvesting or toxicity trials were halted to pre-empt speculative warnings about mistrust). There are also findings suggesting that harms actively caused by caretakers are *less* perspicuous than their harms of omission: in one striking survey, 65% of respondents declared that they would accept surgery to cure cancer even if the surgery were riskier than the cancer.⁴³ Predictions on these nuanced matters require careful, context-specific empirical analysis.

Strikingly, in the considerable bioethics literature that warns of HCT effects on mistrust there is hardly any attempt to provide empirical evidence that HCTs are likely enough to lead to such effects. Virtually the only evidence cited is in the study by Dawson *et al.*²⁵ They mention: (a) a historic article with unclear connection to HCTs and to dissuading recruitment^{37 iii}; (b) the case of Jesse Gelsinger, which I address below and (c) the 2014–16 Ebola outbreak in West Africa, which did not involve any HCTs.^{iv} Overall, the evidence seems scant at best.

The only available empirical data on COVID-19 HCTs' public perceptions suggest striking public support for HCTs. A 'cross-national survey (n=5920) in Australia, Canada, Hong Kong, New Zealand, South Africa, Singapore, the UK and the USA'⁴⁸ found that 'broad majorities prefer for scientists to conduct challenge trials (75%) ... Even as respondents acknowledged the risks, they perceived ... accelerated trials as similarly ethical to standard trial designs'.⁴⁸ Elsewhere, support for HCTs weathered longer deliberations.⁴⁹ Admittedly both of these studies collected data more than a year ago. But currently in the UK, the completed viral dose escalation challenge and approved plans for two full HCTs hardly destroyed vaccine trust. If anything, recent trends in the UK are friendlier to vaccination than in the USA, which had rejected HCTs.

It is conceivable that a terrible accident in an HCT would make public opinions less friendly. Some HCT opponents who 'warned of a risk to public trust in science and medicine' conceded that 'fatality, hospitalisation or long-term symptoms are extremely unlikely scenarios' while insisting that 'even their remote possibility threatens trust in research and vaccines more than necessary'.⁵⁰

But HCTs' danger to public trust that follows serious adverse events may be smaller than that of widely accepted conventional field trials. Properly conducted HCTs' extremely low chance of serious adverse events⁹ may actually be smaller than the risk of serious adverse events (including ones stemming from trialists' active interventions) in properly conducted field trials. The latter expose hundreds of times more participants to the vaccine (greatly elevating the risk of vaccine toxicity events) and many more people to the combination of vaccine and virus (elevating risk of disease enhancement events⁵¹—especially given that many participants could get exposed to the virus shortly after the trial).²⁴

Had the public ethically opposed HCTs in the first place, or if risks were imposed on unwilling or highly vulnerable participants (as they were in so many historical abusive trials, including many non-HCTs), some sections of the public may well lose trust in those who persisted with the trials, then caused an accident. But HCTs may be preferred by the public in the first place, and should meet high-quality consent and other demanding ethical requirements.¹¹

It might seem as though, even if a majority of the public would perceive HCTs as ethical, a large minority who perceive HCTs as unethical would then refuse vaccination. But this exaggerates

how much current refusal to get vaccinated is founded on (perceived) trial ethics qualms. In polls, COVID-19 vaccine refusal is seldom ascribed to pure research ethics qualms and more often to product safety worries (and imagined costs).⁵² When concerns about the ethics of COVID-19 vaccine field trials raised over this past year,^{53 54} those hardly figure in vaccine sceptics' discourse. Understandably, *research ethicists* tend to worry most about public perceptions of *unethical research*; we should remember that trial ethics is not patients' first priority in personal decisions to use or not to use a medical product. So when we are comfortable with the ethics of a trial, to propose to ban it because we speculate that the public would nevertheless perceive it as unethical and consequently refuse to get vaccinated can rest on a misunderstanding of drivers of patients' medical decisions.

The perceived-as-a-sign-that-the-vaccine-is-unsafe pathway

If not comparatively liable to be seen as unethical, might HCTs nevertheless make vaccine products themselves be perceived as unsafe, or at least as insufficient proof of these products' safety? Some HCT opponents may have suggested as much in explaining in this context:

There's always a possibility [in an HCT] that the vaccine won't work—or even worse, will enhance the adverse effects of the virus—which could fuel anti-vaccine sentiment... If people start rejecting vaccines or seeing them as actively negative, many people could be harmed and killed for refusing to take vaccines.²⁶

If anything, however, accidents in conventional field trials are likelier to create the impression that the vaccine itself is unsafe. In a field trial, much more than in an HCT, any accident is likelier to emanate from product toxicity (or from severity enhancement that this product creates in combination with virus exposure).²⁴ While risk from exposure to virus is much greater in an HCT, that risk in no way bears on the risk of the product when used without that exposure. From the viewpoint of product safety, it is akin to accidents that have taken place in vaccine field trials last year, and which the wider public understood were unrelated (say, suicide for unrelated causes). Yet risk of product-related safety events, which is more likely to protect exaggerated concerns about product safety, is greater in field trials than in HCTs!

Another reason why HCTs might initially be considered insufficient signals of product safety is that HCTs provide no safety data.⁵⁵ But HCT supporters have already proposed multiple ways to establish product safety through added components in the HCT route.^{22 56} And for our own purpose of assessing the mistrust argument, it is fair to assume that product safety is otherwise assessable; otherwise, the HCT would have already been pointless and unethical.

IMPACT ON TRIAL PARTICIPATION AND CLINICAL CARE?

There may also be a concern that HCTs, if perceived to carry more procedure risk than conventional field trials, would have problems recruiting—as trials perceived as risky often do⁵⁷; or that an HCT that is widely perceived as unethical would dissuade that HCT's candidate volunteers or volunteers for other trials or even patients who would otherwise seek care (potentially for many years). None of these concerns stands to scrutiny.

There is no shortage of volunteers for an HCT. The British dose escalation study was inundated with >40 000 volunteers for a few dozen spots.⁵⁸

ⁱⁱⁱIf anything, that historic article argues that instead of assuming what would alienate candidate study recruits, one should engage them, an approach that may instead support HCT advocates' proposal^{13 47} to conduct HCTs if engaged recruits affirm their desire to participate.

^{iv}Indeed, Ebola illustrates the exigencies of mistrust arguments: in 2015, some warned of 'erosion of trust' following any Ebola vaccine placebo-controlled trial,⁴⁴ yet when shortly afterwards a placebo-controlled trial began in Liberia, it had no problems recruiting, adherence was high and it coincided with an increase in public trust or at least cooperation there.^{45 46}

Regarding participation in other trials and in clinical care, it is true that historically, some clinical trials which were correctly widely perceived as unethical have dissuaded racial/ethnic minorities, sometimes targeted by those unethical trials,^{59 60} from joining later trials and even from using needed health services. But the COVID-19 HCTs defended here are different. They could be ethical, their supporters argue, with thorough informed consent and external review processes poignantly absent from these historical abuses. Nor would the volunteers need to be disenfranchised minorities. The people who declared willingness to volunteer for COVID-19 HCTs tend to be neither low-income nor racial/ethnic minorities.⁶¹

IMPACT ON REGULATOR-IMPOSED TRIAL INTERRUPTION?

The recurring allusion to the Gelsinger case to support mistrust arguments seems to evoke concern, not precisely about *public* mistrust (few in the wider public, vaccine sceptics included, ever heard of that case), but about the response of a disappointed US Office for Human Research Protections (which halted gene therapy research following the Gelsinger abuse) or other regulatory bodies. The implicit suggestion then has the structure, “If you do X, regulatory bodies might stop the HCT (or even all COVID-19 vaccine research), which would be disastrous. Therefore, please avoid X!”

But when the argument has that structure, the natural answer is, ‘Please regulatory bodies, avoid a misguided decision to delay a perfectly ethical trial, and certainly a decision to delay other trials during pandemic’. For recall that the present article section assumes that the relevant mistrust is *not* because an HCT would be independently unethical. If what is aggravating the ethics regulators is only a false perception of ethical violation or something else that is not an ethical problem with the trial and therefore not their business, *then* ethics regulator interference would be wrong. Certainly collective punishment of non-HCT vaccine researchers would be wrong and, in a pandemic, very wrong. Inasmuch as the argument comes from regulators, Institutional Review Board members and funders with the actual power to halt the HCT or other trials, it can also constitute an inappropriate threat to do so.⁶²

WOULD INCREASING LIKELIHOOD OF SUCH IMPACTS MAKE HCTS UNETHICAL?

In our case of a trial assumed to be otherwise ethical and hence valuable and compatible with proof of product safety, any resulting public mistrust must be, not because the HCT is unethical or thwarting proof of safety, but because it is wrongly perceived as unethical or as thwarting such proof. This should raise some doubt about letting mistrust concerns dictate our devotions. Do we really want to pander to the public when its potential mistrust is based on factual error, or misguided ethics?

Perhaps as a compromise we should sometimes do so, when all else fails. But surely the first thing to do is to try to educate the public, while keeping the trial otherwise ethical,³² or at least to survey the public very cautiously rather than declare HCT-related mistrust without checking. Similar worries arise, after all, about unpopular isolation measures, safe burials, fair vaccine mandates and other pandemic responses. For all, there is a strong presumption in favour of doing what is right for public health while trying to convince the public and sharing the full truth with it. Surrendering to misguided perceptions may actually worsen mistrust if demagogical influencers twist it to

be admission of their false claims, or if their success emboldens them and their funders.

Differently put, the practical implication of ‘X is perfectly right intrinsically but may disastrously upset the public’ is only rarely ‘Avoid X’. More often, it is ‘Explore whether there might be a particular form of X that avoids upsetting the public so much’. Only once that first attempt fails does it usually become wise to settle for the highly suboptimal ‘Avoid X’.

MIGHT COMPLICATIONS ARISE IN USING THE MISTRUST ARGUMENT?

Reliance on the mistrust argument comes perilously close to adopting repugnant ethical and political positions that I suspect most champions of that argument would reject. Consider some:

- *Disregard for rights*: the ridiculous proposal to fire a health sector leader falsely accused of being financially invested in vaccines illustrates a potential problem with preserving trust at all costs. To fire perfectly good workers is problematic among other things because it tramples on worker rights. In the HCT case, saving trust at all costs may trample on the rights of (at-risk) patients to rapid vaccine development.
- *Confusion of the instrumentally and the intrinsically valuable*: the comparatively strong mistrust argument treats cynical, pragmatic compromises that research ethics typically rejects as unethical to the level of fundamental ethical mores. Whether or not all things considered, we should make dirty compromises on trial ethics when misguided vaccine sceptics or exceedingly conservative regulators would object if we acted right, that remains a (perhaps unavoidable) dirty compromise. It is not fundamentally the right thing to do. Consider an analogy. Trialists may occasionally have no available alternative to buckling to drug manufacturer pressures in return for crucial resources that only the manufacturer can provide, like the vaccine doses⁶³ and crucial data. In return, the trialists slightly compromise on the science or on human subject protection. Whether or not the compromise is justified all things considered, it would be misleading to describe such compromise as fundamentally an ethical dictum. We may be compelled to do it, but it is then a last resort not a first one. Yet the mistrust argument presents compromises, in our case with unwarranted public suspicion, as important intrinsically, simply because it ultimately maximises social value.
- *Disrespect*: the paradigm case of the mistrust argument seems to assume that the public will never understand the legitimacy of something that in fact is legitimate (namely, HCTs). Notably, the argument does *not* propose to give the public a chance to change its mind, or to attempt an education campaign before giving up. Typically, moreover, the argument discussed above remains somewhat illicit—often, a mix of the varieties that I parsed apart.^{10 25–28 36} Perhaps the point of that opacity is to avoid having to openly tell the public: “We believe you are off on this one, and instead of respectfully letting you know that and inviting you to change your mind, we will assume you are too stupid or obstinate to do so; we will abide by your demands without ever revealing to you that in our view, you got this one wrong”.
- *Conservatism*: many ethicists who purport to be progressives take on board the mistrust argument. That can compel them to stick to the *status quo* of public opinion, to some extent regardless of its content. The sheer fact that the public is currently against X (in this case, an HCT) and would

therefore lose a measure of trust if X happened, becomes in their argument a powerful reason against X.

- **Arch-conservatism:** at this moment, many of America's ideological vaccine sceptics identify as extremely conservative, even alt-right.⁵² To subserve their baggage of positions, conspiracies and lunacies in order to avoid conflict and further entrenchment is to surrender to their agenda. To avoid a battle, the mistrust argument quietly loses the war.

These worries about paradigmatic mistrust arguments might provoke the following answer. While the mistrust predicted by such arguments would arise from things independent of the HCT's being unethical (eg, from its being *perceived* as unethical or as indicative of product unsafety, perceptions that are not themselves prompted by it being unethical), in fact an HCT *is* unethical. Therefore, that answer could go, there is nothing cynical, hypocritical or manipulative about opposing an HCT. That trial design would be *both* unethical *and* damaging to public trust.

This special variation of the argument would, however, remain vulnerable to other problems noted above, for example, that this special argument assumes that the HCT is independently unethical and therefore begs the question; and that it is also speculative.

SUMMARY

The mistrust argument is either question-begging or, in its strongest versions, relies on unfounded, and probably false, empirical speculation and subject to bad pitfalls. Either way, we should reject it.

To be able to boost public trust in vaccines would be terrific. We should be willing to sacrifice a lot, even in research ethics, for reliably achieving that. But we know hardly anything on what boosts trust. Certainly bioethicists, who are typically doctors, lawyers, philosophers or theologians—not risk communication experts or other social scientists—lack that knowledge. And it is unclear that facts, including the facts about study design, have much influence on stubborn vaccine sceptics and their political-gain-driven and money-driven mendacious influencers.

In the 70s and 80s, conservative bioethicists would regularly warn that this or that step towards women's liberation or technological progress, for example, mothers in the workplace, in vitro fertilisation (IVF) and cloning, is a 'slippery slope' that would lead to disastrous results. IVF and working mothers might cancel motherhood; cloning might breed a Hitler and a third world war. It took some years of science's ignoring these warnings to expose their likely falsehood.

Warnings about 'undermining trust'—in research or in vaccines or in medicine or in public health—are fast becoming progressive bioethicists' 'slippery slope'. These speculative warnings of a hazily stated catastrophic outcome also urge us to forego far more likely and concrete progress on public health and welfare. Let us always remember that trust in science and in medicine, admittedly an important desideratum, is responsive in part to trust-building long-term policies on the economy, policing, rural health and much else and, in the short run, to communication and engagement efforts. Bioethicists do have the jurisdiction to block medical studies, but more suitable long-run and short-run levers should usually address the communication challenge of vaccine mistrust.

Zero tolerance of any risk to public trust can translate into foregoing anything unusual. It then becomes obstructive to progress—scientific and, potentially, moral. Intellectually, it is a conversation stopper. And right now, adopting the mistrust

argument in connection to COVID-19 unwittingly surrenders to extreme vaccine sceptics.

Overall, there are plenty of reasons to be far more circumspect than research ethicists have been in recent times about appealing to effects on public trust, both in general and in relation to HCTs to fight COVID-19.

Correction notice Since this article was first published, an acknowledgement section has been added.

Acknowledgements The author is grateful to participants of a seminar at the Rutgers University Center for Population-Level Bioethics for detailed oral and written comments.

Contributors NE has conceptualised and written this entire essay.

Funding This study was funded by National Science Foundation (Award # 2039320), Open Philanthropy (Award # not applicable).

Competing interests NE serves on the Advisory Board of challenge trial volunteer organisation 1DaySooner (a non-profit promoting human challenge trials in COVID-19), an unpaid position.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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