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Why continuing uncertainties are no reason to postpone challenge trials for coronavirus vaccines

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ABSTRACT

To counter the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), some have proposed accelerating SARS-CoV-2 vaccine development through controlled human infection (or 'challenge') trials. These trials would involve the deliberate exposure of relatively few young, healthy volunteers to SARS-CoV-2. We defend this proposal against the charge that there is still too much uncertainty surrounding the risks of COVID-19 to responsibly run such a trial.

The worldwide COVID-19 pandemic is responsible for tremendous loss of life and health, as well as significant social and economic upheavals. A vaccine would be of immense value and 136 vaccine candidates are currently investigated, with eight in clinical testing. Yet the traditional regulatory pathway to licensure requires large and lengthy phase 3 efficacy trials.¹ In light of the ongoing global health crisis, some have proposed that efficacy testing could be substantially accelerated through the use of controlled human infection (CHI) trials.²⁻⁴ In a SARS-CoV-2 CHI (S-CHI), a relatively small number of participants would be randomised to receive either a vaccine candidate or a placebo, and subsequently, all would be deliberately exposed to SARS-CoV-2, the virus behind COVID-19. S-CHIs could rapidly generate data about vaccine efficacy or separate out more promising candidates for traditional phase 3 testing. They can also allow for efficacy testing even under conditions where the virus has locally abated; currently, in a special phase 3 trial in the UK, a reduction in cases is undermining the possibility of reaching meaningful results.⁵ The ability to speed and secure the testing of vaccines could potentially save countless lives.^{2-4,6}

Decision-makers appear to be seriously considering approving S-CHIs, including, to different degrees, major funders, the WHO,⁶ the US Food and Drug Administration (FDA) and European Medical Authority,⁷ trialists⁸ and vaccine manufacturers.⁷ And there has been significant popular enthusiasm for participation, with the advocacy group *1 day sooner* attracting nearly 30 000 volunteers (including one of the present authors).⁹ Still, these developments towards an S-CHI have occurred against a backdrop of initial ethical controversy, with several bioethicists expressing unease in popular media. A strong common ground for that unease appears to be uncertainty about the risk of CHI for participants; for some, present understanding of the risks of COVID-19, in general or in young patients, is too premature to green light an S-CHI.

Media generally do not allow the bioethicists it quotes the opportunity to fully develop novel arguments, nor is it typically interested in reporting finer conceptual distinctions. The comments we quote are thus, through no fault of the commentators, somewhat open to interpretation. But, notably, we know of no peer-reviewed article to date dedicated to the subject that has unequivocally opposed S-CHIs, so these sceptical comments in the press are worth engaging with. We do so by first offering some normative background, then unpacking and interpreting several potential versions of the concern with uncertainty running through these quotes. For each version of the concern, we offer a rebuttal. We conclude that current levels of uncertainty do not present a good reason to bar S-CHIs from proceeding.

ACCEPTABLE RISKS IN BIOMEDICAL RESEARCH

The fact that an S-CHI stands to save many lives is an important consideration in its favour. Yet standard approaches to research ethics limit the degree to which benefits to society can justify imposing harms on research participants, including by requiring that researchers generally obtain the informed, voluntary consent of the participant, and that participants' interests receive special protection. For the purpose of this article, we fully accept these constraints. Therefore, our evaluation of S-CHIs in no way depends on a brute consequentialist weighing of numbers of lives saved. Rather, that evaluation stems from our assessment that S-CHIs can potentially save many lives *while also remaining consistent with reasonable non-consequentialist constraints*.¹

Recent controlled infection studies, for example, for malaria or seasonal influenza, infect participants with pathogens that are either curable or self-limiting, thereby imposing moderate burdens from, for example, uncomfortable symptoms but only negligible risk of death or long-term injury.¹⁰ If maintaining an appropriate regard for participants' interests required that diseases studied in controlled infection studies *always* be curable or self-limiting, then S-CHIs could not be ethically conducted; COVID-19 is neither curable nor self-limiting, and it poses a non-negligible chance of death. However, we agree with prevailing scholarly opinion that controlled infection studies are not fundamentally ethically distinct from other types of biomedical research that impose risks on participants without

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promising corresponding benefits, and they should be judged by the same fundamental criteria.^{10–13} And we also agree with a broad body of bioethical work, as well as the US Federal Regulations, that informed adults should be permitted to voluntarily assume non-negligible risks of serious harm in the course of participating in socially valuable medical research, provided those risks are not *too high*.^{14 15}

How high is too high? With respect to research that enrolls competent, consenting adults, the two most prominent proposed standards are that net mortality risks should not be permitted to exceed either those of kidney donation,¹⁶ or 1% absolutely.¹⁷ For present purposes, we accept these limits as appropriate. So, although the potential for S-CHIs to save many lives matters, we still allow that they must be tested against their ability to enroll informed volunteers and avoid transgressing those upper limits on individual risk.

THE (UNCERTAIN) RISKS OF AN S-CHI

In recent proposals, S-CHI participants would be competent adults. Risks would be minimised both by selecting participants to be young and in good health, and by providing them priority access to high-quality medical care during the trial.^{2–4 6 18 19} We follow several prominent sources in assessing the risks to such participants by reference to their age group's infection fatality rate in the general population,^{6 13} under that approach, based on current evidence, and even before highly effective therapeutics are developed, overall mortality under these circumstances is expected to be lower than that of kidney donation,^{2 18 20 21} and far below 1% absolutely,¹⁸ and hence to be consistent with limits on individual risk. Furthermore, recent S-CHI proposals include additional risk minimisation measures, and enhanced consent processes aimed at maximally promoting participants' understanding of these risks.^{2 3 6 18 19}

But commentators remain concerned. Christine Grady explains:

We don't yet know why some people get sick and others don't... There's so much emerging information about this sort of clinical course of infection and also susceptibility to infection that it makes an assessment that it's OK to subject a certain age group to risk a little bit too fast for me... I wouldn't take [a S-CHI] off the table, but I certainly wouldn't say we're ready for it now.²²

National Institute of Allergy and Infectious Diseases (NIAID) trialist Matthew Memoli warns, 'Where you're going to give somebody a virus on purpose, you really want to understand the disease so that you know that what you're doing is a reasonable risk.'²³ Holly Fernandez-Lynch adds: 'The ethical issues become more challenging for emerging infectious diseases that are not yet fully understood and that lack effective treatments... it becomes much harder to minimize risks when you don't totally understand disease impact or transmission and when there are no proven therapeutic interventions...'²⁴ Kerry Bowman asks: 'You have consent, but is it really well-informed? Do people fully understand? Because if we don't understand the virus itself, I wonder about the quality of informed consent that you can ask of people.'²⁵

These commentators' remarks are united in grounding concern about S-CHIs in the current uncertainty surrounding COVID-19 and its risks. Yet despite this common theme, they suggest several distinct potential arguments. Let us unbundle these arguments and address each.

UNINFORMED CONSENT?

Bowman's question suggests an argument according to which current levels of uncertainty make it impossible to inform participants enough to obtain valid informed consent, and hence that S-CHIs cannot ethically proceed. The New York Times attributes this concern to the scientific community more broadly: 'Some scientists caution that truly informed consent, even by willing volunteers, may not be possible. Even medical experts do not yet know all the effects of the virus.'²⁶ And a joint statement by two AIDS advocacy organisations states *inter alia* that, because it is not the case that 'pathogenesis and risks are reasonably well characterized ...ensuring appropriate informed consent [for an S-CHI] may be impossible.'²⁷

However, high uncertainty among experts is perfectly compatible with valid informed consent: consent can remain valid when researchers' understanding is highly incomplete, or even completely wrong.²⁸ If a (near-) complete and accurate understanding were really required, then valid informed consent for research would often be unobtainable—research by its nature addresses areas where there are gaps in existing knowledge. And many older studies would have to be viewed as having failed to obtain valid informed consent, and hence as ethically and legally problematic, given prevailing ignorance at the time they were conducted. Yet these implications are implausible. This is because informed consent requires only that researchers communicate their best concurrent understanding of relevant features of the study to participants. Rather than making informed consent impossible, serious uncertainty is itself just another thing that must be responsibly communicated.

AN EASY SAFETY IMPROVEMENT, WASTED?

It is currently unknown what underlying risk factors lead some people, but not others, to experience the most serious complications from COVID-19; for cases that do progress, there is no available cure. Grady and Fernandez-Lynch's remarks can be read as suggesting that it would be best to wait to proceed until researchers develop sufficiently powerful risk-minimising exclusion criteria or an effective cure. It might be argued, in defence of this suggestion, that failing to wait for such safety improvements may involve imposing *gratuitous* risks on subjects.

Researchers have a widely acknowledged obligation to minimise risks to participants, which may be thought to support this line of thought. For example, when researchers can use fewer invasive procedures without compromising the quality of their data and, hence, the social value of the research, they are clearly required to do so. But this obligation's scope is limited by considerations of sound study design.²⁹ When invasive procedures are non-redundant and enhance the ability of a study to answer an important research question, it is no longer obvious that these procedures should be prohibited. Instead, 'reviewers should carefully balance these competing considerations.'¹⁵

Whether or not to wait for further safety improvements before conducting S-CHIs is a decision of the latter sort. Much of the point of an S-CHI lies in its promise of timeliness. Safety gains from waiting for cures or biomarkers of severe disease to emerge must be balanced against sacrificing valuable timeliness.

In our view, unless cures or far better exclusion criteria are right around the corner (eg, as an S-CHI is about to start, the FDA approves a game-changing therapy that could become available for study participants the following week), S-CHIs should proceed as soon as possible. As we mentioned, even without the further safety improvements, running an S-CHI would already involve levels of mortality risk that remain within the

absolute bounds that bioethicists take to be acceptable; whereas every month of inaction in the face of the virus's exponentially growing impact could translate into a month of 'famines of biblical proportions', deaths from disruptions to non-COVID healthcare and, of course, direct COVID-19 deaths for world populations. Given the urgency of the situation, it is sensible, not gratuitous, to proceed without waiting for further improvements in safety.

Notably, this point is not unique to S-CHI designs. One risk posed by SARS-CoV-2 vaccines is that they could *enhance* the severity of COVID-19. During traditional field trials, this risk could significantly harm and potentially kill participants. Although this risk would also be significantly lower once a COVID-19 cure exists, it is widely agreed that we should not wait for a cure before we begin testing the efficacy of vaccine candidates. We believe that this judgment is correct for *both* traditional and S-CHI trials.

IGNORING UNKNOWN RISK FACTORS?

Comments such as 'We don't yet know why some people get sick and others don't' may express concern over the ability of the proposed exclusion criteria to protect *all* participants. For instance, some young and healthy patients with COVID-19 have died of strokes. Perhaps some unknown underlying risk factor explains this outcome, for example, a particular genetic variant. If so, then healthy, young individuals with that risk factor may be at 'objectively' high personal risk from participation in an S-CHI, even given that the average risks for their demographic are low. One might argue that the existence of such (currently) unidentifiable high-risk individuals makes any S-CHI unacceptably risky.

But this applies an interpretation of risk that is irrelevant to the dilemma at hand—and to most medical decision-making. Trialists should assess individuals' risks according to the best available information. So long as it remains unknown and unknowable to them which individuals are at objectively high risk, trialists should treat each individual's risk as being the average in the pool. As noted earlier, that would involve treating each young and healthy individual volunteering for an S-CHI as being at an acceptably low personal risk.

Likewise, a clinician can be in the right in prescribing a medication whose prospect of benefit exceeds its prospect of harm on average, even if she knows that it causes severe but very rare harmful reactions. She can be in the right even if she knows that these harmful reactions track personal genetics of victims, so long as she also knows that science does not know, and could not anytime soon discover, who has the relevant genetic risk factors. In both cases, what matters is risk assessments as made according to the best available information, not the (known) 'objective' existence of *unidentifiable* risk factors.

INSUFFICIENT CAUTION IN THE FACE OF GENUINE UNCERTAINTY?

The uncertainty at play in assessing an S-CHI is 'deeper' than the one involved in, for example, drawing a card from a deck of playing cards. Decks are uniform and well understood, and assessing at 1.92% (1 in 52) a draw for the Ace of Spades is a precise expression of that understanding. By contrast, estimates of mortality risk in an S-CHI for different demographics are based on undesirably sparse and still shifty data. An assessment of 0.03% fatality from infection for people in their 20s,³⁰ which several related articles espouse,^{6 18 20} is more of a best guess. If one

were forced to pick a number, then 0.03% might be the number it made most sense to pick. But it also might not be that much of a surprise if the true rate turned out to be higher or lower. If so, the use of a single number may suggest an undue level of precision. In order to avoid false precision, philosophers sometimes favour representing our position with respect to sparse and uncertain data in terms of a range. For instance, we might think that, notwithstanding our best guess of 0.03%, current evidence still leaves it open that the true risk might range from 0.003% at the low bound to 0.3% at the upper bound. Some critics might then add a further thought: that in such situations it is ethically responsible to proceed pessimistically, where 'pessimism' is defined by acting for practical purposes as if the true risk were at, or close to, the higher end of the range of uncertainty. So this might involve treating the risk of an S-CHI as 0.3%, rather than 0.03% (or 0.003%). Allowing for even wider uncertainty, it may be thought that the upper end of the range exceeds a 1% risk of dying. On a pessimistic approach, and further assuming that deadly risks topping 1% are never allowed,^{17 18} then S-CHIs could not be ethically conducted at present.

This way of thinking about uncertainty and risk may seem to nicely explain why it makes sense to emphasise current uncertainty surrounding COVID-19, even given that the current best guess is a tolerably low risk. The explanation is that it is the upper bound of uncertainty, not the best guess, that determines whether trials may proceed. This upper bound of uncertainty can only be lowered by way of collecting more data, gaining a better understanding and, ultimately, reducing overall uncertainty. That is, it can be reduced by waiting, just as suggested by our commentators.

Of the arguments we have outlined, this one is the most complex and difficult to evaluate, partly because philosophers continue to debate how to handle genuine uncertainty. Still, we believe that it is possible to sketch a reasonable path forward. Our suggestion is that pessimistic approaches to uncertainty are indeed plausibly appropriate for assessing trials whose participants would lack decision-making capacity; however, competent adults who provide fully free and informed consent should be free to make enrolment decisions by employing whatever method of practically resolving uncertainty best expresses their values, provided that method is at least *prima facie* reasonable.

In particular, when ethicists and regulators evaluate the risks of trials that seek to enrol children and decisionally incapacitated adults, ethicists and regulators are in the normative role of benevolent representatives, or fiduciaries, who act on behalf of the potential participants. Several philosophers have argued that benevolent representatives should or could legitimately address genuine uncertainty by employing very conservative strategies.^{31–33} Here, a conservative strategy would plausibly require treating risks pessimistically.

But when it comes to studies that enrol competent adults, the ethicists and regulators do not participate in deciding for the competent adult participant whether to enrol. Rather, the competent adult decides for herself. All existing ethical and regulatory codes agree that this distinction is normatively significant, and, consequently, that studies that enrol competent adults may permissibly carry more risk than studies that do not. We suggest that just as it is appropriate to allow competent adults to determine for themselves whether to take on some level of risk, at least when their decision is *prima facie* reasonable, it is similarly appropriate to allow them to determine for themselves how pessimistically or optimistically to make decisions in light of the uncertainty surrounding those risks, again, at least when their method is *prima facie* reasonable.

Within the realm of the *prima facie* reasonable, there are multiple practical strategies for acting under uncertainty. A person might be optimistic, pessimistic or neutral, emphasising different areas of the range of uncertainty when deciding how to proceed. When it comes to choosing among these different approaches, none need be viewed as inherently unreasonable or confused.^{33 34}

Given the range of strategies available, different individuals can be expected to make different choices when confronted with uncertain risks. Some competent, pessimistic adults may be very concerned that the risks of an S-CHI could be on the more serious end. So they might treat those risks as though they were near the top of their conceivable range, and thus decline any opportunity to enrol.ⁱⁱ Of course, that is their right. At the same time, other capacitated adults with more neutral decision procedures may not decide under worst-case assumptions. For instance, they instead might focus on the best guess of 0.03% and use that probability in deliberating on whether to enrol.

Importantly, these latter adults' choice to anchor their practical reasoning in a current best guess is *neutral*, rather than *optimistic*. Although we must be aware that our current uncertainty could resolve into higher risks than our present best guesses, it can just as well resolve into lower risk. In fact, more recent data show a 0.007% infection fatality rate among people in their 20s, substantially lower than the 0.03% figure quoted above.³⁵ The symmetry of our uncertainty surrounding such numbers might be undermined if there were empirical reasons to suspect that current best guesses are systematically biased for overoptimism—if, for instance, there were reasons to anticipate a surge in deaths being reclassified as COVID-19, leading to much higher fatality estimates. But we are unaware of any such reasons, and that is certainly not the trend,³⁶ so neutrality seems presumptively fitting. Therefore, even if one finds an *optimistic* decision procedure suspect, or, relatedly, if one is concerned about practical complications from recruiting hyperoptimistic decision-makers,³⁷ neutrality with regard to best guesses seems independently reasonable here. And such neutrality makes a candidate participant's assessment of S-CHIs as low risk an adequate ground for enrolling her.

When competent adults deliberate freely and with full comprehension about whether to enrol in a study, their choice generally ought to be respected unless there is something clearly unreasonable about it. Given that there is nothing clearly unreasonable about making an enrolment decision on the basis of a current best guess, effectively treating the mortality risk of an S-CHI as 0.03% (or 0.007%), for reviewers to intercede and to forbid competent adults from so acting would be an overreach. It would also be extremely harmful, given that it would effectively prohibit attempts to make a key contribution to the fight against an ongoing global pandemic. When competent adults are adequately informed of and evidently comprehend the risks, including the range of uncertainty surrounding those risks, yet persist in their desire to volunteer to enrol, they should be allowed to do so.

There is a final response to the concern about insufficient caution in the face of uncertainty. Many further steps must take place before a challenge can start. A vaccine candidate must clear

phases 0, 1, 2 testing, a challenge strain must be developed, and so forth. During that time, more certainty is likely to emerge, potentially resolving the current complication. Risk estimates may go down enough to remove any further worry about transgressing risk limits—as they may already have.³⁵ But even if risk estimates increase, and even if that were to make conducting an S-CHI unethical, the proposal to do so could always be shelved, last minute. Continuing to pursue the possibility of an S-CHI now is reasonable given current evidence, and also keeps our options open in the future.

CONCLUSION

There are likely to be more than enough capacitated adults willing to participate in an S-CHI, even allowing for current uncertainty.⁹ If ethics reviewers intercede to deprive those would-be participants of the chance to participate, that has the doubly undesirable properties of both interfering with competent adults' apparently reasonable choices and, more importantly, possibly delaying the testing of a vaccine that may prevent large numbers of deaths. Even if it is sometimes permissible to restrict autonomy to prevent significant collective harm, medical ethicists should not be in the business of restricting autonomy and thereby interfering with the prevention of significant collective harms. If CHIs to assess SARS-CoV-2 vaccine efficacy fast are as helpful as many suspect they are, they should not be put on hold until greater certainty about their risks surfaces.

Correction notice This paper has been updated since first published to correct references 23, 25, and 26.

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REFERENCES

- 1 WHO. Draft landscape of COVID 19 candidate vaccines, 2020. Available: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines> [Accessed 13 Jun 2020].
- 2 Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect Dis* 2020;221(11):1752–6.
- 3 Plotkin SA, Caplan A. Extraordinary diseases require extraordinary solutions. *Vaccine* 2020;38(24):3987–8.
- 4 Richards AD. Ethical guidelines for deliberately infecting volunteers with COVID-19. *J Med Ethics* 2020. doi:10.1136/medethics-2020-106322. [Epub ahead of print: 27 May 2020].
- 5 Sky News Team. Coronavirus 'disappearing' so fast Oxford vaccine has 'only 50% chance of working'. Sky News, 2020.
- 6 WHO Working Group for Guidance on Human Challenge Studies in COVID-19. *Key criteria for the ethical acceptability of COVID-19 human challenge studies*. 20. Geneva: WHO, 2020.
- 7 Cookson C, Kuchler H. *Researchers prepare for human challenge trials of Covid-19 vaccine*. Financial Times, 2020.

ⁱⁱSuppose, by contrast, that a person has an exceedingly pessimistic decision procedure which practically treats uncertain S-CHI risks as >1%, yet seeks to enrol anyway, out of altruism. Provided trialists' best guess is that the risk for that person is still under 1%, and allowing that 1% is a genuine cap on allowable research risks, the authors remain divided on how to apply the limit in that case.

- 8 Devlin H. *WHO conditionally backs Covid-19 vaccine trials that infect people*. *Guardian*, 2020.
- 9 1Day Sooner staff. *The COVID challenge*, 2020. Available: www.thecovidchallenge.org/ [Accessed 13 Jun 2020].
- 10 Miller FG, Grady C. The ethical challenge of infection-inducing challenge experiments. *Clin Infect Dis* 2001;33(7):1028–33.
- 11 Binik A. What risks should be permissible in controlled human infection model studies? *Bioethics* 2020;34(4):420–30.
- 12 Bamberg B, Selgelid M, Weijer C, et al. Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics* 2016;9(1):92–103.
- 13 Shah SK, Kimmelman J, Lyerly AD, et al. *Ethical considerations for Zika virus human challenge trials*. National Institute for Allergy and Infectious Diseases, 2017.
- 14 HHS. *45 CFR 46 (Human subjects research)*. USA, 2009.
- 15 Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research. *Kennedy Inst Ethics J* 2011;21(2):141–79.
- 16 Miller FG, Joffe S. Limits to research risks. *J Med Ethics* 2009;35(7):445–9.
- 17 Resnik DB. Limits on risks for healthy volunteers in biomedical research. *Theor Med Bioeth* 2012;33(2):137–49.
- 18 Shah SK, Miller FG, Darton TC, et al. Ethics of controlled human infection to address COVID-19. *Science* 2020;368(6493):832–4.
- 19 Eyal N. Why challenge trials of SARS-CoV-2 vaccines could be ethical despite risk of severe adverse events. *Ethics Hum Res* 2020. doi:10.1002/eahr.500056. [Epub ahead of print: 22 May 2020].
- 20 Eyal N, Lipsitch M, Smith PG. Response to Cioffi. *J Infect Dis* 2020;222(1):169–70.
- 21 Eyal N, Halkitis PN. AIDS activism and coronavirus vaccine challenge trials. *AIDS Behav* forthcoming.
- 22 Branswell H. *Infect volunteers with Covid-19 in the name of research? A proposal lays bare a minefield of issues*. *STAT News*, 2020.
- 23 Cohen J. Speed coronavirus vaccine testing by deliberately infecting volunteers? Not so fast, some scientists warn, 2020. *Science magazine*. Available: <https://www.sciencemag.org/news/2020/03/speed-coronavirus-vaccine-testing-deliberately-infecting-volunteers-not-so-fast-some> [Accessed 9/18/2020].
- 24 Healio Infectious Disease News. Working group provides framework that supports controlled human infection trials for COVID-19, 2020. Available: <https://www.healio.com/infectious-disease/emerging-diseases/news/online/%7Bac803653-8234-4929-85f2-d634bc5ad676%7D/working-group-provides-framework-that-supports-controlled-human-infection-trial-for-covid-19> [Accessed 15 May 2020].
- 25 Miller A. Could risky human challenge studies help find a vaccine sooner? 2020. *CBC*. Available: <https://www.cbc.ca/news/health/coronavirus-human-challenge-trials-1.5561951> [Accessed 9/18/2020].
- 26 Sangner DE, Kirkpatrick DD, Zimmer C, et al. Profits and pride at stake, the race for a vaccine intensifies, 2020. *The New York Times*. Available: <https://www.nytimes.com/2020/05/02/us/politics/vaccines-coronavirus-research.html> [Accessed 9/18/2020].
- 27 AIDS Vaccine Advocacy Coalition (AVAC), Treatment Action Group (TAG). *AVAC and tag statement on ethical conduct of SARS-CoV-2 vaccine challenge studies*. AVAC, 2020.
- 28 Eyal N. Informed consent. In: Schaber P, Müller A, eds. *The Routledge Handbook of the ethics of consent*. 1st ed. Abingdon Routledge, 2018.
- 29 Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283(20):2701–11.
- 30 Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020;20(6):669–77.
- 31 Hurley SL. *Justice, luck and knowledge*. Oxford, UP: Oxford, 2003.
- 32 Gardiner SM. A core precautionary Principle*. *J Polit Philos* 2006;14(1):33–60.
- 33 Buchak L. *Risk and rationality*. New York: Oxford UP, 2013.
- 34 Buchak L. Why high-risk, non-expected-utility-maximising gambles can be rational and beneficial: the case of HIV cure studies. *J Med Ethics* 2017;43(2):90–5.
- 35 Salje H, Tran Kiem C, Lefrancq N, et al. Estimating the burden of SARS-CoV-2 in France. *Science* 2020. doi:10.1126/science.abc3517. [Epub ahead of print: 13 May 2020].
- 36 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates. *medRxiv* 2020.
- 37 Hare C. Risk and radical uncertainty in HIV research. *J Med Ethics* 2017;43(2):87–9.