INTRODUCTION

In late 2018, He Jankui announced the birth of Lulu and Nana, the world’s first human beings born with an edited genome. The Chinese scientist had used the novel CRISPR/Cas9 technology to alter the genes of in vitro embryos, which were then transferred to the prospective mother’s uterus, eventually resulting in the twin girls’ birth. The aim was to afford the girls, whose intended father was HIV positive, resistance against the infection by disabling the CCR5 gene, which codes for a protein that allows the HIV virus to enter cells.

He’s announcement was quickly met with condemnation by scientists, bioethicists, and other commentators. Critics particularly stressed that significant uncertainties remain about the effects of altering genes, making the genetic modification of human embryos risky, especially because not only the targeted individual but also its descendants will be affected. They also alleged, inter alia, that He’s conduct violated the international scientific consensus view that ‘germline’ genetic interventions (the introduction of heritable changes into the human genome) are premature; that the couples enrolled in the experiment had not provided valid informed consent; that there are safer ways of preventing father-to-child HIV transmission; and that HIV/AIDS is not a sufficiently serious condition to make HIV resistance a legitimate first goal of human germline gene editing.

Marchione, M. (2018, November 26). Chinese researcher claims first gene-edited babies. AP News. https://apnews.com/4f977b7a36e45449b488e19ac83e86d

Baltimore, D., Charo, A., Daley, G. Q., Doudna, J. A., Kato, K., Kim, J.-S., Lovell-Badge, R., Merchant, J., Nath, I., Pei, D., Porteus, M., Skehel, J., Tam, P., & Zhai, X. (2018). Statement by the Organizing Committee of the Second International Summit on Human Genome Editing. https://www.nationalacademies.org/news/2018/11/statement-by-the-organizing-committee-of-the-second-international-summit-on-human-genome-editing;

Caplan, A. (2019). Getting serious about the challenge of regulating germline gene therapy. PLoS Biology, 17(4), e3000223; Lander, E., Baylis, F., Zhang, F., Charpentier, E., Berg, P., Bourgain, C., Friedrich, B., Joung, K. J., Li, L., Liu, D., Naldini, L., Nie, J.-B., Qi, R., Schepens-Siefert, B., Shao, F., Terry, S., Wei, W., & Winnacker, E.-L. (2019). Adopt a moratorium on heritable genome editing. Nature, 567(7747), 165-168; Savulescu, J., & Singer, P. (2019). An ethical pathway for gene editing. Bioethics, 33(2), 221-222.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. Bioethics published by John Wiley & Sons Ltd
These criticisms notwithstanding, the event had been preceded by a significant shift in attitude in the scientific and bioethical community. For a long time, germline genetic interventions were widely considered ethically out of bounds. However, partly because CRISPR potentially renders such interventions more accurate than earlier gene transfer technologies, scientists, ethicists, and advisory bodies had increasingly come to consider them in principle permissible provided that certain requirements are met. Reflecting this stance, several of He’s critics not only highlighted ethical violations involved in the experiment, but also proposed conditions that, if fulfilled, would make clinical use of human germline gene editing (henceforth GGE) ethically justified. The pursuit of this goal will therefore likely continue.

Supporters of pursuing GGE under certain conditions agree that clinical applications should, at least to begin with, be reserved for avoiding the transmission of devastating diseases in cases where these cannot otherwise be prevented. Crucially, they also agree that such applications must wait until more is known about their safety and effectiveness. Progress in this area will therefore require research, first preclinical studies on animal models and in vitro embryos and then, if warranted by the preclinical evidence, clinical trials where genetically edited embryos are transferred to the uterus of a gestational mother and brought to term. Such research raises ethical issues distinct from those foregrounded in longstanding bioethical debates about germline genetic modification. These debates have mainly concerned how the relevant technologies should be used once safe and effective. However, more immediate questions concern whether they can ethically be developed, i.e. rendered safe and effective, and, if so, how.

This paper contributes to the discussion of this issue by considering whether clinical trials of GGE would comply with the fundamental research ethical requirement of non-exploitation. I argue that it is unclear that they would. This is because participants would face substantial risks and burdens while being in a situation where declining participation is difficult. This concern constitutes a significant ethical obstacle on the path towards clinical use of GGE.

Philosophers and bioethicists generally agree that exploitation involves taking advantage of people in some wrongful way. However, they disagree about which transactions and relationships qualify as exploitative and what, precisely, is morally wrong with them. My argument does not presuppose any particular view on these matters, but merely appeals to certain features that most exploitation theorists recognize. The following paradigmatic example of an exploitative exchange illustrates these features:

Pit: B is alone in a pit in the desert and cannot get out, facing death from dehydration unless the situation changes. A comes along and proposes to extract B, but only if B agrees to transfer his life savings to A. B agrees. The rescue requires minimal effort of A.11

Pit highlights four significant general features of wrongful exploitation. First, even mutually beneficial transactions and relationships can be wrongfully exploitative. In Pit, A stands to benefit considerably from B’s money. But B benefits too, assuming (plausibly) that giving up his life savings is better for him than death.

Second, exploitation can occur even though the victim consents. Of course, in Pit B has ‘no choice’ but to accept A’s proposal given that the only alternative is death. But since B is fully informed and not coerced or manipulated by A, his agreement can plausibly be considered consensual.12

Third, even when exploitation is mutually beneficial, there is always something objectionable about the level (or perhaps nature) of the benefits involved. The exploiter benefits excessively (or...
inappropriately), whereas the victim benefits insufficiently (or ‘inauthentically’). Differently put, the exploitation makes the victim better off than before and better off than he otherwise would be, but worse off than he ought to be.\(^{12}\) In Pit, B derives a significant benefit (his life) but the price A requests in exchange (B’s life savings) is exorbitant, given that A could easily have rescued B for much less. Thus, the exploiter extracts more than he is entitled to from the victim. Call this feature of exploitation the ‘advantage clause’.\(^{14}\)

This feature is closely related to the fourth one, the ‘vulnerability clause’:\(^ {13}\) the exploiter can extract excessive or inappropriate gain only because of the victim’s precarious circumstances. The victim is desperate, needy, or in a weak bargaining position, and is therefore in no position to refuse transacting on beneficial but exploitative terms. In Pit, A can secure B’s agreement to transfer his life savings only because B cannot escape the pit in any other way.

Most exploitation theorists agree that some version of the advantage clause and some version of the vulnerability clause constitute necessary and jointly sufficient conditions for wrongful exploitation. Their main disagreement concerns what makes extracting excessive advantage from the vulnerable wrong: distributive unfairness,\(^ {16}\) a failure of Kantian respect,\(^ {17}\) or domination.\(^ {18}\) However, this disagreement does not affect my argument here.

3 | GENE EDITING TRIALS AND EXPLOITATION

Establishing that GGE trials would raise exploitation concerns requires showing that they would likely fulfill the vulnerability clause and the advantage clause. Let us consider each in turn.

3.1 | Gene editing trials and vulnerability

The vulnerability clause applies when one party to a transaction lacks decent alternatives to transacting on the other’s terms.\(^ {19}\) If, in Pit, B could extract himself through modest effort, he would not be vulnerable in the relevant sense and A’s proposal to extract him in exchange for his life savings would therefore not be exploitative. A necessary part of the reason why there is exploitation here is that B’s only alternative to transacting with A (death) is prohibitively burdensome.\(^ {20}\)

Participants in GGE trials would plausibly face a sufficiently constrained set of options for the vulnerability clause to apply. To see this, note that GGE is (at least in the short-to-medium term) proposed for a very small group of would-be reproducers.\(^ {21}\) Such interventions are mainly considered for severe incurable single-gene disorders (e.g. Tay-Sachs disease) since the genetic basis of more complex conditions (e.g. cardiovascular disease, diabetes) is insufficiently understood to allow reliable editing. Most prospective parents are not at increased risk of transmitting such a disorder, and those at risk usually have other ways of avoiding having afflicted children. Adoption is one alternative, but is not available to everyone and cannot produce the genetic tie that many people strongly desire. However, at-risk couples who would be satisfied with a child that is genetically related to one of them may, in many jurisdictions, reproduce using donor gametes. And those who lack access to or reject this option may create, select, and implant embryos without the condition in question using preimplantation genetic diagnosis (PGD).\(^ {22}\) However, in rare cases, e.g. when one prospective parent is homozygous for a dominant condition or when both are homozygous for a recessive one, these procedures fail to produce any unaffected embryo. GGE has clear utility only in this kind of case, i.e. for prospective parents who are at high risk of transmitting a severe incurable single-gene disorder, who strongly desire a genetic child, and who lack all alternative options just described.\(^ {23}\) These are also considered the primary candidates for participation in GGE trials.\(^ {24}\)

Consider the choice situation of these participants. They strongly desire a healthy genetic child. They are likely to see the fulfilment of this desire as central to their well-being. They could try to reproduce without using gene editing. However, assuming that pregnancy and birth are achieved, this would likely mean caring for a child with a short and agonizing life. Alternatively, they could decide not to become parents at all or seek to adopt. However, either option would leave the desire for genetic relatedness unfulfilled. It is therefore plausible that, when presented with the option of enrolling in the trial—which does offer a chance of a healthy genetic child—this is the only option they do not find

---

\(^{12}\) Mayer, R. (2007). What’s wrong with exploitation? *Journal of Applied Philosophy*, 24(2), 137–150; Malmqvist, E., & Szigeti, A. (2021). Exploitation and remedial duties. *Journal of Applied Philosophy*, 38(1), 55–72.

\(^{13}\) Liberto, H. (2014). Exploitation and the vulnerability clause. *Ethical Theory and Moral Practice*, 17(4), 619–629.

\(^{14}\) Ibid.

\(^{15}\) Mayer, op. cit. note 13; Wertheimer, A. (1996). Exploitation. Princeton University Press.

\(^{16}\) Sample, R. (2003). *Exploitation: What it is and why it’s wrong*. Rowman & Littlefield; Snyder, J. (2008). Needs exploitation. *Ethical Theory and Moral Practice*, 11, 389–405.

\(^{17}\) Vrousalis, op. cit. note 11.

\(^{18}\) This section discusses the lack of alternatives as a vulnerability to exploitation, not as a threat to the voluntariness of consent. On the latter issue, see Wilkinson & Moore, op. cit. note 12.

\(^{19}\) Ibid.

\(^{20}\) Valdman argues a stricter specification of the vulnerability clause, according to which all alternatives to transacting must be unreasonable rather than prohibitively burdensome. See Valdman, M. (2009). A theory of wrongful exploitation. *Philosophers’ Imprint*, 9(6), 1–14. As Liberto argues, this excludes too many cases that clearly seem to involve exploitation, so we should (as I do here) specify the clause somewhat more inclusively. See Liberto, op. cit. note 14.

\(^{21}\) Savulescu & Singer, op. cit. note 2; Gyngell et al., op. cit. note 4; NASEM, op. cit. note 4.

\(^{22}\) Some reject PGD because it involves destroying embryos. However, so does GGE, making it equally objectionable to these reproducers. See Lander, E. (2015). Brave new genome. *New England Journal of Medicine*, 373(11), 5–8.

\(^{23}\) Cwik (2020a), op. cit. note 8; Cavaliere, G. (2018). Genome editing and assisted reproduction: Curing embryos, society or prospective parents? *Medicine, Health Care and Philosophy*, 21(2), 215–225; Rulli, T. (2019). Reproductive CRISPR does not cure disease. *Bioethics*, 33(9), 1072–1082.

\(^{24}\) NASEM, op. cit. note 4.
prohibitively burdensome. 25 And if this is the case, the vulnerability clause applies.

It might be objected that this exaggerates the importance of genetic relatedness. Cannot the goods of parenting be realized by caring for and raising a non-genetic, e.g. adopted, child? There are indeed strong reasons to think so. 26 However, my argument does not assume that the preference for genetic children is defensible, only that it would be deeply held by participants in GGE trials. And this does seem plausible. Absent a strong such preference it is unclear what would motivate these participants to enrol, given the alternative reproductive options surveyed above and the burdens of participation discussed in Section 3.2 below. Indeed, absent this preference, the rationale for pursuing GGE, whose main advantage over other means for avoiding transmitting severe genetic conditions lies in establishing a genetic parent-child link, would significantly weaken. 27

But even granted that participants in GGE trials would strongly prefer a genetic child, it might be argued that a lack of options for fulfilling this preference is not a sufficiently serious vulnerability to raise exploitation concerns. Remaining childless or adopting does not seem quite as bad as dying of thirst in a pit, after all, even for somebody who deeply desires a genetic child. In response, vulnerability is admittedly scalar, and it can be debated just how restricted people’s choices must be for them to be vulnerable to exploitation. 28 However, it does not seem that all alternative options have to be truly catastrophic—like, say, imminent death or loss of a life partner. By analogy, people are plausibly considered vulnerable to exploitation when they enrol in research to access otherwise unavailable medical treatment, even if the treatment is not life-saving but only relieves debilitating symptoms. 29 Similarly, workers are plausibly considered vulnerable to exploitation when they take precarious jobs to escape unemployment, even when unemployment would not mean starvation but rather feeding themselves and their families less than adequately. 30 The alternative option in these cases (experiencing debilitating symptoms, inadequately feeding oneself and one’s family) is not catastrophic, but unattractive enough to make one vulnerable to exploitative arrangements. The alternative option in the GGE case (foregoing the chance of a much-desired genetic child) may well be equally unattractive.

These analogies could be challenged on the grounds that the alternative option is objectively bad in the other cases, but merely subjectively unattractive in the GGE case. Thus, it could be argued that while participants strongly prefer a genetic child, leaving this preference unfulfilled may not ultimately make them worse off. 31 In response, we should use (or at least allow for) a subjective standard when assessing the burdensomeness of options for the purpose of determining whether somebody is vulnerable to exploitation. 32 Clearly, whether people are willing to agree to exploitative arrangements depends on the subjective value they attach to their options at the time of choosing between them, not (directly) on the eventual objective outcome of the options. 33

In conclusion, it is plausible to think that GGE trials would fulfil the vulnerability clause.

3.2 | Gene editing trials and excessive advantage

Regarding the advantage clause, it should be recognized that not all instances of benefiting from (genuinely) vulnerable people qualify as exploitation. If, in Pit, A only requested reimbursement for the cost of the rope (plus perhaps a small fee for his efforts) in exchange for extracting B, we would not call him an exploiter. Rather, the label applies because the gain that A does derive (B’s life savings) is excessive, whereas B’s gain (survival minus his life savings) is insufficient.

Now, as a general matter, determining whether A benefits excessively and B insufficiently from some mutually beneficial transaction is notoriously difficult. However, as a first pass, it seems clear that we need to consider (a) the net gain from the transaction to A, (b) the net gain from the transaction to B, and (c) how A’s and/or B’s gain compares to some normative standard that specifies what A and/or B ought to receive.

Some clarifications and caveats. First, determining the net gain from a transaction (including in research 34) requires adding up all the benefits involved and subtracting all costs or burdens. 35 In the research context, this means that we should adopt a more inclusive view of benefits and burdens for assessing whether a study is exploitative than for making a risk-benefit assessment, at least insofar as the latter is thought to properly exclude certain types of benefit and/or cost. 36 Second, each party’s net gain should be measured against a no-transaction baseline, i.e. a counterfactual situation in which the parties do not transact (or a past situation in which the

---

25While I assume that participants would be vulnerable due to their preference for a genetic child and their unwillingness to consider non-genetic parenthood options at the time of deciding whether to enrol, I do not deny that these preferences might later change if the option to secure a genetic child in this way disappears, e.g. after the trial has failed to produce such a child. On such preference change, see Hendriks, S., Peeraer, K., Bos, S., & Dancet, E. A. F. (2017). The importance of genetic parenthood for infertile men and women. Human Reproduction, 32(10), 2076–2087.

26Rulli, T. (2016). Preferring a genetically-related child. Journal of Moral Philosophy, 13(6), 669–698.

27Cavalli, op. cit. note 23; Rulli, op. cit. note 23.

28See footnote 20.

29Malmqvist, E. (2017). Better to exploit than to neglect? International clinical research and the non-worseness claim. Journal of Applied Philosophy, 34(4), 474–488.

30Snyder, op. cit. note 17.
transaction has not yet occurred.\textsuperscript{37} Third, their respective gains should be assessed from an ex ante perspective, focusing on the expected outcome at the time of entering the transaction rather than the outcome that eventually results.\textsuperscript{38} Otherwise, many clearly exploitative transactions involving uncertainty—e.g. extremely risky human subject research—would be misclassified as non-exploitative merely because of chance.

While these points are fairly uncontroversial, the tricky part concerns (c) above, i.e. what normative standard should be used for assessing A’s and/or B’s gain. Some propose a \textit{comparative} standard: A’s gain is excessive when it is too large compared to B’s gain.\textsuperscript{39} Others defend a \textit{non-comparative} standard: A’s gain is excessive when B’s gain fails to reach some threshold, such as the fulfillment of needs.\textsuperscript{40} However, specifying the standard in greater detail has proven elusive. Indeed, Wertheimer—the leading exploitation theorist in research ethics—concluded a thorough 2011 examination of extant proposed candidates (including one earlier defended by himself) by noting that none was ultimately plausible.\textsuperscript{41}

Absent a compelling standard of excessive gain, the most promising way of assessing whether GGE trials would fulfill the advantage clause is arguably to proceed casuistically, comparing this case to other relevantly similar cases where the clause plausibly is fulfilled. One such case is pharmaceutical trials in low- and middle-income countries (LMICs) in cases where participants enrol to gain temporary and/or uncertain access to needed but otherwise unavailable medicines or healthcare, and the investigational drug will be marketed in affluent countries but will be unaffordable in LMICs.\textsuperscript{42} Another is phase 1 trials involving paid healthy volunteers in cases where participants depend economically on trial income, but are paid modestly, lack insurance, and risk exclusion from the study without pay, while assuming health risks and enduring unpleasant or intrusive research procedures, strict diet and resting regimes, and weeks of confinement.\textsuperscript{43}

Both these cases are plausibly thought to involve excessive gain to researchers and sponsors and insufficient gain to participants (and, since the latter are vulnerable, to be exploitative). The following features support this judgment: the potential gain to the powerful party—the sponsors and researchers—is substantial, yet not, in a single case, necessary to secure an adequate level of well-being. On the other hand, the potential gain to the vulnerable party—the participants—is necessary to their well-being; this is what makes them vulnerable. However, this gain is uncertain or insufficient to fully meet that need, and the burdens incurred in pursuing it are quite substantial. Crucially, these features suggest that researchers and sponsors benefit excessively even though their net gain may be considerably smaller than that of the participants, who, after all, stand to benefit from much-needed medicine or income. As in many other cases (including Put), the victims of exploitation, due to their vulnerability, have more to gain than their exploiters from the exploitative transaction.\textsuperscript{44}

It is plausible to expect GGE trials to display similar features, which provides reason for thinking that they would indeed fulfill the advantage clause. To begin with, such a trial would be a prestigious and sensational scientific project. Thus, the researchers would stand to benefit from massive scholarly and public attention, boosted funding and career prospects, and, possibly, increased salaries and intellectual satisfaction. Moreover, the investors that would likely back them could expect a handsome return on investment, whereas the universities (or private firms) employing them would derive significant reputational gain and a competitive edge over other universities (or firms). These benefits seem considerable, yet not essential to these parties’ well-being. The researchers would likely already be quite established in their field, the sponsors would have other investment options, and the employers would have alternative ways of competing and building reputation.

Of course, these reputational, economic, and career benefits are not guaranteed. First, they are contingent on the experiment being perceived as scientifically and ethically legitimate by a sufficiently large proportion of scientists, other experts, and (perhaps) the general public. Absent such legitimacy, the researchers, employers, and sponsors would risk ostracism, reputational damage, legal sanctions, etc.—as the He Jankui case illustrates. Second, the magnitude of these benefits would likely depend on whether the experiment is successful. They would presumably be significantly greater if the trial yields a healthy genetically edited child than if it does not. However, even an unsuccessful trial would likely provide some such benefits, as long as it is perceived as scientifically and ethically legitimate. Moreover, recall that benefits should be assessed ex ante. Despite the risk of failure, the expected gain to these parties seems substantial, assuming (again) that the trial is seen as legitimate.

Turning now to the participants, the experiment would expose them to significant risks and burdens. This is partly because producing a genetically edited child would require the prospective mother to undergo IVF, pregnancy, and delivery.\textsuperscript{45} IVF using her eggs, which would be needed to create a genetic link to the child, would require hormonal stimulation, which commonly causes mild abdominal pain, bloating, nausea and vomiting, and mood changes. A more serious complication is moderate or severe ovarian hyperstimulation syndrome,\textsuperscript{46} which is associated with severe abdominal pain, severe nausea and vomiting, rapid weight gain, respiratory difficulties, and, exceptionally, death. Since IVF has a modest

\textsuperscript{37}Mayer, op. cit. note 13; Wertheimer, op. cit. note 16; Wertheimer op. cit. note 34.

\textsuperscript{38}Wertheimer, op. cit. note 16; Wertheimer, op. cit. note 34.

\textsuperscript{39}Mayer, op. cit. note 13; Wertheimer, op. cit. note 16.

\textsuperscript{40}Snyder, op. cit. note 17; Sample, op. cit. note 17.

\textsuperscript{41}Wertheimer, op. cit. note 34.

\textsuperscript{42}Hawkins, J. S., & Emanuel, E. J. (2008). Exploitation and developing countries: The ethics of clinical research. Princeton University Press.

\textsuperscript{43}Lamkin, M., & Elliott, C. (2018). Avoiding exploitation in phase I clinical trials: More than unjust compensation. Journal of Law, Medicine & Ethics, 46(1), 52–63.

\textsuperscript{44}Wertheimer op. cit. note 34.

\textsuperscript{45}Baylis, op. cit. note 3.

\textsuperscript{46}This complication occurs in 3.1–8% of all pregnancies. See Royal College of Obstetricians and Gynaecologists. (2016). The management of ovarian hyperstimulation syndrome. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guide lines/gtg_5_ohss.pdf
success rate, the woman may face these IVF-related risks and burdens repeatedly. Once pregnant, she would incur several additional costs, including discomforts like nausea, fatigue, and pain; liberty-restrictions related to diet, recreational drug use, and physical activity; temporary and/or permanent undesired changes in bodily appearance and/or function; risks of pregnancy-related illnesses like pre-eclampsia and gestational diabetes; and a risk of miscarriage. Finally, delivery is at minimum painful and exhausting, often causes injuries requiring surgery or follow-up care, is not uncommonly followed by postpartum depression, and may, in rare cases, prove fatal. The fact that this particular pregnancy and delivery would likely be exceptionally closely monitored might somewhat mitigate the health risks involved but would also add a further cost: interference with the woman’s privacy.

It might be argued that the risks and burdens of IVF, pregnancy, and delivery should not be considered risks and burdens of GGE trials, either because they do not result directly from the GGE intervention or because people willingly (and often unobjectionably) assume them when reproducing outside of the research context. However, as argued earlier in this section, when analysing whether some transaction involves exploitation, we should take into account all benefits and burdens involved and assess these against the alternative of not transacting. As argued in Section 3.1 above, at the time of deciding whether to enrol in a GGE trial, these participants would likely have no other reproductive option they consider viable. Thus, at this time, their no-transaction alternative does not involve the risks and burdens of IVF, pregnancy, and delivery. This justifies including these risks and burdens in the analysis.

Moreover, many uncertainties remain about the effects of altering the genome, making such interventions risky to the resulting child (and, possibly, to future generations). Should the child experience serious harm due to off-target or unwanted on-target effects, this would severely set back the participants’ interest (qua parents) too. However, even if no such harm occurs, the risk of harm will likely engender significant anxiety. On the inclusive approach to benefits and burdens defended above, these burdens, too, should be included in the analysis.

On the other hand, the trial would represent an opportunity for the participants to fulfill their desire for a healthy genetic child. Since (as argued in Section 3.1 above) they can be assumed to have a powerful such desire while lacking other ways of fulfilling it, this is clearly an important potential benefit—one that is plausibly central to their well-being. However, given present knowledge gaps about the effects of altering genes and the modest success rate of IVF, the experiment may very well fail to yield a healthy child, or indeed any child. Thus, unlike some of the key burdens involved, the main benefit to participants would be highly uncertain.

This analysis suggests that GGE trials, much like better known cases of exploitative research, would involve excessive gain to researchers, sponsors, and employers and insufficient gain to participants, i.e. that the advantage clause would apply.

4.1 | Participant selection

One approach could be to enrol participants who are not vulnerable in the relevant sense, either because they do not strongly desire a healthy genetic child or because they could fulfill that desire in some other way. However, while this would defuse exploitation concerns, it would also make it difficult to recruit sufficiently many participants. It is not clear that people would agree to undergo IVF, pregnancy, and delivery without a strong interest in parenting the resulting child, nor that they would opt for experimental gene editing if they could secure healthy offspring more easily by means of PGD or donor gametes.

Moreover, this move would make the risk-benefit profile of the experiment hard to justify. As argued in Section 3.2 above, assessing whether research meets the non-exploitation requirement is distinct from making a risk-benefit assessment. Nonetheless, a defensible risk-benefit profile is a necessary ethical requirement on all human subject research. Selecting non-vulnerable participants would arguably conflict with this requirement, since these participants would face all risks and burdens of IVF, pregnancy, and delivery without enjoying the main compensating benefit: a unique chance of fulfilling a powerful reproductive desire.

---

47Pregnancy may involve significant benefits too, including increased attention and care from others, and it might be argued that these outweigh the costs. However, since many of the benefits specifically aim at easing the burdens involved, it is unclear that pregnancy is on balance beneficial. See Gheaus, A. (2012). The right to parent one’s biological baby. The Journal of Political Philosophy, 20(4), 432–455.

48This is supported by empirical research demonstrating that parents of children with chronic conditions suffer seriously reduced quality of life. See Hatzmann, J., Heymans, H. S. A., Ferrer-i-Carbonell, A., van Praag, V. M. S., & Grootenhuys, M. A. (2008). Hidden consequences of success in pediatrics: Parental health related quality of life – results from the Care Project. Pediatrics, 122(5), e1030–e1038.

49This refers to standards that figure in major international guidance documents and enjoy widespread institutional and scholarly support. For synthesis, see Emanuel et al., op. cit. note 9. By taking these standards for granted I assume a mild form of ‘research exceptionalism’, the view that human subjects research is properly regulated more strictly than many other risky activities. See Wilson, J., & Hunter, D. (2010). Research exceptionalism. The American Journal of Bioethics, 10(8), 45–54.

50Emanuel et al., op. cit. note 9; Rid & Wendler, op. cit. note 36.
4.2 | Payment

Another, perhaps related, approach could be to pay people to enrol in GGE trials. This would increase the level of net gain to participants, addressing the worry that they benefit insufficiently. Moreover, if high enough, payment would presumably help incentivize participation, as it does in other research, potentially overcoming recruitment problems.

However, this approach would potentially clash with established research ethical norms in two ways. First, since the risks and burdens would be high, the payment would also need to be high to effectively incentivize participation. This would raise familiar worries about ‘undue inducement’, i.e. worries that the prospect of large sums of money may entice people to participate against their better judgment. Second, while offering payment to incentivize enrolment or reimburse costs that participants have incurred is considered acceptable, there is widespread resistance against the idea of paying to offset risk. Now, this resistance concerns risk-benefit assessment, not the evaluation of whether the research is exploitative, which (again) is a distinct issue. However, it does not seem unlikely that the reluctance of ethics committees to consider payment a benefit for the purposes of the former assessment may affect their consideration also of the latter issue.

Of course, both the notion of undue inducement and the rejection of payment as a benefit may be criticized. But whatever the merits of these criticisms, both notions are parts of research ethical thinking and practice. So regardless of whether paying people to enrol in GGE trials is permissible in principle, it may well be unfeasible in current circumstances.

4.3 | The long road

The most promising mitigation approaches are likely more long-term than those considered so far. As noted in the Introduction, proponents of developing human GGE agree that clinical trials must be preceded by rigorous preclinical studies on animal models and human embryos. This requirement limits the burden on participants that stems from the uncertain effects of gene editing and associated risks to the resulting child, and more so the higher the bar for necessary preclinical evidence is set. However, preclinical research can only reduce this uncertainty, not eliminate it. Moreover, such research will not reduce the risks and burdens of IVF, pregnancy, and delivery, which I have argued are substantial. Thus, some concern about excessive advantage will remain no matter the quality of preclinical research.

Given these limitations, it is worth asking whether exploitation could instead be mitigated by reducing participants’ vulnerability, which arises from a powerful desire for healthy genetic offspring and a lack of alternative options for fulfilling that desire. While addressing this vulnerability by participant selection seems difficult (see Section 4.1 above), there might be another way. People’s desire for genetic offspring is partly produced by social norms that attach great importance to genetic relatedness. Social norms change, however, and these particular ones are arguably being challenged by new kinds of family constellations and increasing reproductive options among groups previously lacking them. Should the societal preference for genetic offspring significantly weaken, people may be less inclined to enrol in risky and burdensome experiments to satisfy it, and hence less vulnerable to exploitation in such experiments.

Perhaps GGE trials will not raise exploitation concerns in a future where the societal preference for genetic relatedness has significantly weakened. However, in such a future, the attraction of GGE will also be smaller since the main rationale for the procedure is to provide an opportunity of securing genetic offspring to those who otherwise lack it.

5 | CONCLUSION

Many scientists and ethicists now advocate the pursuit of clinical uses of human GGE. However, before this technology can be rolled out its safety and efficacy must be established in clinical trials involving human subjects. I have argued that such trials would potentially conflict with the fundamental research ethical norm of non-exploitation. This is because they would expose people who are in a vulnerable situation to quite significant risks and burdens. Moreover, this problem seems hard to mitigate without undermining the main rationale for GGE. Some may disagree with my analysis of participants’ vulnerability or of the risks and burdens they face. However, I hope to at least have shown that GGE trials raise a potential exploitation concern that warrants serious attention if (or when) such trials are considered.

ACKNOWLEDGEMENTS

This paper was first presented at the workshop ‘Gene Editing in Human Reproduction: Experimenting on Future Children’, which was held at the Brocher Foundation, Geneva, January 14–16, 2020. I wish to thank the organizers for the opportunity to present my work, the Foundation for hosting the event, and other participants for useful feedback. I also thank audiences at Linköping University and the University of Gothenburg, as well as two anonymous reviewers for Bioethics, for helpful comments.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ORCID

Erik Malmqvist https://orcid.org/0000-0003-3071-9609
ERIK MALMQVIST is Senior Lecturer in Practical Philosophy at the University of Gothenburg, Sweden. He conducts research on various topics in moral and political philosophy and bioethics, including exploitation theory and ethical issues raised by antimicrobial resistance.

How to cite this article: Malmqvist E. Clinical trials of germline gene editing: The exploitation problem. Bioethics. 2021;00:1–8. https://doi.org/10.1111/bioe.12903