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Role of Ethics and Philosophy in Facilitating Research and Translation

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Gene Editing

“China Condemns Baby Gene Editing Scientist” BBC
“Gene-editing Chinese Scientist He Jiankui Could Face Death Penalty” ABC
“China’s gene-edited babies may have been given boosted intelligence” News.com.au
“‘Gene-edited babies’ is one of the most censored topics on Chinese social media” Nature
“Scientists call for global moratorium on gene editing of embryos” The Guardian

Note: enhancement, not treatment

Monstrous Gene Editing Experiment Press Release

- Chinese researcher He Jiankui of Shenzhen claims to have gene edited two healthy embryos, resulting in the birth of baby girls born this month, Lulu and Nana. He edited a gene to make the babies resistant to HIV. One girl has both copies of the gene modified while the other has only one (making her still susceptible to HIV).
- If true, this experiment is monstrous. The embryos were healthy. No known diseases. Gene editing itself is experimental and is still associated with off-target mutations, capable of causing genetic problems early and later in life, including the development of cancer. There are many effective ways to prevent HIV in healthy individuals: for example, protected sex. And there are effective treatments if one does contract it.
- This experiment exposes healthy normal children to risks of gene editing for no real necessary benefit.
- It contravenes decades on ethical consensus and guidelines on the protection of human participants in research.
- In many other places in the world, this would be illegal, punishable by imprisonment.
- These healthy babies are being used as genetic guinea pigs. This is genetic Russian Roulette.

Table of contents

June 2001 - Volume 27 - 3

Prev issue

Next issue

EDITORIAL 1

Future directions of the journal (1 June, 2001) FREE

Julian Savulescu

EDITORIAL 2

Harm, ethics committees and the gene therapy death (1 June, 2001) FREE

Julian Savulescu

Jesse Gelsinger

- an 18 year old man with mild ornithine transcarbamylase (OTC) deficiency, a disorder of nitrogen metabolism.
- controlled by diet and drug treatment.
- Sept 13, 1999, James Wilson's team at the University of Pennsylvania's Institute for Human Gene Therapy (IHGT) injected 3.8 X 10^{13} adenovirus vector particles (one of the highest doses)

Gelsinger

- virus particles were injected directly into the major artery to the liver.
- died 4 days later
- first death directly attributed to gene therapy.

Infants or Adults?

- Newborns with a severe form of the OTC deficiency are likely to die early in life
- Adults with mild OTC deficiency like Gelsinger can leave a reasonable quality of life on diet and drug therapy.
- Should the trial have been performed on severely affected newborns or mildly affected adults?

The Justification for Adult Participation

- “There are serious risks including a risk of death associated with participation in this trial. Since the risks are significant, it is better that the trial be conducted on humans who consent to those risks rather than on those who cannot consent.”

- Consent prioritised over harm

Mildly affect adults or severely affected newborns?

- *Put simply, Gelsinger had something to lose while the seriously affected newborn did not.*

- There is no good reason to prefer more harm to less harm, regardless of whether someone is prepared to consent.

Weighing values and expected harm

- Expected harm = Probability of Harm x Value of Harm
- Minimize expected harm
  - **Shortest life expectancy**
    - Gelsinger normal life expectancy (another 70 years), newborns with sev def very short (year)
  - **Lowest probability of survival**
  - **Poorest quality of life**
    - Gelsinger normal quality of life, newborns severe impairment of quality of life

The Expected Harm of Adult Participation

- Simplifying assumptions:
  - only harm was death from the virus vector.
  - perfect health has a value of 1
  - death has a value of 0
  - Jesse's existing quality of life was was 0.8.
  - he would have lived another 50 years.
  - the risk of the gene therapy killing him was small – 1/10 000

Expected Harm

- the expected harm of Gelsinger participating was 0.8 X 50/10 000 = 40/10 000= 0.004 quality-adjusted life year.
- This is a very small expected harm

The Expected Harm of Newborn Participation

- Simplifying assumptions
- newborn's quality of life will be much worse, say 0.2.
- die very early in life, say in one year.
- expected harm of gene therapy in a newborn is 1/10 000 X 0.2 X1 = 0.00002 quality-adjusted life year.

- 0.004>> 0.00002
- 2 orders of magnitude higher!!

Nature, Nov 28, 2018: "Translational Pathway"

- "In the opening presentation of the day, George Daley, dean of Harvard Medical School in Boston, Massachusetts, pointed to **Huntington's disease or Tay–Sachs disease as examples of diseases** that, in some circumstances, might be averted only through gene editing."

- "Fears are now growing in the gene-editing community that He's actions could stall the responsible development of gene editing babies. In a lecture on the second day of the summit, ahead of He's talk, Daley urged support for pursuing germline gene-editing research despite recent events."

    - "It's possible that the first instance came forward as a misstep, but that should not lead us to stick our heads in sand and not consider a more responsible pathway to clinical translation," he said.

5 Stage Translational Pathway and Expected Harm

1. Terminal conditions in early life
    - Tay Sach's Disease
    - BRAT-1
        - This could be attempted now

2. Conditions which undermine development of autonomy and rational agency [shortening of life and severe cognitive impairment]

    - Fragile X syndrome
    - Down Syndrome

5 Stage Translational Pathway and Expected Harm

3. Non-avoidable serious risk
    - Cystic Fibrosis,
    - Huntington Disease
4. Avoidable (by acceptable non-genetic interventions - eg social) serious risk
    - immunity to infection (resistance to HIV)
    - decreased probability of chronic disease (polygenic interventions),
5. Enhancement of normal characteristics - unavoidable risk to well-being or autonomy
    - Enhancement of “low normal IQ” (IQ 70-85)

Concept of Expected Harm

- Applies to embryo, embryoid, organoid etc research
- Applies to any risky research, eg challenge studies

OPEN ACCESS

Two kinds of embryo research: four case examples

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ABSTRACT

There are ethical obligations to conduct research that contributes to generalisable knowledge and improves reproductive health, and this should include embryo research in jurisdictions where it is permitted. Often, the controversial nature of embryo research can alarm ethics committee members, which can unnecessarily delay important research that can potentially improve fertility for patients and society. Such delay is ethically unjustified. Moreover, countries such as the UK, Australia and Singapore have legislation which unnecessarily captures low-risk research, such as observational research, in an often cumbersome and protracted review process. Such countries should revise such legislation to better facilitate low-risk embryo research.

We introduce a philosophical distinction to help decision-makers more efficiently identify higher risk embryo research from that which presents no more risks to persons than other types of tissue research. That distinction is between future person embryo research and non-future person embryo research. We apply this distinction to four examples of embryo research that might be presented to ethics committees.

Embryo research is most controversial and deserving of detailed scrutiny when it potentially affects a future person. Where it does not, it should generally require less ethical scrutiny. We explore a variety of ways in which research can affect a future person, including by deriving information about that person, and manipulating eggs or sperm before an embryo is created.

THE ETHICAL IMPORTANCE OF RESEARCH

We conduct research to systematically examine and gain insight into the complexities of life and the world around us, and use this knowledge to improve the human condition. Research for such purposes that is conducted in accordance with international standards is therefore an ethically good enterprise.[1] Given our ability to systematically examine aspects of human existence that deeply impact our lives, research aimed at promoting human health and well-being is a moral imperative. This imperative also applies to research that has the potential to improve fertility and reproductive health. If we accept that procreation is a moral good, then society has an obligation to support scientific research that is broadly aimed at improving fertility.

This obligation arises from two considerations: first, improving fertility for those segments of the population requiring scientific interventions to procreate enables such individuals to pursue a life that is meaningful to them while at the same time not infringing on others' fundamental interests[2] and second, such scientific research addresses issues relating to the right to fair and reasonable access to healthcare. If we are to consider the instrumental value of procreation, the motivation becomes stronger in countries where major demographic shifts are contributing to ageing populations with decreasing fertility rates that have fallen well below replacement levels.[3 4] For example, total fertility rates in 2018 for the USA were 1.7, 1.7 for the UK, 1.4 for Japan and only 1.1 for the Southeast Asian city-state of Singapore.[5] With an estimated replacement fertility rate of 2.1,[6–8] countries such as these must rely on immigration policies to maintain their current population levels.

We acknowledge that the effects of unchecked population growth in combination with ever-increasing consumption rates impact on environmental degradation and the critical preservation of limited resources.[9] However, we do not view the solution to population growth control as being achieved by depriving only some persons from procreating, simply because they face fertility issues. Rather, there are global collective moral obligations that need to be considered in reducing consumption and human impacts on environmental health and climate change, if we are to discuss this complex and confronting problem with issues of justice in mind. In this paper, we are not able to further elaborate on this important aspect of the argument.

While both men and women are living longer in these countries, they are also deciding to have children later, which affects the health and quality of their reproductive tissues.[3 10 11] Maternal age is one of the strongest predictors of oocyte quality.[12] Therefore, the quality and quantity of ovarian follicles are vital for a woman's reproductive lifespan. A condition known as premature ovarian insufficiency (POI), where the loss of normal ovarian function is due to the loss of ovarian follicles (ie, loss of quantity) before the age of 40 years, affects approximately 1% of women under 40 years old and 0.1% of women under 30 years of age.[13] Hence, this exemplifies that quantity is equally important in a woman's reproductive lifespan, especially when POI occurs in young women, and ovarian follicles and the oocytes are perceived to be of better quality than in older women. Furthermore, young women who have undergone gonadotoxic treatment and have high numbers of good quality ovarian follicles destroyed can have problems conceiving due to the sheer low number of ovarian follicles and will go into the POI state and be rendered infertile despite the likely presence of low numbers of perceived better-quality oocytes due to her younger age (barring the fact that these oocytes could have been affected by the medical treatment).

During normal ageing in women, the culmination of clinical menopause occurs because of loss of both quality and quantity of ovarian follicles, which signals the end of a woman's reproductive lifespan.

Concepts of Coercion and Exploitation

- Incentives in research, including payment

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Payment in challenge studies: ethics, attitudes and a new payment for risk model

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ABSTRACT

Controlled Human Infection Model (CHIM) research involves the infection of otherwise healthy participants with disease often for the sake of vaccine development. The COVID-19 pandemic has emphasised the urgency of enhancing CHIM research capability and the importance of having clear ethical guidance for their conduct. The payment of CHIM participants is a controversial issue involving stakeholders across ethics, medicine and policymaking with allegations circulating suggesting exploitation, coercion and other violations of ethical principles. There are multiple approaches to payment: reimbursement, wage payment and unlimited payment. We introduce a new Payment for Risk Model, which involves paying for time, pain and inconvenience and for risk associated with participation. We give philosophical arguments based on utility, fairness and avoidance of exploitation to support this. We also examine a cross-section of the UK public and CHIM experts. We found that CHIM participants are currently paid variable amounts. A representative sample of the UK public believes CHIM participants should be paid approximately triple the UK minimum wage and should be paid for the risk they endure throughout participation. CHIM experts believe CHIM participants should be paid more than double the UK minimum wage but are divided on the payment for risk. The Payment for Risk Model allows risk and pain to be accounted for in payment and could be used to determine ethically justifiable payment for CHIM participants.

Although many research guidelines warn against paying large amounts or paying for risk, our empirical findings provide empirical support to the growing number of ethical arguments challenging this status quo. We close by suggesting two ways (value of statistical life or consistency with risk in other employment) by which payment for risk could be calculated.

Linked

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BACKGROUND

Challenge Studies, more formally known as Controlled Human Infection Model (CHIM) research studies, involve the infection of otherwise healthy participants with disease. CHIMs are employed in medical research for varied reasons, primarily to study causation of disease, incubation periods, clinical symptomology and most importantly to advance drug and vaccine development.[1] Compared with traditional field trials, in which a novel vaccine is given to a large sample group and the incidence of disease is consequently assessed, early vaccine evaluation using CHIMs offer numerous advantages; in particular, they are cost and time effective because they allow for the quick differentiation between promising and poor vaccine candidates. This allows the development of effective vaccines to be accelerated, while poor vaccines can be discarded to prevent further expensive, wasteful and unsuccessful trials.[2] CHIMs also require only a small number of participants, which means that fewer people are subjected to the risks involved with taking a novel vaccine.[1] Partly for these reasons, CHIM research has recently experienced a resurgence in popularity with an estimated 22 000 participants involved in CHIMs over the past 70 years.[3] Recent CHIMs have led to many clinically valuable breakthroughs including the proof of efficacy of the new oral cholera vaccine, Vaxchora (CVD 103-HgR),[4] and the proof of efficacy for a Vi-tetanus toxoid conjugate vaccine.[5]

The current COVID-19 pandemic has led to millions of cases and hundreds of thousands of deaths. It underscores the importance of supporting and fostering effective fast track pathways for testing vaccines. Quickly discovering a vaccine for the SARS-CoV-2 responsible for COVID-19 will save millions of lives. To this end, it is unsurprising a coronavirus CHIM using less virulent strains is already in the pipeline,[6] and there are increasing calls for a SARS-CoV-2 CHIM.[7] Both of which are likely to have prompted the WHO to release an ethical guidance document for these studies.[8] Growing antimicrobial resistance[9] and concerns of climate change increasing the climate suitability for the transmission of infectious diseases[10] are further issues highlighting the pressing need for more CHIMs.

There has been much debate surrounding the ethical issues that CHIMs raise, namely regarding informed consent, acceptable levels of risk in research and the payment of participants.[11 12] The intentional introduction of disease to participants by medical professionals may seem to contradict the Hippocratic principle of 'first do no harm'. Unease surrounding CHIMs may also arise from unethical studies performed in the past on vulnerable populations without consent. For instance, in the 1960s, children with intellectual disabilities at The Willowbrook State School in New York were purposely infected with hepatitis.[13] Despite this dark past, there is a strong argument for the continued support of this research, as long as it is properly regulated through appropriate Institutional Review Board (IRB) oversight, due to its potential to prevent suffering and deaths from infectious disease.[12] It is important to note that central to any CHIM is a focus on participant risk minimisation through rigorous participant screening, often using an inpatient setting and employing altered, safer strains

Balancing incentives and disincentives for vaccination in a pandemic

Mandates and incentives are being considered to increase uptake of vaccines against COVID-19, but payment for vaccination may be the fairest approach.

Julian Savulescu, Jonathan Pugh and Dominic Wilkinson

The COVID-19 pandemic has given rise to the fastest development and rollout of novel vaccines in human history. Initial clinical trials suggested that these vaccines were well tolerated and had a high degree of efficacy[1]. Those results have since been confirmed by real-world data[2,3].

However, the vaccines have been associated with rare serious adverse events. Many countries suspended the use of the AstraZeneca vaccine due to rare cases of fatal blood clots and thrombocytopenia. There have also been concerns about an association between the mRNA vaccines and myocarditis and/or pericarditis[4]. At the time of this writing, The UK Joint Committee on Vaccination and Immunisation is not currently advising routine vaccination of children under the age of 16, outside of specified high-risk groups.

Many countries have seen high vaccine uptake. As of the middle of June 2021, approximately 45% of the UK and US population were fully vaccinated. However, in Australia, Japan and Malaysia, less than 5% of the population were fully vaccinated[5]. Somewhere between 70% and 90% of the population may need to be vaccinated to achieve herd immunity[6].

Vaccine hesitancy is a considerable obstacle and varies widely between countries[7]. A UK study suggests hesitancy of 18% across the population[8], whereas a US study suggests a level of 22.1% (ref. [9]). However, vaccine hesitancy differs substantially between demographic subgroups. There has been particular concern about vaccine hesitancy among healthcare workers, with some UK National Health Service data suggesting lower rates of vaccination against COVID-19 among Black, Asian and minority ethnic healthcare workers[10].

A number of strategies have been deployed to increase uptake, including community-engagement work, tailored communication to hesitant populations from trusted sources, and improving flexible access to vaccination[11]. However, as viral variants emerge, some countries are considering other strategies: disincentives or incentives (Table 1).

Table 1 | Examples of disincentives and incentives currently used for vaccination

Disincentives for COVID-19 vaccine refusal	Incentives for COVID-19 vaccination
Fines People who refuse vaccination may be made liable to fines (e.g., in Indonesia) • Non-COVID-19 example: €2,500 fine for parents who fail to vaccinate children against measles in Germany	**Financial payment** Citizens receive a lump sum in return for being vaccinated (e.g., Serbia paid citizens the equivalent of €25 to undergo vaccination)
Withholding state benefits People who refuse vaccination may have state benefits withheld or suspended (e.g., in Indonesia) • Non-COVID-19 example: Australian 'No Jab, No Pay' scheme	**Cash Lottery** Vaccinated people are entered into a lottery for a substantial cash prize (e.g., in Ohio and Kentucky)
Vaccination as a condition of access to publicly accessible social goods Unvaccinated people may not be permitted to access certain goods, such as education (e.g., vaccination as a condition of entry to campus at some US colleges) • Non-COVID-19 example: immunization as a condition for enrollment in public school in various US states	**Investments** People may be offered savings bonds if they get vaccinated (e.g., in West Virginia, people 16–35 years of age are offered a US$100 savings bonds if they get vaccinated).
Vaccination as a condition of employment People may be prevented from entering or continuing in a professional role if they have not been vaccinated (e.g., staff in care homes in England, or service staff in Moscow) • Non-COVID-19 example: vaccination against hepatitis B for healthcare workers	**Payment in kind** Vaccinated people are offered a non-financial payment (e.g., free beer in Connecticut, or guns in West Virginia)

Disincentives and mandatory vaccination

It is a basic tenet of liberal societies that state restriction of liberty (coercion) is justified only to prevent harm to others. Harm to self is never a sufficient justification[12].

Vaccination generally offers a benefit and protection to those vaccinated. But it also affects others. Two key ethical features of pandemics are that people carrying an infection, even if asymptomatic, may pose a lethal threat to others, and second, that if large numbers of people fall ill simultaneously, this may overburden health systems and prevent others from accessing healthcare.

It is on the basis that an individual person may harm others that coercive measures can be ethically justified in a pandemic. These can include various mandatory measures such as lockdown, quarantine, isolation, mask wearing, testing, and vaccination.

For vaccination, a variety of coercive measures could be deployed, ranging from requirements to attend education sessions, to withholding of benefits, fines, imprisonment and, in the extreme,compulsion (involuntary vaccination)[13].

In choosing between different approaches, one commonly cited principle

Moral imperative to gene edit

- Imagine there is a pill which will cure cystic fibrosis
- It would be wrong of parents to refuse such a pill for their child
- Doctors should seek a court order to administer the pill
- Gene editing is the ultimate cure for genetic disorders – it corrects the abnormality in every cell
- Doctors should seek court orders to do gene editing in those who refuse selection once it is safe
- Gene editing is different to genetic selection: a future child can justifiably complain, “You should have tried to cure my genetic disorder.”

Selection vs Gene Editing?

- “there is no persuasive medical reason to manipulate the human germline because inherited genetic diseases can be prevented using embryo screening techniques, among other means”
  - Marcy Darnovsky, the executive director The Center for Genetics and Society

- This view was also expressed in a recent *Nature* commentary, whose authors stated that we "*cannot imagine a situation in which its use in human embryos would offer a therapeutic benefit over existing and developing methods."*

WRONG!

- 3 groups who should consider gene editing now:
  1. Those with limited numbers of embryos all affected by severe genetic disorders
  2. Couples homozygous for a genetic disorder
  3. **Those with religious or moral objections to genetic selection or embryo/fetal destruction** – ultimate treatment

- The worse the genetic disorder, the stronger the reason to attempt gene editing

The Major Reason to Gene Edit: Polygenic Conditions

Genome wide association studies

- 44 genes involved in diabetes;
- 35 genes involved in coronary artery disease;
- 300 genes involved in common cancers.

It is impossible using current techniques to use selection techniques like IVF and preimplantation genetic testing to target to polygenic conditions like this.

- Say 20 genes contribute to a particular trait. If a couple want to use PGD to select for 20 different genes in an embryo, they would need to create around 10,000 embryos to make it sufficiently likely that one will have the right combination at all 20 loci.

Thank you.