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Heritable human gene editing in global perspective: national and international policy challenges

Achim Rosemann, Egenis - Center for the Study of the Life Sciences, University of Exeter, Exeter, UK. (Corresponding author: a.rosemann@warwick.ac.uk)

Adam Balen, Centre for Reproductive Medicine, University of Leeds, Leeds, UK.

Brigitte Nerlich, School of Sociology and Public Policy, University of Nottingham, Nottingham, UK.

Christine Hauskeller, Department of Sociology, Anthropology and Philosophy, University of Exeter, Exeter, UK.

Margaret Sleeboom-Faulkner, Department of Social Anthropology, University of Sussex, Brighton, UK.

Sarah Hartley, School of Business Studies, University of Exeter, Exeter, UK.

Xinqing Zhang, Centre for Bioethics, Peking Union Medical College, Beijing.

Nick Lee, Centre for Education Studies, University of Warwick, Coventry, UK.

Research Report

Heritable genome editing in global context: national and international policy challenges

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Abstract:

The prospect to engineer heritable genetic changes in humans is presently the subject of worldwide debate. This overview presents findings from a multi-stakeholder project that has aimed to identify challenges and options for the governance of heritable genome editing (HGE), in a diverse international environment that is characterized by differences in regulatory frameworks, human values, scientific and health care cultures and socio-economic inequalities. Designed around the methodological approach of forward engagement the paper draws on data from a multi-stakeholder workshop and interviews in the UK. It focuses on challenges related to: (i) the situation and wellbeing of fertility patients and babies whose genomes are edited, and (ii) the situation of researchers, fertility clinics and corporations, with a focus on responsible cross-border research practices. The final sections of the article present six broad policy options to address some of the identified issues and challenges.

Keywords: germline gene editing; artificial reproduction; genetic enhancement; international governance; science policy; global regulatory variation.

1. Introduction

In July 2018 the Nuffield Council on Bioethics in the UK published a report that concluded that 'the use of heritable genome editing to influence the characteristics of future generations 'could be ethically acceptable in some circumstances', as long as specific preconditions are met.[1] The report follows a 2017 publication from the US National Academies of the Sciences, Engineering and Medicine (NASEM) that

recommended permitting clinical trials for the prevention of severe monogenetic disorders, as long as these are conducted within a robust and effective regulatory framework.[2] These reports and a range of other publications [3] have also demanded that clinical research and applications should be preceded and accompanied by 'extensive and inclusive public participation',[4] so as to collectively consider the possible uses, limits and risks of gene editing technologies. A central concern of many of these studies has been to anticipate and reflect on the short and long-term societal implications of heritable genome editing (HGE), not only for people who are born as a result of genome editing but also for current and future societies at large. Issues that have been raised were, for instance, the significance of solidarity, social justice and responsible innovation, in order to prevent medical adverse effects, discrimination, disadvantages and societal divisions.[5]

Then, on the 25th November 2018, just days before the start of the Second International Summit on Human Genome Editing in Hong Kong, news broke that a woman had given birth to two babies whose genome had been edited by a research team in China.[6] This incident was widely condemned as irresponsible and as failing to conform with international norms.[7] It also had a significant impact on regulatory debates. The organizing committee of the Hong Kong Summit concluded, for example, that a 'rigorous, responsible translational pathway toward clinical trials of germline' was needed that establishes international 'standards for preclinical evidence, accuracy of gene modification, assessment of competency for clinical trial practitioners and enforceable standards of professional behavior'.[8] This statement was criticized, however, by both scientists and social scientists because it de-emphasized the commitment to a "broad societal consensus", that was evident in previous reports by the NASEM, the Nuffield Council on Bioethics, and other publications.[9] A group of scientists and ethicists working with the geneticist Eric Lander, for example, now demanded the adoption of a temporary global moratorium on all clinical uses of human germline editing, arguing that the decision to lead towards clinical applications should not be taken by the scientific or medical community but by societies as a whole.[10] The World Health Organization, on the other hand, responded to the news of the genetically modified babies in China by setting up a new advisory committee to develop global standards for the governance and oversight of human genome editing, aiming to work towards a strong international governance framework.[11] In a first step, this panel suggested the creation of a global registry of all human gene editing

research, which would allow oversight and transparent access to the details of current and future studies by interested parties.[12]

A central problem for the international governance of germline gene editing is that there are important differences in attitudes and values as well as ethical and health care considerations around the world. This is reflected in a complicated and diverse regulatory landscape. Several publications have sought to develop a broad, comparative understanding of existing regulatory conditions in different countries [13] and to sample international legal and regulatory frameworks that may influence the governance of clinical applications in this field.[14] However, a systematic investigation of the possible effects of international regulatory differences, and of the challenges that are likely to arise for national governments once clinical applications in this field become available at a global scale, has not yet been conducted. Neither the recent report of the Nuffield Council on Bioethics, nor previous reports by the NASEM or other studies have systematically addressed this issue. This is an important shortcoming. Different forms of regulatory oversight as well as differences in social environments, clinical cultures and patient needs, as the recent incident in China has shown, are likely to result in premature and irresponsible applications of heritable genome editing, which could expose (prospective) parents and their embryos, fetuses, and of course, born children and their descendants to substantial risks.

In order to address the lack of information, systematic comparative studies are required that explore issues related to the governance of this technology from different national and international perspectives. In this research report we contribute to filling this gap by presenting views on the challenges to the governance of heritable genome editing from stakeholders in the UK. We present findings from a multi-stakeholder study conducted in the UK between October 2016 and January 2018 and funded by the Wellcome Trust. This research included interviews, literature analysis and a workshop. We involved leading UK scientists, in-vitro fertilization (IVF) clinicians, representatives from regulatory bodies, patient organizations and other civil societal organizations as well as fertility companies.

Part I of this article explores stakeholder perceptions of possible global developments, risks and governance challenges of HGE, in relation to two overarching themes. First, issues related to the situation and wellbeing of fertility patients and babies whose genomes are edited. For this purpose, the paper focuses on the potential challenges of (i) germline gene therapy tourism, and (ii) the emergence

of "illegal" or "rogue" clinics that are likely to offer germline editing for non-therapeutic (or potentially even commercial) purposes. Second, issues for researchers, fertility clinics and corporations that aim to develop, apply and commercialize this technology in the context of international research and/or commercial partnerships.

The first of these two themes (reproductive tourism and "rogue" clinics) refers to commercial clinical applications that are offered to parents for their embryos/babies outside of systematic clinical research protocols and oversight, in a way that is scientifically and ethically problematic. However, as in other fields of medicine, some clinics may in fact (claim to) provide commercial clinical applications as part of a research framework. This can make it difficult to draw a clear line between ("rogue") clinical applications and clinical research, with many clinics offering treatments in a "grey zone" between the two poles of "rigorous science" and "quackery".[15] The second theme addresses issues related to the governance of cross-border collaborations between scientists, IVF clinics and/or companies. These partnerships can either be built around the co-organization of clinical research studies, or alternatively target the provision of unproven, or non-systematically evidenced, clinical interventions on a commercial basis in permissive locations.

Part II of the paper presents a range of policy options that were generated during the workshop, in relation to the challenges discussed in Part I of the paper. While the presented options for regulation represent the views of stakeholders in the UK, they address issues and possible clinical (and commercial) developments that are of relevance internationally. The surfacing of premature, irresponsible or "rogue" applications, the potential emergence of cross-border germline therapy tourism and the possibility of genetic enhancement are shared global challenges. For this reason, the policy options put forward in this report have the potential to contribute to international dialogue and inform the development of collective responses to heritable genome editing. Before getting to these empirical findings, we briefly discuss possible applications of HGE technology, and provide a more detailed overview of the study's methodology.

2. Heritable genome editing: three possible forms of applications

According to the bioethicist and policy analyst Tetsuya Ishii heritable gene editing has been projected to be used for three likely objectives: (1) the prevention of

monogenic conditions (e.g. Huntington's, Tay Sachs, Cystic Fibrosis), (2) the maximization of reproductive choices during IVF (e.g. choice of eye, hair and skin color, prevention of baldness), and (3) genetic enhancement (e.g. height, muscularity, learning and memory – although the latter are not solely due to genetic traits).[16] Current recommendations to permit clinical trials with genetically modified gametes, zygotes or embryos relate exclusively to the prevention of severe genetic disorders. However, as Ishii has pointed out, while increased reproductive choices and genetic enhancement are seen by many as problematic, in a diverse regulatory environment the emergence of these applications in artificial reproductive technology (ART) centers seem likely in the mid to long term.[17]

Others have made similar assessments. The NASEM Committee on Human Genome Editing warned, for instance, that '"regulatory havens" could emerge that would tempt providers or consumers to travel to jurisdictions with more lenient or nonexistent regulations' to undergo procedures that in other countries are prohibited.[18] Such a situation can quickly arise. Developments in the field of regenerative medicine have shown, for instance, that in many countries for-profit applications emerge long before reliable regulatory controls are in place, often in a legal grey area and with problematic consequences.[19] Considering the potential implications of heritable gene editing for human societies and the fact that germline engineering will be difficult to control at a global level [20] an exploration of possible developments, challenges and risks in this field is important.

3. The challenge to distinguish between clinical research and clinical applications

A more general problem with the clinical translation of HGE technology is that it is difficult to draw a clear line between clinical applications and clinical research. Some clinics, as we have stated above, may offer clinical applications of HGE on a commercial basis outside of rigorous (i.e. internationally accepted) research protocols and oversight, but still be involved in preclinical research or implement follow-up procedures that monitor the genetic or functional effects of the intervention during pregnancy, after birth and/or during childhood and adulthood.

Another problem is that the established clinical translation pathway for new therapies - namely multi-stage, controlled trials to determine the safety and efficacy of a tested treatment – is not available for heritable genome editing. Germline therapy

cannot be part of a controlled study design, because there are no controls (except other "unmodified" individual embryos/human beings) for comparison. Also, exploratory (phase zero or phase one) trials that use only very small doses of a new drug in a small number of patients to establish its safety cannot be conducted for germline therapy. In standard first-in-human trials an administered drug can be withdrawn instantaneously after the emergence of adverse effects. And, if necessary, treatments can be provided to counter adverse effects. For germline gene therapy these options do not exist. Once a genetically modified embryo has been implanted into the uterus, the intervention cannot be reversed. When prenatal diagnosis reveals a defect that will seriously affect fetal development and the future life of a person after birth, the primary options to prevent the negative effects of the treatment are through abortion or postnatal euthanasia. In any other case, a newly born person has to live with the consequences of the intervention for the rest of her/his life and may transmit the effects to subsequent generations. In consequence, every reproductive intervention, even first-in-human applications that are part of a systematic research protocol, is an immediate, full clinical application, whose effects cannot be reversed.

These considerations do not rule out the possibility of making and maintaining a clear distinction between systematic fully monitored and recorded research-based applications and other - ethically more problematic - forms of experimental for-profit applications. Nevertheless, the fuzzy boundaries between clinical research and clinical applications will have important regulatory implications, if and when a translational pathway and oversight for heritable genome editing are developed.

4. Methodology

The project has been designed around the methodological approach of forward engagement, which aims to identify challenges that arise from new technologies as well as possibilities for adaptation and governance as far in advance as possible.[21] Our aim was to initiate a systematic thought process among multiple stakeholders in the UK about long-range issues in the governance of human genome editing, and to help devising collective responses and policy responses at an early stage.[22] To achieve this aim, we have combined multi-stakeholder deliberation, semi-standardized interviews, video interviews and documentary research. The project consisted of two phases. Phase one involved 18 semi-standardized in-depth interviews with UK stakeholders

with varied professional backgrounds (as described in the introduction) as well as documentary research (policy reports, public commentary and relevant academic publications).

Phase two consisted of the organization of a 1-day multi-stakeholder workshop that was held in June 2017 in London. The workshop methodology involved focus group discussions, plenary discussions and short video interviews. Hypothetical case scenarios were used as a focus device, in order to stimulate discussions of likely challenges and reflection on possible responses in a systematic way. The case studies were derived on the basis of the interviews (phase one) and complementary insights from newspaper and media coverage. Three potential scenarios that are likely to occur in the next ten to thirty years were discussed: (1) clinicians from countries in which heritable gene editing is prohibited collaborate with IVF clinics in more leniently regulated countries to achieve first-in-human applications in a legal grey area; (2) the emergence of cross-border germline gene therapy tourism; and (3) the surfacing of commerce-driven (and possibly fraudulent) applications of "genetic enhancement". Parallel to the workshop six 10-15 minutes video interviews were conducted. All data presented in this article have been anonymized to protect the interests of project participants and the organizations they represent.

The participants in this research were UK based stakeholders and our findings have been shaped by that perspective. Stakeholders from other countries may express other views or have different priorities. However, all of the possible clinical developments discussed in this report address shared global challenges and risks that are likely to affect humanity in general. Thus, the ideas and options presented here contribute to the ongoing international dialogue and inform academic and policy debates on HGE at national and international levels.

5. Findings

Following on from elaborate speculative bioethical debates in the past two decades, recent articles on heritable genome editing have explored the social and ethical dimensions of this technology in relation to a variety of topics, such as the interests and rights of people with disabilities [23] reproductive autonomy [24] the history of eugenics and racism [25], the gendered, ethnic and socio-economic dimensions of

genome editing [26], the consequences of gene editing for future generations [27], and challenges related to informed consent [28]. Other work has compared existing regulatory frameworks for basic and preclinical research as well as potential reproductive applications of human genome editing [29]. A central point of discussion in these studies was whether reproductive uses would currently be legally permissible in individual countries, and whether clinical applications could emerge in the context of regulatory gaps and grey areas [30]. However, systematic investigations of the possible effects of cross-border regulatory differences, and of the opportunities that arise from these differentials for researchers, corporations and clinicians, has not yet been reported.

5.1 Challenges for fertility patients/parents and babies whose genomes are modified

During phase I of the project two central themes emerged that were examined further in the context of the multi-stakeholder workshop: the rise of reproductive tourism and the expansion of so-called "rogue" IVF clinics that offer gene editing for non-therapeutic purposes. Both of these scenarios refer to for-profit applications that are offered to parents and their embryos outside of systematic clinical research protocols and oversight (and prior to reliable clinical studies for these interventions).[31]

5.1.1 The challenge of germline therapy tourism

Reproductive tourism is a form of medical tourism in which fertility patients travel to other countries to 'receive a specific treatment or to exercise personal reproductive choice' [28][32]. These reproductive travels are frequently based on the legal prohibition of specific technologies in some countries, which results in journeys to other countries, where these interventions are legal or tolerated in a grey area. The legal analyst Glenn Cohen has called these forms of medical travel 'circumvention tourism', because they circumvent domestic prohibitions on accessing specific medical services [33]. Surrogacy is a good example. As the South African sociologist Amrita Pande has shown, fertility patients from high-income countries in which surrogacy is banned travel to India and other societies where surrogacy is permitted and surrogacy mothers can be hired for a low payment [34]. Many of our research

participants expected that this could also happen with heritable gene editing, at least as long as these treatments are not accessible in the UK. Participants assumed that IVF clinics in countries with no, permissive, or flexibly enforced regulatory frameworks were likely to provide germline gene therapy for monogenic disorders much earlier than clinics in countries with more restrictive regulatory controls. This was seen as both a threat to the wellbeing of parents and children and a challenge to the future development of this field.

While most participants said they understood the motivation of prospective parents to seek germline gene therapy for children who would otherwise suffer from severe genetic disorders, they also expressed a range of concerns. Some of these concerns are summarized in the following quotation of a senior IVF clinician:

> Parents, [have] the desire to seek the best for their future children. So we understand why, if the treatment was not permissible in the UK, parents may wish to go overseas. However, we felt strongly that any such treatments needs to be part of a continuum of appropriate preclinical and then clinical studies, transparent and open with proper ethical review and follow-up. And of course we were concerned about […] a child being born, [and coming] back to the UK needing to be looked after and followed-up by the NHS, and the potential implications [of this]. (Workshop discussion, July 2017)

The main concern here is that early-stage reproductive applications in countries with no or lenient regulatory conditions could and seem likely to be provided outside of a systematic research framework and also independent of the review and approval mechanisms of regulatory agencies. Most interviewees stated that this would be problematic for the responsible development of HGE technology as a whole, because it would prevent the generation and publication of reliable data, including of negative results.

One issue that was highlighted in interviews and workshop discussions was that the early-stage provision of germline therapies in some clinics was likely to be driven primarily by financial motives or professional vanity, instead of a strong clinical justification and reliable preclinical data. As several interviewees mentioned, in a global environment where the generation of profits is often more important than scientific integrity, clinical applications may be offered in premature and irresponsible

ways. As a result, fertility patients, their embryos, children, and subsequent generations could be exposed to significant unjustified psychological and health risks. Potential adverse effects or problems such as increased miscarriage rates are likely to be kept secret and not to be shared with the scientific community. It is also likely to remain unclear on the basis of which criteria institutional or ethical review boards have assessed and approved reproductive applications.

Another concern raised was the risks of missing long-term follow-up monitoring in overseas IVF clinics, especially if patients travel to these clinics from abroad. In order to establish a reliable evidence-base, the USA National Academies of the Sciences [35] and other researchers [36] have recommended long-term, possibly multi-generational, follow-up of individuals who have received heritable gene editing. Interviewees expected that if patients travel to IVF clinics abroad there will be significant logistical challenges that will prevent long-term follow-up monitoring.

Still another concern related to legal responsibilities: who is liable for reproductive applications in other countries if something goes wrong. Can patients take legal action against an overseas clinic if their child suffers from (potentially irreversible) adverse effects? Will the UK National Health Services (NHS) be ready to pay for subsequent treatments and care arrangements? As research on other areas of medical tourism has shown, medical tourists paying out of pocket often face the problem of legal liability. Patients face a lower likelihood and amount of recovery for adverse effects or injuries that are sustained as result of medical tourism.[37] Moreover, such adverse effects may require follow-up treatment in patients' home countries, which can cause additional costs for national health systems.

5.1.2 Concerns over "rogue" IVF clinics that offer germline therapy for non-therapeutic purposes, including genetic "enhancement"

A different but sometimes related phenomenon to reproductive tourism is the existence of "illegal" or so-called "rogue" clinics that offer unapproved but potentially beneficial (and at times outright fraudulent) fertility and medical services to patients, either in a legal grey area or in direct violation of the law. The existence of illegal surrogacy and sex selection in China is a case in point. While these reproductive services were prohibited in China in 2001, a large informal market has emerged for these services since then. Despite repeated efforts of the Chinese

government to close down on this illegal market, ART clinics have been incentivized by a steady demand for surrogacy and sex selection, despite the risk of punishment.[38] Illegal or grey area applications in stem cell medicine are another example. As reported by McMahon [39] a global industry of stem cell clinics has emerged since the mid-2000s that offer unauthorized and non-systematically proven stem cell interventions to patients in hundreds of clinics in numerous countries all over the world, including in the USA and other high-income countries.[40]

Many of our interviewees expressed concern that similar developments might occur with regard to heritable gene editing. The surfacing of "rogue" clinics was seen as particularly likely in countries with no regulation or leniently enforced regulatory infrastructures. A senior researcher stated in this regard that excitement about heritable genome editing could lead to hype, and fuel the provision of heritable genome editing in illegal or grey area ART clinics, which were insufficiently qualified for conducting HGE procedures. He and other respondents regard it as very likely that unscrupulous, misguided or also inexperienced clinicians will offer germline therapy to patients who desire a child without a genetic disease. Similar concerns have also been expressed by the bioethicist and legal scholar Alta Charo, who also has warned of the surfacing of germline therapy tourism.[41] According to Charo, medical and reproductive tourism is not necessarily a bad thing, but it should only follow after the development of safe and effective interventions, and not precede or be a part of the clinical research and development process.

Interviewees expected that these clinics would initially focus solely on the correction of monogenic medical conditions, but that over time, once germline therapy for single gene disorders was more widely available and accepted, clinics would also provide treatments for polygenic conditions and non-therapeutic purposes, including forms of genetic enhancement. Similar concerns were also expressed by CRISPR co-inventor Jennifer Doudna, who stated in her 2017 visit at the Royal Society stated that:

> I certainly hear about work […] that is aimed at helping in-vitro fertilization clinics to apply [germline gene editing] for correcting genetic diseases, or for making other kinds of genetic changes. And also to commercialize that. And that is […] where I feel more uncomfortable. I certainly feel more uncomfortable,

with a company trying to make money, telling people… 'Hey, you can have a better child… when you do this…'.

Project participants defined "rogue" IVF clinics in various ways. The most important criteria that were used to differentiate these clinics from providers of more "legitimate" clinical services were that they were likely to:

- Provide insufficient information on the kinds of methods and protocols they use
- Work with false claims and misleading advertisement strategies
- Provide clinical services that are based on insufficient forms of preclinical and/or clinical evidence
- Offer non-therapeutic or enhancement applications in a legal grey area or even in the context of legal prohibition
- Sell potential "snake oil" interventions, which would not involve gene editing at all, despite the fact that they were sold and advertised as such
- Expose IVF patients and their offspring to uncertain and unjustifiable risks

Participants identified three key policy challenges related to "illegal" or "rogue" IVF clinics offering heritable gene editing to patients.

A first challenge was to make sure that germline gene editing is only provided in a well-regulated, controlled environment. This would include preventing unscrupulous clinical entrepreneurs from trying to exploit the desire of (prospective) parents to have a healthy baby or a child with specific physical, mental or cognitive characteristics; at least as long as the clinical utility of these interventions was not reliably established and a public consensus on the desirability of these applications was not yet achieved.

A second challenge was to protect patients from deceptive marketing and advertising, without being sufficiently informed of possible adverse effects and risks. Public education of risk groups and caregivers was seen as a means to achieve this goal, to inform publics of the most recent stage in the technique's developments, and of potential individual and societal consequences, possible adverse effects and risks.

A third challenge was the emergence of enhancement-oriented forms of germline therapy. Numerous interviewees expected that, mid-to-long term, clinical

applications that sought to achieve some form of genetic enhancement would be offered to patients. Because these interventions would inevitably involve the modification of large numbers of gene locations, the risk of adverse effects was expected to be considerably higher than for the treatment of monogenic disorders. Most respondents argued in favor of a prohibition of enhancement applications, but recognized that at a global level such a ban would be difficult to achieve.

A fourth challenge that research participants identified was to avoid the provision of fraudulent interventions, i.e. of clinical applications that *claim* to involve germline therapy while in fact they do not. The likelihood of such deceitful interventions was seen to be particularly high with regard to non-therapeutic or "enhancement" applications——because the actual efficacy and effects of these "treatments" will be extremely difficult to verify. Interviewees pointed out in this respect that:

> - "In principle – as happened with for-profit stem cell interventions, clinics or corporations can work with entirely fraudulent claims." (IVF clinician 1)
> - "One would never know how well it would have worked" (Senior Researcher)
> - "There will be a lack of evidence for these interventions, but private clinics and corporations are likely to do it nonetheless". (IVF clinician 2)

These concerns reverberate closely with Ishii's estimation that non-therapeutic and enhancement applications are probably inevitable at a global level, and are only a matter of time.[42] They also resonate with Koenig's assessment that there is an "illusion of control" in many of the current policy debates on germline engineering.[43] He has pointed out, a central assumption in current discussions on the governance of heritable genome editing is the notion that 'technologies can be prohibited […] until they are 'safe enough'—and, moreover, that this can be done globally'.[44] According to Koenig it is an illusion that such a universal level of control can be achieved, partly because current regulations for germline genome editing vary considerably across the globe, partly because there exist different ethical and moral ideas on human genome editing, and partly because of the economic incentives that drive innovation processes in this field.[45]

5.2 Challenges related to the situation and activities of researchers, fertility clinics and corporations

A second set of policy challenges that the project examined related to the situation and activities of researchers, fertility clinics and corporations that are likely to develop, apply and commercialize this technology over the course of the next years and decades. Throughout the interviews and workshop, our aim was identify obstacles to the realization of responsible forms of cross-border research and corporate practices, in an international environment that is characterized by significant differences in research cultures, regulatory structures as well as business and commercialization practices. For this purpose we now consider project findings related to two aspects of the internationalization of HGE clinical research and applications: (i) the possibility that UK researchers and corporations provide HGE treatments in permissively regulated countries to avoid regulatory restrictions in the UK (or alternatively, to avoid going through an expensive, long-drawn out clinical evaluation process), and (ii) the involvement of UK researchers in overseas clinical research studies. The first of these two scenarios refers to the realization of "quick" commercial clinical applications (that are offered without systematic preceding research studies). The second relates to participation in clinical studies that involve systematic research protocols.

5.2.1 UK researchers and corporations operating abroad to avoid regulatory restrictions in the UK

A widespread concern among participants was that UK researchers, clinicians and fertility companies would seek opportunities to provide and commercialize HGE applications in more permissive countries, especially as long as the technology was not permitted in the UK. An example that came up repeatedly in interviews and group discussions was the first application of mitochondrial gene transfer in Mexico in 2015, where US clinicians travelled to Mexico to create a "3-parent" embryo which then developed into a healthy baby, despite the fact that the technology was not approved in the USA.[46] Participants expected that a similar development could also occur with regard to heritable genome editing. In open discussions of the workshop there was unanimous consensus that if these clinical applications were not part of

systematic and formally approved clinical studies this was bad practice, which should be addressed and prevented by UK government bodies, research councils and scientific and medical organizations.

In interviews a widely expressed concern was that the operation of UK researchers and corporations in more permissively regulated countries could harm the scientific status of the UK and prevent progress for the clinical validation of HGE by looking for profit opportunities rather than robust data. However, some interviewees supported the idea that UK researchers and fertility companies could provide HGE treatments in more leniently regulated countries, if these collaborations would enable UK patients to access potentially beneficial interventions for severe genetic disorders that are not yet available in the UK. This view was held in particular by representatives of patient organizations. These spokespersons argued that preventing patients to travel abroad to seek potentially beneficial treatments, was a violation of patients right and ignored patient suffering. One of the representatives stated in this regard that the acknowledging of reproductive freedom and parental autonomy is especially important in the context of the burden and inevitability of serious genetic diseases, and the instinctive and intuitive desire of parents to have an unaffected child. The spokesperson of another patient organization stressed that the knowledge that a potential treatment was available, albeit in a different country with less rigorous regulations, instils a psychological motivation to use this treatment. That is why, from his view, inaction by the UK government to permit heritable genome editing for monogenic disorders, would ultimately encourage patients to travel to other countries.

5.2.2 Involvement of UK researchers in overseas heritable genome editing research trials

Another form of cross-border interaction that the project discussed was the involvement of UK researchers in overseas clinical research studies that would involve heritable genome editing. While interviewees thought that at present any form of clinical research in this field was premature, there was a general consensus that once the technology was proven to be safer and more reliable, participation in international clinical studies was seen as acceptable. There was also a widespread agreement that such interventions must be provided as part of a systematic, science-driven clinical study format, and that these studies should be formally approved by a

government agency and conducted in line with international guidelines. As a set of minimum criteria participants suggested the following benchmarks: (i) open and transparent treatment protocols; (ii) independent ethical review; (iii) approval by a national-level government agency; (iv) clinical applications must be based on sufficient preclinical evidence on safety and efficacy; (v) follow from a convincing medical rationale that justifies the interventions; and (vi) be conducted in an international dialogue and under systematic, independent peer review. If these conditions were met, involvement of UK researchers in overseas HGE trials was seen as acceptable, also if such trials would in the UK still be prohibited.

6. Policy options to address identified challenges

How should policy makers, professional bodies and other stakeholders respond to the challenges described in this paper, so as to maximize patient safety and to enable responsible forms of clinical translation and ethically robust forms of international research and corporate collaborations? In the context of interviews and workshop, project participants developed six broad policy options.

6.1 Proactive regulation

To avoid some of the identified problems the majority of participants argued in favor of proactive legislation that would enable clinical HGE research under carefully defined conditions. As the director of an IVF unit put it, the creation of a permissive, but carefully regulated research environment for HGE in the UK would prevent reproductive tourism, and allow initial clinical applications under a systematic research framework:

> 'If [this technology] is found to be safe, and only if it is found to be safe, [we must] ensure that we have tight, permissive regulation enabling those parents who may want to go through these therapies for their future children to have the ability to have safe therapies in the UK, rather than feeling the need to go overseas and to be potentially treated by rogue clinicians, rogue scientists, in rogue clinics, where we won't necessarily have insight into the failures, the mistakes, the problems that may occur' (Interview Nr 14, May 2017).

Several participants emphasized that the UK has a comprehensive and mature regulatory framework that governs ARTs, embryo research and the creation and use of human embryos for research purposes, and that this framework can in principle be extended to regulate first-in-human applications of heritable gene editing. While there was a shared understanding that at present it was too early to change legislation and permit clinical applications, various participants thought it was crucial that the UK government starts to anticipate and address some of the key concerns of HGE technology, and to begin developing appropriate policy responses. A senior researcher, for instance, mentioned that the UK government needs to 'think about what forms regulation would take to govern this area of potential clinical practice'. He also stated that, 'it is quite clear that we are not ready yet. There are still lots of issues that need to be sorted out. But it is important to have government to start thinking about this now, as an issue' (Interview Nr 12, April 2017). This view is also reflected in the statement of a senior IVF clinician:

> 'This technology field is developing extremely quickly and so we need to take stock of things that it is properly regulated and that we have appropriately published preclinical studies before we bring this technology into clinical practice.' (Interview Nr 21, July 2017).

While project participants did not have an answer to the question when first-in-human applications should be allowed, they acknowledged that there is a fundamental tension between the development of a slow and careful regulatory framework in the UK, and the pressures that are likely to arise on UK science from developments in other parts of the world:

> At the moment I think it is essential I think that we move cautiously, that we move slowly, but at the same time we have to recognize that there are scientists out there in the world, who may be moving faster than we would like and that brings the danger of people going overseas for treatments that are not regulated in the UK. So if we accept that these sorts of therapies are going to come into clinical practice, we need to ensure that our regulation occurs in a timely manner. (Interview Nr 21, July 2017).

6.2 Broad public engagement

A closely related policy option that project participants repeatedly emphasized was the initiation of far-reaching public engagement exercises. A widespread view was that the UK is currently lacking in public and policy debates on reproductive gene editing and on the potential uses of HGE. Broad public engagement was seen as a central requirement to ensure that regulatory options and policies would correspond to the needs and perceptions of patients, laypeople and society at large. A senior researcher summarized this as follows:

> Accompanied with [a reflection on how clinical applications could be regulated] there has to be robust public engagement exercises, where you really get to – not only give the information to the public, but of course also get the feedback from the public of what they think might be useful, might be acceptable and where are the limits. Because of course, there has to be limits applied to the use of this technology. There are potential uses which are beneficial, to avoid having serious genetic diseases. But there is a whole spectrum going towards more trivial applications, or even of enhancement, which would be really unhelpful and potentially lead to a public rejection of the whole notion. (Interview Nr 11, May 2017).

Several participants emphasized that in the UK a revision of the law, which would enable clinical HGE applications, could only take place if the wider public embraces this idea and it these applications lie within the limits of what society considers acceptable. In Great Britain, a decision to change the law is ultimately initiated by the Department of Health (DOH). As part of this process it would, before doing anything, commission the Human Fertilisation and Embryology Authority (HFEA) to conduct public dialogue activities. The HFEA, in its function as a government regulatory body, is supposed to be neutral about any legislative change; and HFEA staff would not lobby government to change the law. However, following an order from the DOH, the HFEA would start reaching out into the public sphere and start a multi-stakeholder deliberation process. Based on the results from this process, the DOH does then take a final decision. This was the procedure, for example, that has led to the legislative

change, which has permitted mitochondrial replacement therapy in the UK in 2016 [34][47].

However, for heritable genome editing a different procedure might be used. In its recent report, the Nuffield Council on Bioethics recommended that the coordination of societal debate on genome editing should be done by an independent body or commission, and not a government body [2][48]. Similar views were also expressed during the workshop and interviews that inform this paper. As a senior policy advisor pointed out, a robust public discussion should go way beyond the deliberation activities of the HFEA. Consultation of public opinions, according to this policy specialist, should be instigated by various parties, independent social scientists, the HFEA, but also from within patient organizations as well as religious groups and other social and civil societal organizations.

> There is a need to have early upstream public engagement that […] can feed into the policy making process. […] I think it should be [initiated by] all sorts of different people. Researchers and [scientific] institutions have to be willing and open to talk about what their researchers are doing. Funders have to be open about it. It [this openness] has to be part of public discourses, you got to allow patient groups and consumer groups and all other people to have access to this information, when they go to these [deliberation] fora and talk about how they feel about this. (Interview 9, April 2017).

Patient groups and other organizations are of course likely to use results from public deliberation to press for a more permissive legislation, at least if the majority of their members want this. The representatives of the two patient organizations that took part in our project stated, for example, that they would actively seek to lobby for regulatory change if their communities considered reproductive gene editing as a desirable option.

6.3 International guidelines

Virtually all interviewees agreed that the development of an international consensus and international guidelines that define how HGE should be translated into clinical practice was essential. While participating stakeholders acknowledged that the

development of international standards would not reach all clinics or researchers in this field, certainly not at a global level, many project participants supported the idea.

They saw international guidelines for the clinical translation of the technology as a way to (i) promote unified technical and safety standards that could facilitate international knowledge exchange, dialogue and collaborations, and (i) as a basis to identify "rogue" clinics so as to warn patients of irresponsible or premature applications. However, a challenge for the development of international is, that the technical procedures and effects of clinical HGE interventions are different for each disease. As the head of an IVF unit stated, the genetic manipulation for each genetic condition will be different and there will be different risks. There needs thus to be a clearly defined strategy and pathway for each genetic problem (Workshop Discussion; July 2017). This statement points to the potential limits of general international guidelines. It indicates that beyond the development of a set of broad, overarching criteria such as transparent treatment protocols, reliable preclinical evidence, careful peer review, approval by regulatory agencies, etcetera, more detailed criteria and considerations will be required for specific genetic conditions, so that the health and safety of newly born offspring can be ensured.

Another problem that participants mentioned is that international guidelines are not legally enforceable and that the implementation of these standards is likely to differ across the world. A widespread expectation was that individual clinics and researchers would try to circumvent these international norms, possibly at a larger scale:

> History has shown that certain jurisdictions have been willing to tolerate, or perhaps turn a blind eye to irresponsible therapeutic applications, [more recently] particular in relation to stem cell therapies, which have been offered without any evidence-base for their human use. […] I am more skeptical of international regulations and treaties and their effects, because […] there are those who are willing to pursue commercial gain over the responsible practice of medicine, and there is a limit to what is going to effectively be done on a global scale to prevent this happening. (Interview 19; July 2017).

While most participants acknowledged these challenges, they thought nevertheless that international guidelines would be an important and necessary regulatory

instrument, which would help to prevent misuse and to establish a solid evidence base.

6.4 Scientific sanctions

Another policy option that project participants generated was scientific self-governance and the enactment of scientific sanction. While participants assumed that irresponsible clinical practices in the UK could be prevented (or if necessary addressed) by national law, the use of scientific sanctions was especially seen as a tool to discipline UK clinical researchers or corporations who would engage in irresponsible research or commercial activities overseas. Participating stakeholders were concerned that, by operating outside of the UK and in countries with permissive, ineffective or not yet fully formed regulatory frameworks for HGE, these clinicians, researchers or companies could effectively circumvent UK law. Most participants saw scientific sanctions as the most effective way to prevent problematic clinical commercial and research practices. A senior IVF clinician summarized this as follows:

> I think what worries many of us is how this technology could be abused and misused and taken further than the desire to prevent debilitating diseases, more towards the slippery slope toward enhancing the human race in ways that are akin of the eugenics programs that we are all too aware of, from the last century. That is not a route that we want to go down. And therefore, I think that this technology needs to be very carefully considered, and that we need not only to have international consensus, but the ability to use sanctions against those who may misuse the technology. (Interview 21; July 2017).

According to most participants, strong sanctions were in the interest of both patients and the scientific community. The following types of sanctions were mentioned: (i) excluding researchers from professional societies and international bodies or committees; (ii) preventing researchers from access to funding; (iii) prevention publications in top journals; (iv) notifications of fraudulent work in scientific journals and the media, (v) put pressure on overseas clinics that collaborate with

"irresponsible" UK researchers and corporations, by clarifying that they operate outside of internationally acknowledged norms.

A challenge with these sanctions is that they all apply to researchers, yet clinicians and entrepreneurs who are not part of the mainstream scientific community may not be effectively controlled by them. While the nature and implementation of these sanctions requires further thought, interviewees thought that the enactment of sanctions should lie in the hands of a variety of stakeholders such as professional organizations, funding bodies, review committees and journals.

6.5 Public and Patient Education

A forth policy option addressed the question how patients could be prevented from seeking access to risky and premature HGE applications overseas. Representatives of patient organizations and IVF clinicians concluded that alerting patients of up-to-date facts on the current stage of clinical development, details on possible adverse effects and risks, as well as information of deceptive marketing and advertisement strategies – would be the most promising strategy to influence patient behavior.

The dissemination of such information, as several participants pointed out, should involve multiple stakeholder organizations, such as Human Fertilisation and Embryology Authority (HFEA), the Medicines and Healthcare Products Regulatory Agency (MHRA), the National Health Services (NHS) and other government bodies, scientific associations and of course patient organizations. The representative of a patient organization mentioned in this respect:

> [D]isease societies […] need to put [this information] prominently on the front page, of their websites. If you are seeking a treatment for this and you contemplate going abroad, make sure that what is being offered is being done as part of a properly conducted trial for the following condition. And do not do it otherwise, because you are most likely not benefitting yourself. (Interview 14, May 2017).

A different mechanism to create awareness among patients that participants suggested was to publish examples of irresponsible or fraudulent treatments and clinics in the

media, social media, and websites of patient organizations and the NHS. As one participant said:

> It is going to happen somewhere. It might happen because of the vanity of scientists or clinicians. It might happen because of the vanity or ego of prospective parents: 'I slip you 100.000 dollars to do this'. Whether they [clinicians] keep it quiet or whether they publish it, depends on how vain or ego driven they are. […] So, make big examples of those [cases]. Publicize those examples and hopefully this will deter clinicians, bad clinicians, from offering these treatments, and hopefully it will deter members of the public seeking them out. (Interview 9; April 2017).

6.6 Adjust advertisement regulation

Another option that project participants identified was to look at, and possibly adjust, existing advertising legislation. In order to protect patients from false claims, careful consideration of acceptable forms of advertising for HGE therapies will become important; at least once first clinical applications become available. This might require the adjusting of advertising legislation so that it is compatible with the specific characteristics of HGE therapies, and to create the legal basis for penalties, sanctions or punishments and the introduction of a consumer focused complaints system.

A potential problem, especially in the context of cross-border reproductive services, is differences in advertising legislation across jurisdictions. Moreover, the expansion of the Internet and social media have created new possibilities for the marketing of reproductive and therapeutic services. The ability of online advertising to reach worldwide audiences makes the enforcement of national laws more difficult, if not impossible.[49] Due to the decentralized and borderless nature of the Internet, and more affordable international travel, national governments alone cannot solve the problem of irresponsible, transnational advertising practices.[50]

A key question discussed in the workshop was whether UK companies that provide HGE therapies abroad, and that use false or misleading advertisements to attract customers in the global market, could be prosecuted under the UK legal framework for advertising. A legal expert in international health law contributed that

this was conditional on where the company operates and where it is advertising. Much depends on the legal situation in the countries where the advertising is taking place, and whether false advertising can be prosecuted under domestic law. In the UK, for example, the Advertising Standard Authority can take steps to enforce the removal or amendment of ads that breach the rules of Consumer Protection from Unfair Trading Regulations, a statutory instrument that was introduced in 2008. Failure to abide by the regulations can also result in fines and prosecution.[51] In other words, at least in the UK legal action has to come from within the country where companies operate and advertise their services.

There was widespread consensus that problematic advertisement strategies of UK companies abroad should be criticized from within the UK. Numerous interviewees thought that the UK government should take an active role in liaising with governments in countries where UK companies are likely to offer controversial HGE therapies. Another option that emerged during discussions, was that the UK government should actively discourage companies to offer controversial clinical interventions overseas, for example by imposing sanctions for UK professionals and companies planning to offer non-medical or "enhancement" applications overseas, including for participation in research studies.

7. Conclusions

This article identified challenges and options for the responsible governance of germline gene editing, by considering differences in regulatory, scientific and health care cultures, human values and socio-economic inequalities from the perspective of UK-based stakeholders. For this purpose, we have focused on challenges related to the situation of fertility patients and genetically modified children on the one hand, as well as researchers, IVF clinicians and fertility companies on the other hand. The paper has explored the views of a variety of stakeholders, which has provided insights into possible future developments, challenges and risks, when the technology is translated from the laboratory into clinical practice.

Some of the comments presented in this article may be making unwarranted assumptions or provide interpretations that may look unusual from other national or regional perspectives. However, at present there is no comparable work from other settings. Further, there is no global viewpoint available from which these

assumptions, expectations and interpretations could be judged. This matter of perspective points up the benefits of conducting this kind of research. It is exactly these expectations – well founded or not – that will inform policy development in the UK.

The research findings presented raise important points for discussion of the future governance of HGE. They demonstrate the complexity of the task to consider the prospects, risks and the regulatory requirements and conditions within which this technique might be developed safely. Research participants suggest that there is an urgent need to engage with these challenges at an early stage of public deliberation and policy development. They have suggested six policy options that, if developed further, may have the potential to address and possibly prevent some of the challenges that this article identified. At a more general level it will be crucial to raise awareness of these issues in various contexts and to conduct further research to assess the impact of regulatory, social, scientific and cultural variation in greater detail, with the aim to inform policy making as the technology develops and a consensus to translate it into clinical applications becomes more widespread.

Medium-term, public engagement with multiple stakeholders at an international level will be of particular importance. This would allow to bring into dialogue and compare expectations and assumptions from different countries, and initiate a conversation on the development of potential future solutions to identified challenges.

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