Global Forum on Bioethics in Research

Meeting report:

Genome editing for human benefit: ethics, engagement and governance

Singapore

12 and 13 November 2019

W: www.gfbr.global **E:** gfbr@wellcome.ac.uk

Global Forum on Bioethics in Research

CONTENTS

Executive Summary

Grounding: The Global Forum on Bioethics in Research (GFBR) convened in Singapore in November 2019, to explore the topic of 'Genome editing for human benefit: ethics, engagement and governance'. A total of 80 participants from 36 countries attended the two-day meeting, with the majority from low- and middle- income countries (LMICs). Case studies and policy and guidance papers were used as the basis for discussion.

Summary: Emerging human genome editing and gene drive technologies present several potential opportunities for LMICs, including the treatment of sickle cell disease (SCD) and β-thalassemia and the control of disease vectors (e.g. mosquitoes to prevent malaria). However, LMIC perspectives have been underrepresented in international debates. This meeting provided an opportunity for LMIC colleagues to discuss the ethics and governance of genome editing and the role of engagement when these technologies are introduced. It was clear from the discussion that many LMICs have had little or no national or regional debate on these issues. The general sentiment was that genome editing technologies as a type of biotechnology should not be regarded as exceptional. Like many emerging technologies, they are characterised by uncertainty, which can elicit fear. But they also offer hope as new tools to treat or prevent disease. Finding an acceptable way forward requires continued global debate and assessment of genome editing applications on a case-by-case basis. GFBR participants were encouraged to take the meeting discussions back to their national and regional contexts and to promote debate locally about the uses and governance of genome editing technologies in their setting.

Human genome editing

- Human genome editing can take place in either somatic or germline cells. Somatic changes affect the individual only whereas germline changes are passed on to the next generation. Ethical issues for both applications include: safety and efficacy; balancing risk and benefit; concerns about interference in the genome; the blurred lines between enhancement and treatment and prevention and equity of access to the resulting technology. **The general view amongst GFBR participants was that somatic cell genome editing can be appropriately evaluated within existing regulatory and ethical frameworks for clinical research** (where these exist). **Germline editing was considered to bring additional ethical and governance challenges** and these were the focus of the GFBR discussion. Ethical issues include implications for future generations who are unable to consent to intervention and broader societal concerns about the preservation of the human genome, and its diversity, and the possibility that permanent 'enhancements' could exacerbate social inequities through the selection of 'socially-desirable' traits.
- Recent international debate on **germline genome editing** has been driven by Jiankui He's announcement in November 2018 about the birth of genome edited twins. This case demonstrates significant failures in scientific self-regulation, given Jiankui He's individual actions and the lack of reporting by international colleagues who were aware of his work. The case also represents a failure in law, regulations and oversight and highlights how national research policies (e.g. to derive economic benefit from the translation of research) can incentivise misconduct. This can be especially problematic if national law, policies and guidelines on ethics (especially on how to manage conflict of interest) are lacking or not enforced. **A new global reporting system is required that promotes responsible scientific stewardship and encourages a duty to report suspected misconduct**. This work could be led by the World Health Organisation (WHO) as part of its international registry of clinical research

using human gene editing. The reporting systems should be open to a range of stakeholders, including funders and journalists.

- **LMICs have the opportunity to learn from governance structures adopted elsewhere and to adopt an approach that is fit for purpose for their setting** e.g. to learn from restrictive regulatory regimes and find a nimbler approach. However, national guidelines or regulation will take time to develop in LMICs due to constraints on resources. A global response is essential in the short term, i.e. the guidance being developed by the WHO's expert panel on human genome editing. WHO's guidance can pave the way to national governance and will be particularly helpful and efficient where LMICs have limited relevant expertise. The guidance could also be used as a starting point for public and professional debate in LMICs.
- International guidelines have proposed criteria that must be met before clinical germline editing can take place. There can be tensions between these criteria and the realities faced by LMICs. For example, **the requirement for 'broad societal consensus' can present challenges for LMICs that lack the capacity and resources for societal deliberation**. As such, the criteria could amount to a prohibition in some LMICs if the criteria cannot be met, denying countries the potential benefits of human germline genome editing.
- Countries will interpret criteria for germline editing in the context of their diverse historical, cultural, and social characteristics. It is currently unclear how conflicts between a contextual, national approach and the global position would be handled, and by whom. For example, if a country decides to pursue the clinical application of germline genome editing, amidst the current international consensus that such work is premature. **An international arbiter could review all proposed clinical uses on a case by case basis, working with individual countries to help them assess whether the criteria have been met.** However, it would be essential for the arbiter to have the legitimacy, expertise and resources to undertake this role.

Gene drive research

- Ethical issues in gene drive research include: safety and efficacy; balancing risk and benefit (to people and the environment); fundamental concerns about interfering with 'nature' and how to engage with the affected communities. Gene drive organisms are broadly agreed to fall under the scope of the international Convention on Biological Diversity, under which implementation and decision-making falls to individual countries. However, **not all LMICs have the appropriate governance structures to evaluate gene drive organisms and manage their release. Even where such structures exist there may be little experience in applying them and uncertainty can exist regarding which national body has the authority to approve the use of gene drive organisms** e.g. whether this falls to the Ministry of Environment only or whether the Ministry of Health should also be involved.
- Similar to other 'area-wide' public health interventions, individuals are not able to opt-in or opt-out of research involving gene drive organisms. In this context, engagement with the community is essential. **Researchers should work with the affected communities to better understand their social, historical and cultural context so this understanding can be used to inform culturally appropriate engagement approaches.** Likewise, **a model for community acceptance or consent should be co-developed with the community taking on board their preferences for how they want to make decisions**. **Guidance or principles on models for community acceptance or inclusion in gene drive field trials would be helpful to ensure a level of quality and confidence in the decisions reached**.

- Gene drive organisms may cross geographical and/or jurisdictional borders and affect proximal countries. **Governance of gene drive organisms requires consideration of trans-border issues and may require a sub-regional approach and agreement by a number of countries**, especially if and when the intervention moves beyond research and is rolled out as a public health measure.

Governance – overarching issues

- **The governance ecosystem includes – and needs – both formal and informal elements** e.g. national regulation; international, national, funder or institutional policies, codes of conduct and guidance published by organisations like the WHO, along with structures and processes for decision making. **Regulation alone can be problematic in the field of emerging technologies as it can become quickly out-of-date and be difficult and time-consuming to revise**. A breadth of governance mechanisms, e.g. including codes and principles of conduct is required and can help create a culture of responsibility and accountability.
- **International and regional organisations, governments and funders must take responsibility for creating a research environment that promotes transparency, openness and dialogue on emerging genome editing technologies**. Funders in particular have a key role to set standards for the research that they fund e.g. promoting compliance with accepted norms, defining principles for professional conduct and having appropriate sanctions for misconduct.
- RECs provide important oversight and monitoring but their role has not kept pace with emerging technologies. **The constitutions RECs work under should be re-evaluated in light of these technologies and their capacity should be strengthened** through self-education and more structured professional development on the science and ethics of gene-editing.

Engagement - overarching issues

- There are multiple methods for public and community engagement and multiple roles it could play during the introduction of genome editing technologies (e.g. to inform the public, to develop trust, to help assess social acceptability and influence policy decisions). **The full spectrum of engagement is valid and what matters is clarity and transparency about purpose and integrity of the process, who is doing the engaging and who is being engaged.** Transparency is especially important where engagement is undertaken by those who have – or are perceived to have – vested interests (e.g. government, funders). **The method of engagement should be tailored to the context, taking account of language, prevailing social and cultural norms and governance systems**.
- It is important to acknowledge the history of anti-Genetically Modified Organism (GMO) sentiment toward current gene editing applications and engagement sentiment. **Researchers, funders and others need to be careful not to allow the pendulum to swing too far the other way where they initiate ill-considered engagement strategies (in trying to avoid 'mistakes of the past').** It is important to learn from history and the past body of work that exists especially in environmental and public health domains that is rich in engagement experience and past lessons.
- Public engagement can contribute to building trust in research and is vital for addressing the beliefs or cultural norms that may impact on the social acceptability of genome editing technologies. Social acceptability will be context specific and may range from the public not objecting to the technology to the public positively embracing it. In addition, what is socially acceptable to one group (e.g. patients with sickle cell disease who have an interest in the potential of genome editing technologies) might not be acceptable to others. To this end, **it is important to understand and address the issues that communities themselves are raising and the barriers to acceptability**.

- Engagement is also required between sciences and other science professionals to promote the integration of social sciences and natural sciences to co-create knowledge that is ethical and implementable. If the research community seeks to understand public attitudes, to engage more widely, to conduct science ethically, then it should also be working harder to integrate across disciplines, (humanities, sciences) so that the social and human dimensions of science decision-making are incorporated more fully.

Introduction

The Global Forum on Bioethics in Research (GFBR) convened in Singapore in November 2019, to explore the topic 'Genome editing for human benefit: ethics, engagement and governance'. The meeting focused on human genome editing and gene drive research – two emerging applications of genome editing that are designed to benefit human health.

Case studies and policy and guidance papers were invited through an open application process. Responses to the open call determined the focus of the Forum. For example, two sessions focused on human germline genome editing reflecting the many applications that we received on this topic, and how few we received on somatic cell editing. This is perhaps understandable given the societal implications of germline editing and international attention in 2018 and 2019 on the germline editing research of Jiankui He (see Part 1).

An international, expert Planning Committee[1] selected the speakers and structured the meeting around the following themes:

- Theme 1: Human germline editing: Jiankui He case
- Theme 2: Human germline editing: regulatory and policy responses
- Theme 3: Governance of genome editing: national and regional perspectives
- Theme 4: Engagement and social acceptability
- Theme 5: Governance of gene drive research

With experts in bioethics, research ethics, genome editing, policy, regulation, journalists and research from 36 countries (see map of GFBR participants' countries), the meeting delved into the common challenges presented by human genome editing and gene drive research, including the need to negotiate a high degree of uncertainty and demonstrate technical feasibility and safety through complex risk assessments, social acceptability and the need for appropriate governance systems.

This report summarises the meeting discussion and the range of views that were expressed. The report does not provide a full account of the cases studies and policy and guidance papers. Instead, it provides enough details to give context to the discussion. The full cases studies and policy and guidance papers can be found on the GFBR website.[2]

[1] Jantina de Vries, South Africa; Peter Mills, UK; Lucy Carter, Australia; Fabiana Arzuaga, Argentina; Teck Chuan Voo, Singapore; Maneesha Inamdar, India; Paulina Tindana, Ghana; Elinor Wanyama Chemonges, Uganda; Jim Lavery, USA; Claudia Emerson, Canada; Samantha O'Loughlin, UK; Michael Selgelid, Australia; Katherine Littler, Switzerland.
[2] http://www.gfbr.global/past-meetings/14th-forum-singapore-12-13-november-2019/

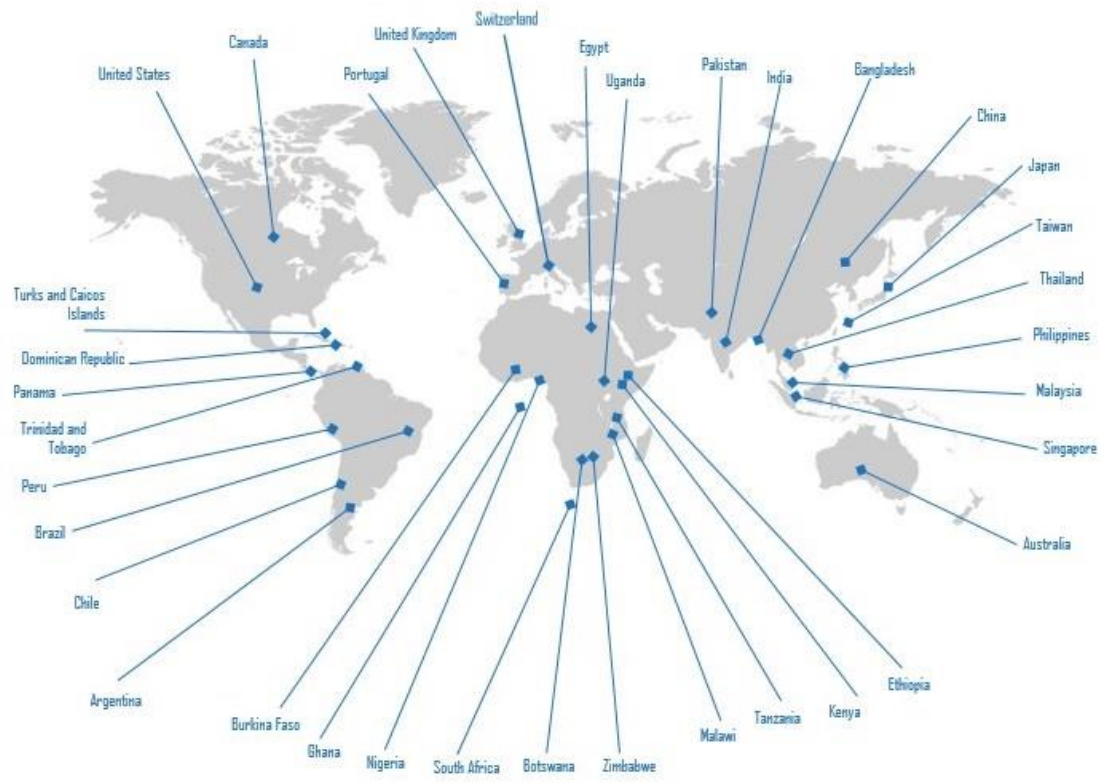

Figure 1 GFBR participants: 80 participants from 36 countries came together to discuss this important issue with a wide range of expertise: bioethicists, clinicians, genomic researchers, community practitioners, policymakers, social scientists, journalists, regulators, and funders, at all levels career stages. 51 participants were from LMICs.

1. Human genome editing

Gene editing technologies can be used to change a person's DNA by adding, removing, or altering genetic material at particular locations in the genome. Changes to **somatic** cells affect the individual only, whereas changes to **germline** cells (i.e. sperm, egg or embryos) transmit to the next generation.

There has been a recent expansion of research using **somatic** cells with many trials underway and ethical debates well established. In October 2019 the US NIH and the Bill & Melinda Gates Foundation announced a joint investment of at least $200 million over four years to develop gene-based cures for sickle cell disease (SCD) and HIV. **The general view amongst GFBR participants was that somatic cell genome editing could be appropriately evaluated within existing and evolving regulatory and ethical frameworks for clinical research (where these exist)**.

Germline editing remains controversial with discussion ongoing as to whether it should be pursued and if so, under what conditions. There is a variation in – or a lack of – regulation around the globe and debate about whether oversight should be national or global, and what this should look like. In 2018, the Organizing

Committee of the Second International Summit on Human Genome Editing concluded that 'proceeding with any clinical use of germline editing remains irresponsible at this time'. However, given recent progress and scientific developments they suggested that it is time to define a 'rigorous, responsible translational pathway toward such trials'.

Ethical issues

GFBR participants identified a number of ethical issues in common to both somatic and germline editing, which are reflected in the literature:

- safety, efficacy and risk assessments
- enhancement (and blurred lines between therapy, prevention, and enhancement)
- fundamental concerns about interference in the genome and of 'playing God'
- equity of access to new genome editing technologies

In addition, the prospect of heritable modifications using germline editing was identified as raising the following distinct issues:

- preservation of the human genome, and its diversity, and the value of biological difference
- future generations being unable to give their consent
- implications for future generations who will carry the genetic alterations
- ongoing follow up of people who have received germline editing in the research context. Who is responsible – the research funders, governments etc.?
- intrinsic concerns about the use of embryos in research
- the possibility that permanent 'enhancements' could exacerbate social inequities

As mentioned above, the majority of case studies and policy and guidance papers submitted to GFBR related to germline editing. The remainder of this section is dedicated to the first two themes at the meeting, focusing on the Jiankui He case and on regulatory and policy aspects of germline editing more broadly.

Germline editing: Jiankui He case

In November 2018, Jiankui He, a Chinese scientist, claimed to have created twin girls with a modification using CRISPR-Cas9 to reduce the risk of HIV infection. Among other reasons, the research was condemned by researchers in China and internationally as being:

- scientifically premature (risk and efficacy was unproven)
- medically unnecessary (the research intended to reduce the risk of HIV infection, for which other interventions are available)
- lacking oversight and robust consent procedures

Yonghui Ma presented a Chinese perspective on the case, arguing that there is no ethical divide in terms of moral values between China and the West and there is no China-specific ethical framework that supports Jiankui He's research. On the contrary, He's research challenges China's fundamental ethical norm for medicine – *yi nai renshu* (medicine as the art of humanity or humaneness). According to this norm, rooted in the moral and political philosophy of Confucianism, biomedical research and science should not serve primarily the personal ambitions of scientists or the interests of any one nation. Biomedical science should practice "the art of humanity". From a broad sociological and historical perspective, however, Jiankui He's controversial research is unsurprising. A series of political, social and economic forces in China in the past several decades have

created a fertile environment that recognises and rewards Chinese researchers to undertake "world first" research.

Gene-edited babies: the political, governance and cultural issues and why China?

Yonghui Ma, Xiamen University, China

Jiankui He's research was a result of his personal ambition, situated in the context of China's policies on innovation-driven development. Pursuing a nation strong in science and technology, the Chinese government has promoted the transformation of scientific discoveries and technological inventions into clinical practices and economic benefits. Researchers from the university, including students, are encouraged to translate their scientific investigation and technological invention and this has become an evaluation standard. This policy gives rise to ethical issues where pressures and financial incentives present serious conflicts of interest. This is especially problematic while China still lacks rigorous ethics governance and oversight of research, especially on conflict of interest.

GFBR participants agreed that incentives meant to drive science excellence **may also distort researchers' behaviours** (e.g. the desire for peer recognition and to get published). Government and institutional policies – e.g. to maximise publications or derive economic benefit from the translation of research – may compound this situation by putting pressure on researchers and distorting individual and institutional values and cultures. This can be especially problematic if national law, policies and guidelines on research ethics are lacking or not enforced.

Qi Chen explained that Chinese law prohibits genetic manipulation of human embryos for reproductive purposes. However, at the time Jiankui He undertook his research there were no obvious penalties for breaking the law. The issue of appropriate penalties and consequences was raised by GFBR participants as not being sufficiently aligned to the seriousness of the misconduct, as identified by the Chinese government and internationally. This lack of accountability also raises questions about the integrity of oversight on a national level. It was noted that China has subsequently revised its relevant laws in light of the Jiankui He case.

Public participation and regulation of human germline gene editing in China

Qi Chen, Xiamen University, China

Government departments should play a key role in increasing public awareness in China of germline editing e.g. by cooperating with mainstream media to release accurate information. A national advisory department could be established to undertake consultations and provide guidance services for patients and the public interested in learning about the science, ethics and governance of gene editing. Stakeholders (including the public) should not only be informed, but also engaged as a core part of governance at all stages of the technology's development and application. This engagement, which could help develop more acceptable ethical norms, should be a shared responsibility between the government, researchers, and the national advisory department. There is also a need to strengthen the law and oversight process for germline editing research in China, including penalties for misconduct.

GFBR participants discussed the role of the ethics review system in the Jiankui He case and the challenges faced by RECs in China and other LMICs:

- insufficient training in new emerging technologies, meaning issues may go unnoticed (e.g. Jiankui He's research was described as a vaccine trial and this was not identified by the REC)
- paper-based authorisation processes which do not allow sufficient communication between researchers and RECs

- REC membership being unequal in terms of voice and power (e.g. lay members being less confident to speak in comparison to other members who may come from institutional positions of power).

Inadequate law and oversight mechanisms are common to many LMICs; these issues are not distinct to China. Further, there is a limit to what law and committees can do. In addition, individual researchers, and the scientific community as a whole, also have a responsibility to foster responsible research cultures.

Responsible research as an individual and collective responsibility

Inside and outside of China, Jiankui He has been portrayed as a 'rogue' scientist. However, GFBR participants agreed that this was not simply a matter of individual responsibility; other stakeholders knew about the research but did not appear to stop it. **Owen Schaefer** explained that around sixty international colleagues were aware of Jiankui He's work before the story broke, but no one alerted the broader scientific community before the babies were born in October 2018.

Yonghui Ma questioned whether Jiankui He's research constituted ethics dumping, the practice of conducting research in a country with lower standards of protections in order to avoid regulations elsewhere. Ethics dumping can also be understood as exploitation to gain advantage due to insufficient ethics awareness on the part of the researcher, or because of the low research governance capacity in the host nation. By disregarding Chinese law, Jiankui He could be accused of ethics dumping in his own country. It could also be argued that by remaining silent, Jiankui He's international colleagues and collaborators indirectly allowed ethics dumping and were complicit.

Owen Schaefer argued that Jiankui He's conduct undermined the integrity and trustworthiness of the scientific enterprise, something which all members of the scientific community should uphold. Failure to report Jiankui He's conduct underlines a failure of international self-governance. **GFBR participants agreed that researchers should have an ethical duty to report scientific misconduct but there is currently a lack of clarity regarding who misconduct should be reported to and the consequences for individuals who do report**. **A new reporting system is required that has the necessary resources and safeguards to investigate and judge the merit of claims and to manage concerns about mis-reporting** (e.g. due to personal vendettas). **Owen Schaefer** proposed that a formal international notification channel could be connected to the work of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. GFBR participants agreed that the reporting mechanism should be open to stakeholders beyond the scientific community e.g. funders, journalists etc.

Silence and complicity in the case of the first gene-edited babies

Owen Schaefer, National University of Singapore, Singapore

The case of Jiankui He highlights that relying on researchers and local institutions/authorities to prevent unethical conduct may be inadequate in the area of germline modification. Before Jiankui He conducted his experiment, he was in contact with a number of international colleagues. However, none of his international colleagues reported the work, which at the time was generally considered by the international scientific community to be unethical, premature and risky. The scientific community should seriously reflect on researchers' duties in relation to internationally unacceptable gene editing conduct. This would encompass what should be done if another clinical application of germline editing occurred, as well as what institutions should be set up to better manage notifications/reporting of this kind in the future.

The proposed **WHO registry dedicated to clinical research using human gene editing was regarded by GFBR participants as a positive and necessary initiative**. The Jiankui He case demonstrates that current mechanisms for registering research are not an effective governance tool: his research was on a register but it was a journalist, rather than a regulator, who searched the register and brought the research to international attention.

The need for public debate

Some GFBR participants reported a significant mistrust of science in their countries, especially where it is perceived that the research is coming from the North. However, in part this is the product of a failure to communicate well about medical research and its potential benefits. Emerging, novel technologies are complex with science often moving fast, presenting a challenge for communication efforts. However, **it is the ethical responsibility of researchers, funders and others to rise to this challenge and communicate in a clear, timely and accessible way**. **Qi Chen** called for governments to foster and support public discussion about genome editing research and public participation in the formulation of guidelines. GFBR participants also saw a significant role for the media in providing the public with basic information about genome editing. (See section 3 on Engagement and social acceptability.)

GFBR participants identified some positives to come from the Jiankui He case, including that it:

- promoted international dialogue
- raised public awareness and discussion
- instigated the current work by the WHO to develop global standards for governance and oversight of human genome editing
- resulted in collective international pressure from scientific community more broadly to conduct research responsibly.

Germline editing: regulatory and policy responses

Prohibition vs precaution

Ana Palmero reflected on the regulatory prohibition of germline editing in Argentina, which resulted in halting embryo gene editing research for the treatment or prevention of disease. She argued instead for a precautionary approach that is guided by criteria that must be met before clinical trials using germline editing can take place. Such a precautionary approach reflects international debates and the recommendations of the National Academies of Sciences, Engineering and Medicine (NASEM) Committee on Human Gene Editing. The Committee proposed a number of criteria, including ongoing, rigorous oversight during clinical trials and continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public.

Is prohibition a solution? A reflection on embryo gene editing in the Civil and Commercial Code of Argentina

Ana Palmero, National Ministry of Health, Argentina

The new Civil and Commercial Code of Argentina entered into force in 2015. It recognizes human dignity as a fundamental principle which acts as a source for civil rights. In this context, a set of rules related to bioethics issues were incorporated based on the inviolability of the human person. Article 57 on prohibited practices, states: *"Any practice designed to produce a genetic alteration of the embryo transmitted to their descendant is prohibited".* Although the original Code exceptionally allowed these practices for the prevention of genetic diseases or the predisposition to them, gene editing with embryos was forbidden in the new Code. This was based on international global consensus not to allow this practice. However, in recent years, the global consensus seems to have shifted from prohibition towards permission under strict criteria. This precautionary approach is preferable and offers an opportunity to put in place public engagement strategies that promote valuable public participation and regulatory debate.

There was concern amongst some GFBR participants that prohibition could stifle valuable scientific research. **Legislation can be hard to reverse and so an approach that permits research under strict criteria would be preferable**. However, **GFBR participants agreed that it will be difficult for many LMICs to satisfy the criteria proposed by NASEM, given their limited resources to undertake the necessary scientific and regulatory assessments and the prerequisite dissemination and engagement activities**.

GFBR participants recognised the tension between the need for controls and flexibility. Even where the precautionary principle is engaged, which is a strategy to cope with possible risks where scientific understanding is yet incomplete, this might result in research being hindered if countries are unable to meet the required criteria. Some GFBR participants argued for '*informed legislation'* co-developed by legislators and researchers so criteria – and their implications – can be discussed before the law comes into effect.

The criteria recommended by the NASEM Committee are broad, recognizing that different societies will interpret the criteria in the context of their diverse historical, cultural, and social characteristics. **GFBR participants recognised the need for a contextual, national approach but also that this may at times be in tension with the global position**. For example, what are the implications if a country decides to pursue the clinical application of germline genome, amidst the current international consensus that such work is premature? **A solution may be to establish an arbiter that reviews proposed clinical uses on a case by case basis and that works with individual countries to help them assess whether the criteria have been met.** This mechanism would need to have the expertise, resources and legitimacy to take on this role (e.g. through international representation).

Currently, many LMICs have no national legislation or guidelines on germline genome editing. The lack of expertise in genetics, and in the bioethics of emerging technology, presents a significant challenge for LMICs in drawing up such guidelines and regulations. The Human Heredity and Health in Africa (H3Africa) Consortium was cited as a successful initiative that provides training for RECs to help them address the challenges of genomic research. LMIC RECs – as well as policy makers and regulators – need similar support to help them navigate the specific issues related to genome editing research.

GFBR participants considered that, as well as being unhelpful, a nationwide ban on human germline editing may also be ineffective as research may move overseas to countries that have no regulation, or comparatively lax regulation.

Societal consensus as a requirement for germline editing

The 2015 International Summit on Human Gene Editing stated it would be irresponsible to proceed with any clinical use of **germline** editing unless and until the relevant safety and efficacy issues have been resolved and there is **broad societal consensus** about the appropriateness of the proposed application. The second summit statement noted that **public consensus will be relevant within each individual country**. Using their own political systems, each country's citizens can express their views and decide whether to ban germline editing, even if it is shown to be safe and effective. Those that propound societal consensus as a requirement for germline editing have not defined what it means in practice, or given criteria for realising it.

Markus Labude argued that in order for societal consensus to be valid, it must emerge from a certain type of deliberation, with broad civil participation. This, however, presents a number of challenges for LMICs given:

- the lack of capacity and resources for engaging the public in bioethical debate or consensus finding, which can be a major obstacle to the inclusion of a range of perspectives
- 'democratic deliberation' can be difficult to achieve if there are power imbalances
- the influence of certain institutions can skew public debate
- decision-making cultures in many countries may not align with the idealized process that is being envisaged (i.e. governing bodies may normally make societal and policy decisions without public consultation or deliberation)

'Societal consensus' as a requirement for germline gene editing

Markus Labude, National University of Singapore, Singapore

The requirement for establishing societal consensus on the application of human germline editing poses formidable challenges on its own. Additional challenges arise in the context of LMICs where some nations might be unable to establish societal consensus because resources and capacity are lacking. Meanwhile, in other countries, where governing authorities tend to make decisions without open consultation in matters of social import, the requirement to reach societal consensus via a deliberative democratic process or open public consultation would be at odds with the country's larger political culture. Alternative models of global engagement could be considered, although, these alternative models would fall short of what was envisaged by societal consensus.

Many questions were raised during the discussion on the concept, purpose and meaning of societal consensus:

- on what basis is the requirement of societal consensus justified? Why is consensus required when it is not necessary for other novel technologies? Does the requirement reflect genome editing exceptionalism?
- who should be responsible for developing a consensus?
- what level of consensus should be sought – local, regional or global?
- who should be engaged and who to take consensus from (i.e. everyone or beneficiaries). This will greatly change the reception to the technology.
- what is the intended aim of seeking consensus (e.g. to bring the public on board or to shape practice)?
- how do you know if and when consensus has been reached?

Colleagues from Nigeria and Uganda explained that achieving consensus in their countries would have to start with building trust within the community. **Input from the community at the local level requires significant time investment to engage and to educate so discussions are informed**. In Kenya, there is a constitutional requirement for public consultation for 'anything that touches on the public'. These engagement activities

would include community and religious leaders and could draw on existing Community Advisory Boards. Such activities would help to bring the public *closer* to consensus, even if the ideal of consensus is unlikely to be reached.

GFBR participants agreed that the requirement for societal consensus is especially problematic if externally imposed (e.g. through international guidelines) on countries that have constraints of resource and bioethics capacity. The requirement for societal consensus could, in effect, amount to prohibition of germline editing in many LMICs if they do not have the resources for the prerequisite public consultation and bioethical debate to establish consensus. Even where the capacity for deliberation exists, **societal consensus would be difficult to achieve**.

For these reasons, **GFBR participants favoured an approach of education, engagement and consultation (where not everyone needs to agree) and the inclusion of representative voices in decision-making processes**. However, it was noted that in some cultures, society expects government to decide what is best and would not expect to be engaged.

2. Gene drive research

Synthetic gene drives use genome editing technologies to increase the probability that a particular gene of interest is inherited to increase its prevalence in a population. There are many potential applications of genomic editing in the fields of human health, agriculture and conservation. This meeting focused on the role of gene drives in vector-borne disease control e.g. targeting mosquitoes to control malaria. There are two approaches in this context:

1. "population suppression": reduce the number of disease vectors by inactivating or knocking-out genes involved in the mosquito's survival or reproduction
2. "population modification": modify the vector so it no longer acts as an effective vector

Gene drive organisms exist in the laboratory but safety and efficacy have yet to be proven. The move from a contained, laboratory environment to possibly being used as a public health intervention within communities has raised questions about how to engage – or seek consent from – the affected communities and whether existing governance mechanisms are adequate.

Ethical issues

A number of ethical issues were identified in the case studies and at the meeting:

- **Consent**: The area-wide application of gene drive organisms means that individuals are not able to opt-in and opt-out. Data are not collected on individual people so there is no 'human subject'. In this context:
  - what constitutes fair and legitimate authorisation for field trials of gene drive organisms?
  - is consent required for field trials? If so, at what level (e.g. individual, household, community) and from whom?
  - how can the research community acquire the necessary legitimacy and authority to proceed and how best can affected populations be engaged?
- The **potential benefits and harms for people**, including how these compare to existing prevention strategies.
- The **impact and spread of genetically engineered mosquitoes in the environment**:

- how to limit release to a defined geographical region?
- what impact might altered mosquitoes have on the existing ecosystems?
- are transborder agreements required?

An underlying point of concern for some GFBR participants was the existing power differentials where Northern technologies and values are often imposed on more vulnerable (Southern) nations. This point was made in the knowledge that gene drive research is not the only method of reducing disease burden. However, other GFBR participants considered that if it proves to be effective, feasible and cost-effective enough to implement in LMIC settings, there may be an ethical imperative to use the technology.

Governance

Isabelle Coche provided an analysis of the governance landscape for gene drive research, arguing that discussions of governance and decision-making on gene drive should be examined through a layered system, where different forms and levels of governance and decision-making exist and build upon each other at international, national and local levels. Further, "gene drive" as a concept covers a broad range of approaches, which could result in organisms with very different characteristics and potential uses and so these need to be evaluated on a case-by-case basis.

Providing sound policy frameworks for responsible gene drive research: An analysis of the governance landscape and priority areas for further work

Isabelle Coche, Outreach Network for Gene Drive Research, Portugal

The experience of the Outreach Network for Gene Drive Research Network has shown that the topic of gene drive governance is broadly articulated around the following topics:

- Are international frameworks, such as the Convention on Biological Diversity's Cartagena Protocol, relevant and adequate for gene drive organisms?
- Are national regulatory and policy frameworks in LMICs with limited or no prior experience of approving GMOs sufficient to ensure safe or responsible gene drive research? Where should the power to make decisions about evaluations and use of gene drive organisms reside?
- Are there forms of gene drive or uses of gene drive which should not be allowed?
- How do different values, norms and visions of human relationship to nature shape the acceptability of using gene drive organisms, and how can different visions coexist?
- How are the communities in the field evaluations phases to be engaged? What would meaningful and legitimate community acceptance for field evaluations entail?

Outlining processes or frameworks to allow researchers and other stakeholders to consider these issues in a case-by-case and systematic way, is essential to ensure research is carried out responsibly.

Gene drive organisms are broadly agreed to fall under the scope of the international Convention on Biological Diversity, under which implementation and decision-making falls to individual countries. Additional guidance includes the NASEM report "*Gene Drives on the Horizon"* and the WHO's *Guidance Framework for testing genetically modified mosquitoes.* One GFBR participant noted that other UN agencies have issued guidance which can be contradictory. This can be unhelpful and demonstrates the need for more co-ordination between UN Agencies.

GFBR participants agreed that the **power to make decisions should be at a national level, with the involvement of relevant ethics committee(s) and engagement with the communities who will be affected**. However, it was acknowledged that not all LMICs have national laws relating to genetically modified organisms and may not have processes to evaluate and monitor their use. Even where laws exist, countries may have little or no experience in applying them and uncertainty can exist regarding which national body has the authority to approve the use of gene drive organisms e.g. whether this falls to the Ministry of Environment only or whether the Ministry of Health should also be involved. This speaks to the need for interagency or intergovernmental mechanisms to evaluate and monitor the use of gene drive organisms.

GFBR participants agreed that **regulatory agencies should require evidence of a robust public engagement plan, with clearly stated goals**. The resulting engagement – and the process of acquiring consent of the affected communities, where this is sought – should be checked by external auditors or RECs. Respecting local communities and values was considered important and ensuring that the voices of marginalised and vulnerable populations are heard.

Community acceptance or consent for gene drive field experiments

GFBR participants agreed that engagement with affected communities during gene drive field experiments should be tailored, early, sustained and mandatory. Often, funding proposals engage communities after a grant is awarded – but consultation should start earlier and inform the project proposal. Information about the science of gene drive research is a necessary first step in order for engagement to be meaningful.

Engagement is an essential component to build and assess community acceptance or consent. However, it was unclear from the discussion what the right community acceptance or consent model for the development of gene drive field experiments might be. **Delphine Thizy** explained that existing guidance documents provide little practical guidance for researchers on how community acceptance for gene drive research should be obtained, measured and recorded and there is no clear-cut answer on how and how deeply to engage.

Guiding community acceptance processes for gene drive research – available guidance, gaps and experiences from Mali, Burkina Faso and Uganda

Delphine Thizy, Target Malaria, Imperial College London, UK

Specific and formal guidance on community consent for field studies of gene drive organisms is currently absent. It is a relatively novel area of research which presents specific and distinct challenges for engagement and consent, and as such there are still questions and unresolved issues about what constitutes adequate processes and models for community consent. Given the diversity of context in which research is taking place, there is great awareness that a 'one size fits all' approach would not be productive, and that at the same time, decision making should remain as much as possible with those directly affected, rather than be entrusted to more removed mechanisms, diminishing the voice of those at the heart of the matter. But in order to ensure there is a level of quality and confidence in the decisions reached, a set of principles endorsed by researchers, funders and major organisations in the field would help provide clarity to researchers and policy-makers.

GFBR participants identified that a community consent model could be based on:

- majority vote
- consensus
- identifying people in the community who can speak and give permission on the community's behalf

Within all these scenarios it is important to consider:

- (how) should community power dynamics be taken into account?
- gender and minority representation and how best to balance an inclusive model with community values (e.g. in patriarchal societies where women are not empowered to make decisions)
- which communities should be consented (using what parameters, e.g. geographical boundaries)
- what constitutes adequate levels of information and understanding?
- what level of consensus is needed – should approval be based on majority or 100%?
- whether a veto by individual(s) would be allowed
- how dissent can be discussed and negotiated, for instance between communities in an area where gene drive technologies are piloted, or within communities
- if the views of those who most stand to benefit or are most at-risk should be prioritised
- how to promote legitimacy while respecting local dynamics and local governance structures

GFBR participants agreed that it is important for researchers to build trust with the affected community**. Researchers should not impose a model of community consent but should bring a proposal to the community and ask for their feedback**. This provides an opportunity for engagement and, while it could mean delaying the research, it should result in a model that is more appropriate and acceptable to the community.

Léa Paré Toé presented Target Malaria's research in Burkina Faso, which is regulated by national authorities. Existing regulation in Burkina Faso makes provision for public consultation during the regulatory process but it is limited in terms of the role of the affected community in decision making. Target Malaria adopted a step-by-step process for the co-development of an acceptance model, that aimed to draw on the community's knowledge and experience to respond to the question of what constitutes fair and legitimate authorisation. However, the legitimacy of this model has been questioned by external stakeholders who bring their own values and perceptions regarding the process given the context in which it has taken place. This experience demonstrates the need for a more broadly collaborative and reflexive process on how to establish appropriate acceptance models while still ensuring that models can be co-developed with communities to ensure they are respectful and context specific.

Co-developing community-wide acceptance model with affected stakeholders for genetic approach of vector control

Léa Paré Toé, Institut de Recherche en Sciences de la Santé, Target Malaria, Burkina Faso

Target Malaria is a non-for-profit research consortium developing an innovative vector control against malaria using gene drive technology. The consortium has partners from three continents: Africa, Europe and North America. The aim is to release genetically modified mosquitoes that will ultimately reduce the malaria vector population. The question of an appropriate level of community acceptance to proceed to a small-scale release has been a central ethical issue for the consortium. A community-wide acceptance model was co-developed with affected stakeholders. Through this process, different governance mechanisms were put in place with stakeholders trying to address several challenges – for example, grievance management, research monitoring, and national level engagement. Balancing existing governance mechanisms in the community and other ethical considerations – such as gender or minority representations – were a challenge. It is important to learn from these experiences and the experience of others and through cross-sectorial dialogue to elaborate a common ethical framework for area-wide public health interventions.

GFBR participants recognised tensions in the governance principles and approaches for public health applications. For example, why would controlling vector-borne disease through suppressing mosquito populations require community acceptance or consent, whereas cluster randomised trials testing public health interventions in large cluster sizes generally do not. With this in mind, some GFBR participants agreed that the decision on whether or not to use gene drive organisms should not be left to the community alone. Instead, communities should be engaged in the decision-making process and this should be built-in to an appropriate governance framework. The final decision on the public health imperative to perform the research should rest with the relevant national authority.

Uses of gene drive that should not be allowed

Many new technologies have potential for dual-use (and misuse) and can be used for both beneficial and nefarious purposes. There are likely to be a range of potential uses of gene drive technology but, beyond research for weaponization, GFBR participants did not identify specific applications that should be prohibited. It is difficult to predict the full set of applications that may be proposed in the future and to regulate this uncertainty. GFBR participants agreed that gene drive research needed to be carried out responsibly with approval on a case-by-case basis.

Transborder spread

Gene drive organisms may cross national boundaries and so proximal neighbouring countries could be affected by the release of a gene drive organism. This could require a sub-regional approach and agreement by a number of countries, especially if and when the intervention moves beyond research and is rolled out as a public health measure. Countries with current regulatory frameworks for GMOs can be applied to gene drive organisms, and would include thorough risk assessments, including environmental impacts (e.g. potential spread of the mosquitoes).

GFBR participants identified examples of precedent for international governance action and collaboration that could be informative, e.g.:

- smallpox research governance, which WHO influenced at an international level
- use of insects for classical biological control, e.g. introducing natural predators. There is some experience of this being done collaboratively across countries

3. Engagement and social acceptability - broad themes

There are multiple methods for engagement and multiple roles it could play during the introduction of new technologies (e.g. to inform the public, to develop trust, to help assess social acceptability and influence policy decisions). **GFBR participants agreed that the full spectrum of engagement is valid and what matters is clarity and transparency about purpose and integrity of the process, who is doing the engaging and who is being engaged**.

The method of engagement should be tailored to the context, taking account of language, prevailing social and cultural norms and existing governance systems. A mapping exercise could be used to assess who the full set of stakeholders are. This will inform the choice of the most appropriate engagement method and the different tools that can be used. It is important to assess the reach and impact of the research when considering who to engage, consult or involve in decisions. For example, for public health applications, because it is a public interest issue, an issue where shared concerns of a given community should be raised and discussed, there might be more of a practical, political and ethical justification to engage with a community or the public in a more deliberative way. However, **not everyone needs to be engaged deliberatively all the time**.

GFBR participants agreed that engagement should be more than simply informing and we should avoid undertaking engagement for the sake of being seen to engage (i.e. a tick-box approach). It is also important to acknowledge the history of anti-GMO sentiment toward current gene editing applications and engagement sentiment. Researchers, funders and others need to be careful not to allow the pendulum to swing too far the other way where they initiate ill-considered engagement strategies (in trying to avoid 'mistakes of the past').

There is a body of work, especially in environmental and public health domains, that is rich in engagement experience and past lessons. **It is important that we do not re-invent the wheel and that we learn from past engagement work, including failures**. Anecdotal examples were given from Nigeria where polio vaccine program failed because of misinformation, distrust and politics and in China where a lack of communication between different bodies led to people being arrested in needle-exchanges.

A range of potential engagement strategies and activities were demonstrated at the meeting. **Sebastián Barbosa** described a large scale, government-led public engagement activity in Argentina that aimed to raise awareness on genome editing technologies broadly. **Léa Paré Toé** focused on a funder-led programme of community engagement in Burkina Faso that aimed to gain community consent for the release of genetically modified mosquitoes as part of gene drives research (see page 17 for summary). The cases demonstrated that both public engagement and community engagement can be relevant depending on the purpose of the engagement. GFBR participants discussed differences between 'public' and 'community' engagement.

Public engagement

GFBR participants understood 'public' to comprise broad segments of the population. Publics can have aspects in common e.g. language and location but they are not as closely bound as a 'community'. Public engagement is generally more global and less targeted than community engagement e.g. communicating with the public on a wider subject and providing more general information as a way of informing and empowering them. It can involve multiple communities and languages and, if there are multiple languages, the engagement may need to

be language independent and use appropriate visual methods. Examples of methods of public engagement include, public meetings, citizen juries, lectures, theatre and film.

While the concept of 'public' was generally understood, it may not resonate with everyone. A perspective was provided from Nigeria where the mindset of cohesion and the idea of community is so strong, 'public' is a foreign concept.

An unprecedented outreach event in Argentina to raise awareness about gene editing: A communication challenge to engage the general public

Sebastián Barbosa, Ministry of Science, Technology and Productive Innovation, Argentina

In December 2018, a consortium of Argentine government organisations co-convened the first public symposium on gene editing in Argentina. The primary objective of the event was to engage the public on the status of gene editing in Argentina, focusing on the health, agriculture and food sectors. Accountability, trust and transparency were at the centre of how the meeting was designed. Recommendations for others looking to run a large public event include: tailor communication methods to the audience; be honest about the potential of the technology (i.e. don't oversell it, which would undermine public trust) and be specific about the purpose (i.e. avoid making generalised statements and recognise that each individual application has distinct benefits and disadvantages).

Community engagement

In contrast to the notion of 'public', GFBR participants understood 'community' as a group bound by something shared e.g. values, beliefs and/or interests. Often the 'community' is geographically close e.g. a village. The term 'community engagement' evokes a process that is different in depth and breadth to public engagement and targets specific groups, such as a local community in the case of gene drive research or an affected community in the case of human genome editing. Community engagement can have specific goals e.g. to understand the opinions and concerns of a group who will be affected by the introduction of a technology or to ask the community who has the legitimacy to speak on their behalf. **In community engagement, it is important to establish some proximity, in order to better understand the community and tailor information to their specific context**. This can take a long time and be intensive, e.g. requiring weekly visits and overnight stays to develop rapport, relationships and trust. Some GFBR participants advocated for deliberative engagement to reveal concerns, fears, taboos, misconceptions, personal belief systems and entrenched values, before fuller community engagement occurs.

The community being engaged needs to be defined through careful research planning. This may be by common values, cultural understanding, location etc. The interests and values that are common in a community – and what is at stake if the research takes place – are key to determining the appropriate community engagement strategy and its purpose e.g. whether the strategy is to inform and hear community views or whether community consent is being sought. **Some GFBR participants considered that community engagement should be mandatory in cases where there is some risk and where individual consent is not appropriate or could not be obtained (e.g. gene drive research).**

Léa Paré Toé described an ethnographic study in which the Target Malaria research team engaged with a community to select appropriate community representatives. Individuals from the village's different social groups were interviewed and asked who can represent their village and who can speak on the community's

behalf. The resulting list was discussed with different groups from the village to see if they recognised the recommended people as having this role. The list included both women and men and not just traditional leaders. However, young people were not included as they were not recognised in the village as having the legitimacy to speak on behalf of the community.

GFBR participants agreed that there are challenges with community-based decisions when there is a tension between respecting community norms (even if exclusionary) and accepting those norms without challenge. It can be uncomfortable if the decision-makers that the community regard as legitimate are not representative in the way that the researchers would regard as legitimate. However, it is unclear to what extent (if any) a researcher should engage or challenge the community on these cultural beliefs and assumptions, or simply accept them.

Language can be a challenge to communicating and engaging with communities about complex science. Target Malaria addressed this issue by working with a linguist and anthropologist in all the areas and countries where they work. Understanding that the word 'gene' does not exist in some countries, tools have been developed and published on the project's website, including visuals and videos that explain about malaria and genes. The tools take time to develop but help people of all literacy levels to make decisions about gene drive research and to be part of the governance process.

Who is responsible for engagement?

GFBR participants agreed that trusted bodies may differ greatly between countries, and between LMICs and HICs. As such, the question of who engages should be context specific. The following groups were identified as having potential responsibility for engagement:

- government
- regulators
- policy makers
- funders
- scientists
- technology developers (including private companies)
- bioethicists

However, not every of the above stakeholders needs to engage, nor is everybody a good engagement practitioner. There are science communicators, knowledge brokers, engagement practitioners and other facilitation professionals who the science community and regulators can work with to engage others. **GFBR participants identified the need to increase the number of science communicators in LMICs**. Multidisciplinary engagement teams are needed as they bring different perspectives and may have different ways of communicating.

The scale of the scientific activity could dictate who should engage. For example, engagement on specific projects could be led by the scientists while engagement on wider issues, such as the acceptability of a type of technology, may more appropriately be led by government. Scientists will need to be involved in the latter, to provide the knowledge for the government to disseminate. Some GFBR participants considered government involvement necessary in order to convey to the public that the technology is something that will benefit everybody in society. This point was made by **Qi Chen** where the involvement of the Chinese government was considered to add legitimacy to the engagement process (see p9 for summary). However, in many LMICs it can be challenging for governments to take the lead on engagement, given their limited resources.

Engagement by government may also be difficult in contexts where there is an insufficient level of trust. An example was given from Peru where indigenous communities are likely to be suspicious of government entities due to their historical relationship. There may also be concerns about governments trying to shape the engagement agenda to meet their political and economic agenda. In this context, there is a need to unpack the differences between promotion (e.g. of a new technology) and engagement. **It is important for those who have an agenda to be transparent about what their interest is and be upfront that they are not engaging with complete neutrality**. GFBR participants recognised the importance of balanced engagement so that the public can make reasoned choices. The public is entitled to hear both sides of an argument about the pros and cons of genome editing technologies, understanding that both perspectives should be based on sound science and ethics.

Funders have a key role in engagement and should provide funding as an integral part of research on new technologies. The level of funding should reflect the nature and scale of the engagement and the fact any engagement will take time to do well. There is a need to set clear goals and objectives for public engagement when research is at the planning stage and funders, as well as RECs, should be responsible for making sure an engagement plan is in place.

The **WHO could also play a role in defining what engagement on genome editing technologies should look like**. As part of its current work, it could produce policies and a framework for countries to use, incorporating case studies to demonstrate public and community engagement approaches.

Role of media and journalists

The media and journalist have a key role to play in enhancing scientific literacy amongst the public. All types of media should be used to empower audiences so they can spread the word about new genome editing technologies e.g. print, online, TV, radio and social.

Anecdotal examples were given of research projects that actively engage with journalists, providing training to help them understand the science. This promotes the accuracy of reporting and is critically important for novel fields of research where the technology is moving quickly. However, other examples were given of scientists who prefer not to talk to journalists as they are concerned about past or potential mis-reporting of facts. **GFBR participants agreed on the need to build trust between science (including bioethics) and the media**, given media's crucial role in building trust between science and the public. However, it must be recognised that some media outlets may have a particular agenda that influences their reporting. An example was given of media establishments circulating information that was in accordance with their own beliefs, and which was not necessarily trustworthy. GFBR participants also identified that, even where mainstream media reports responsibly, there is a risk of social media distortion and misinformation.

Social acceptability and social licence

Public engagement can assess social acceptability and may help facilitate understanding and acceptance of new genome editing technologies. However, conflicts of values between publics and those responsible for engaging may surface during the engagement process. A policy of trying to convince the public of a particular view will likely be unsuccessful; there should be a realistic opportunity for a community or society to reject a technology or project.

GFBR participants agreed on the need for the research community to unpack what is meant by social acceptance. This will be context specific and may range from the public not objecting to the technology (i.e. tolerating the outcome) to the public positively embracing it. In addition, what is socially acceptable to one group (e.g. patients with sickle cell disease who have an interest in the potential of genome editing technologies) might not be acceptable to others. To this end, **it is important to understand and address the issues that communities themselves are raising and the specific barriers to acceptance**. An anecdotal example was given from gene drive research, where there was a concern about the potential release of sterile mosquitoes and whether women bitten by these mosquitoes would become sterile also. Such understanding can have a significant impact on acceptance and should be addressed appropriately.

Even where social acceptance exists this does not necessarily equate to moral acceptability and is not sufficient to authorise use of a new technology – issues of safety will need to be managed and assessed against potential public benefit, within the broader governance framework. Conversely, even if research with a new technology is legal this does not necessarily mean it has social acceptance.

GFBR participants agreed that more discussion is required on whether there is a difference between the level of acceptability required for a technology that has a 'private' health impact (somatic human genome editing) vs a public health impact (gene drive research). For some innovations, individuals will make choices about whether to use the new technology, so attaining social acceptance may not be needed across all the community. However, an argument can be made for the need for social acceptability for both 'private' and more 'public' gene editing as they both present broad societal challenges. Some GFBR participants questioned why social acceptability is required for gene drive research when other anti-mosquito initiatives are used without much investigation of acceptability, e.g. spraying. The main reason seemed to be because gene-drive is new and comes with uncertainty, which suggests that a key concern is about safety.

Social licence is the tacit ongoing acceptance or approval for the deployment of a technology, granted by the community and other key stakeholders. A question remains as to what happens if research does not achieve social licence and whether research should move forward anyway. Examples were given of vaccine hesitancy or where some communities reject experiments on animals and would never accept drugs developed in this way. Some parts of society will inevitably not accept new gene editing technologies, but there may also be dissenting voices who are more open. Researchers, governments and others should communicate the potential benefits of new gene editing technologies, to demonstrate their anticipated societal value.

Interdisciplinary engagement between the sciences

Engagement for the responsible conduct of science is also required between scientific disciplines and other science professionals to promote the integration of social sciences and natural sciences, and other knowledge types to produce knowledge that is ethical and implementable. If the research community seek to understand public attitudes, to engage more widely, to conduct science ethically, then it should also be working harder to integrate across disciplines, (humanities, sciences) so that the social and human dimensions of science decision-making are incorporated more fully.

4. Governance – national and regional perspectives

Governance of gene editing technologies was discussed throughout the meeting. However, one session focused specifically on national and regional perspectives from Japan, Botswana, Brazil and the Caribbean. The speakers reflected on the potential uses for genome editing technologies in their country and how cultural or religious beliefs and norms might inform national or regional perspectives on genome editing and its governance.

Research governance of heritable genome editing rooted in salient value sharing

Mika Suzuki, Center for iPS Cell Research and Application, Kyoto University, Japan

We need a 'grand design' for research governance of germline gene editing that constitutes hardware (infrastructure), software (regulation and education), and heartware (the application of one's own principles to professional conduct). The Japanese Society for Regenerative Medicine "Standards of Conduct for Researchers related to Regenerative Medicine" is an example of heartware, that proposes a set of principles to help researchers reflect on their own professional and ethical behaviour in their research. We also need to share salient values regarding the kind of society we want. For example, in Japan some people view disease as part of their identity and do not see it as something that should be removed. Instead, treatment should be for improving quality of life. In this context, as a society we need to consider the basic question, "what is a disease or disability?" and understand that quality of life, health and welfare, are broader than improving physical health.

Prudence in germline gene editing: The urgent need for collaborative partnerships in Africa

Gerald Michael Ssebunnya, Africa Institute for Human Dignity, Botswana

The potential applications of germline gene editing in Africa, include the prevention of SCD and oculocutaneous albinism. Potential benefits of these applications include physical and emotional healing; stigma reduction; and prevention of social harms. Although Africa is not a homogeneous entity, and has many value systems, the common strands of its postcolonial sociocultural and geopolitical realities, as well as the commonality of its disease burden, warrant a unified assessment of the risks and benefits of germline editing. While most countries in Africa have no position on germline editing, there is an urgent need for African engagement in the debate and comprehensive articulation of the key concepts and values involved. Importantly, any acceptable germline intervention in Africa would have to authentically engage with African communitarian values (such as 'humaneness', or *ubuntu/ botho/ obuntubulamu/ utu*) and the African reverence for human life.

Readiness level of the Brazilian regulatory framework: Can we face genome editing?

José Ricardo Jensen, DVM, Former Head, CEUAIB (IACUC - Butantan Institute), São Paulo, Brazil

Brazil's regulatory framework for human genome editing and gene drive research demonstrates the complexity and difficulty of regulating a rapidly evolving area of science. While the current framework is appropriate for clinical studies using somatic gene editing, human germline research is in essence forbidden in Brazil. The regulation of human germline and disease vector genome editing technologies is challenging because they did not exist when the Brazilian National Biosecurity Law was passed in 2005. There is an ongoing debate in Brazil on whether CRISPR-mediated gene editing should be classified together with other recombinant DNA technologies and fall within the National Biosecurity Law. There are also grey areas for regulation as the responsibilities of the Environmental, Health, Agriculture and Ethics government regulatory bodies are not sufficiently defined. For example, it is unclear whether approval for gene drive research should be the responsibility of the National Technical Biosecurity Commission only and/or whether approval for safety in human populations is also required.

Policy on gene editing and gene drive research in the Caribbean

Derrick E. Aarons - Caribbean Research Ethics Education Initiative

Most Caribbean countries currently lack regulation and the capacity to ensure the ethical acceptability of gene editing or gene drive research that may be proposed within their jurisdictions. However, countries have been approached by high income partners, specifically for gene drives research. There is an opportunity to update legislation that has been mandated by the Council for Human and Social Development, which is the Council of Health Ministers from across the Caribbean community (CARICOM). The legislation regulates human subjects research in CARICOM countries and defines sanctions for non-compliance. Drafting of the legislation pre-dates the current era of gene editing research, but its scope could be expanded to include this new field of research. A task force could also be established to recommend a governance framework for genome editing for all CARICOM countries, that draws on international knowledge and reflects cultural nuances in the region.

Speakers and GFBR participants identified several potential opportunities of genome editing for their countries and regions e.g., treating SCD and β-thalassemia and controlling malaria, dengue, chikungunya and Zika. They also identified the danger of missed opportunities in LMICs because of a lack of good governance e.g. if a country adopts an outright ban.

LMICs have the opportunity to learn from governance structures adopted elsewhere and to adopt an approach that is fit-for-purpose for their setting e.g. to learn from restrictive regulatory regimes and find a nimbler approach. However, **national guidelines or regulations will take time to develop in LMICs due to constraints on resources. A global response is essential in the short term, i.e. the guidance being developed by the WHO's expert panel on human genome editing.** WHO's guidance can pave the way to national governance and will be particularly helpful and efficient where LMICs have limited relevant expertise. The guidance could also be used as a starting point for public and professional debate in LMICs. Currently, there is a disparity between LMICs and HICs in terms of available infrastructure and capability and this was considered a hurdle to good global governance.

The presentations in this session demonstrated that **the governance ecosystem includes – and needs – both formal and informal elements e.g. national regulation; international, national, funder or institutional policies, codes of conduct and guidance published by organisations like the WHO, along with structures and processes for decision making**. Regulation alone can be problematic in the field of emerging technologies as it can become quickly out-of-date and can be difficult and time-consuming to revise. A breadth of governance mechanisms, e.g. including codes and principles of conduct is required and can help create a culture of responsibility and accountability.

Cultural beliefs and norms will inform perspectives on human genome editing, as they do in other areas of scientific development (e.g. an example was given from Trinidad and Tobago where there is strong resistance to HPV vaccination because it is seen as promoting promiscuity). These perspectives could impact on the adoption, use and governance of genome editing. Some GFBR participants questioned why some beliefs e.g. acceptance of disease in Japan, should be regarded as ethically significant. Public consultation on the benefits of genome editing, and on how widespread such beliefs are accepted, is needed to help understand if and why such beliefs are significant for ethical governance.

Cultural and social beliefs, including accepted norms may also influence the breadth of potential uses and what uses are regarded as acceptable. For example, whether genome editing should be used to alleviate lethal disease only or be extended to issues like albinism where the principal harm is caused by social attitudes.

Religious beliefs may also have an impact on the acceptability and governance of genome editing in some countries. The influential role of cultural and religious leaders in Africa was mentioned by a number of participants and the need for consultation to be one-on-one in order to promote understanding of the risks and benefits of the technology and to address concerns. The influence from religious organisations has been positive in some areas of science – an example was given at the meeting of religious leaders positively influencing vaccine uptake in their community. However, some GFBR participants identified that religious groups may challenge the uptake of genome editing technology if it is perceived that scientists are 'playing God' or where there are strict views on the use of embryos in research.

Ethics review and oversight

RECs provide important oversight and monitoring but their role has not kept pace with emerging technologies. **The constitutions RECs work under should be re-evaluated in light of these technologies and their capacity should be strengthened** through self-education and more structured professional development on the science and ethics of gene-editing.

GFBR participants discussed whether new mechanisms are required for projects involving genome editing with long-term ethical and social risks, or whether to build on existing structures and review committees. Examples of national review committees were provided e.g. in Malawi, Brazil and China where the committees review all genetic research proposals. Some GFBR participants considered it preferable to use national committees (where they exist) to assess and monitor long term risks, rather than local RECs, as RECs may not have the time, resources or remit to undertake such an assessment and long-term monitoring.

Recognising genome editing as one of many emerging technologies, **some GFBR participants suggested the need for an advisory board on emerging technology more broadly**, as it is unproductive to look at these technologies in isolation. However, the feasibility of such a committee in LMICs is compromised by the lack of relevant experts.

Annex 1: Background information on GFBR and meeting content

The Global Forum on Bioethics in Research (GFBR) is the principal global platform for debate on ethical issues pertaining to international health research. Its core aims are to give voice to low- and middle- income country (LMIC) perspectives in debates about global health research ethics and to promote collaboration.

The Forum meets annually to address a specific topic in research ethics and is generally case study based. This approach enables participants to understand the practical issues 'on the ground' in addition to broader ethical and policy questions. In 2019, the approach was slightly different because the topic was 'future looking'. There are very few actual examples of genome editing research, especially involving human genome editing and especially in LMICs. The open call generated papers that focused on broader ethics, policy and governance issues, and, for the first time, we received more papers on policy and governance issues than case studies. This seems entirely appropriate for the governance of an emerging technology to be discussed in advance of it being broadly adopted and researched.

15 case studies and 17 policy and guidance papers were submitted for this meeting. A further 51 applications were received from potential participants. 5 cases studies and 9 policy paper were selected for oral presentation (see insets throughout the report). Six other case studies and policy and guidance papers were presented at the meeting in the form of short Pecha Kucha presentations:

Pecha Kuchas

1. **Governance of gene editing in Africa**
   Syntia Nchangwi, University of Cape Town, South Africa
2. **Pathway to genome editing in Nigeria**
   Simisola Akintola, University of Ibadan, Nigeria
3. **"Mirror, mirror on the wall…who is the most ethical of us all?" Decoding genetic studies from Pakistan: A review of international, regional and local guidelines and compliance**
   Natasha Anwar, Aga Khan University Hospital, Pakistan
4. **Articulation between an Argentine patient organization, the Argentinian state and researchers from the University of Huazhong (China) for inclusion of 10 Argentine patients in a ND4 gene therapy trial for Leber hereditary optic neuropathy**
   Marcela Ciccioli, Stargardt APNES-Retina, Argentina
5. **Analysis of China's CRISPR babies using the Emanuel Framework**
   Sofia Salas, Clínica Alemana Universidad del Desarrollo, Chile
6. **Challenges of a Latin American startup using CRISPR for diagnosing sub-tropical diseases**
   Federico Pereyra-Bonnet, National Council of Science and Technology, Buenos Aires University, Argentina

Up to 100 participants are selected for each meeting through a competitive process. Participants come from a diverse range of disciplines, countries and career stages and awards are available to LMIC colleagues to cover

travel and accommodation. This year, for the first time, journalists were invited to apply and three journalists attended. Accurate journalistic reporting is essential to ensure that the public are engaged and well informed about the potential benefits and risks of research – especially so for emerging technologies like genome editing.

All participants were encouraged to report the meeting recommendations in their home countries and to continue the discussion in their local context. Fellowships were available for LMIC participants to explore issues that arose during the GFBR meeting in greater detail, establish new collaborations, and develop new ideas for resolving issues that could not be resolved at the meeting itself. Past GFBR participants have given presentations on the meeting theme to their local RECs and at other conferences and published papers. It is anticipated that participants from this GFBR meeting will likewise take the discussion home and foster debate in their local context.

Annex 2: List of abbreviations

GFBR: Global Forum on Bioethics in Research

LMIC: Low- and middle-income country

HIC: High income country

REC: Research ethics committee

WHO: World Health Organization

H3Africa: Human Heredity and Health in Africa

NASEM: National Academies of Sciences, Engineering and Medicine

UN: United Nations

SCD: Sickle cell disease

GMO: Genetically Modified Organism

Acknowledgements: We are grateful to the presenters whose work forms the basis of this report and want to thank all the GFBR participants for their engagement with the theme and each other. Thanks in particular to the session and breakout group chairs, rapporteurs and also to the notetakers.

GFBR funders*:* Wellcome; the National Institutes of Health; the UK Medical Research Council; and the Bill & Melinda Gates Foundation.

Author: Adrienne Hunt

Map credit: The Pixel/Shutterstock.com

Full case study and policy paper write-ups are available on the GFBR website.