Background paper:
Genome editing for human benefit: ethics, engagement and governance

Meeting in Singapore, 12-13 November 2019

Purpose of this document and introduction

The ability to manipulate the genome has been available for many years; however, the pace of innovation recently has brought a series of ethical, social and legal questions forward. In particular, CRISPR-Cas9 has made precise, simple and cheap editing of a genome a realistic possibility. Genome editing could be used to alter an individual's genome to address a specific health issue or used as a public health intervention through genetic changes to disease vectors like mosquitoes. Historically, research using emerging genomic technologies has largely taken place in high income countries (HIC) with the ethical debates focused in these settings. The 2019 Global Forum on Bioethics in Research (GFBR) meeting will engage low- and middle- income country (LMIC) perspectives so their voices are heard in the research phase and early development of genome editing technologies. The meeting will focus on human genome editing and gene drive research - two emerging applications of genome editing that are designed to benefit human health. Common challenges presented by these applications include 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 paper outlines the scope of the meeting theme and maps out some of the key ethical issues associated with genome editing research in health contexts. Sections 1 and 2 provide an outline of the key ethical issues that are distinct for each application. Section 3 and 4 address the common themes that cut across both applications:

1. Human genome editing
2. Gene drive research to prevent disease transmission to humans
3. Engagement and uptake
4. Governance, guidance and best practice

Gene drive research in health settings is moving forward with a specific focus on low-resource settings that have a high burden of vector borne disease (e.g. malaria, zika, dengue). It is applied at a population level, to vectors of disease with potential environmental implications, and in such a way that individual human consent is not generally feasible or legally required. Human genome editing involves changes to an individual's somatic cells or to germline cells (i.e. sperm, egg or embryos). Somatic changes affect the individual only, in contrast to germline changes which are heritable and transmitted to the next generation. While somatic cell research has gained momentum in recent years, there is broad consensus that germline genome editing is not ready to progress beyond the laboratory. However, there have been calls to define a translational pathway toward clinical trials.

The GFBR meeting will focus on ethics in research. It will promote discussion on what it means for engagement, uptake and governance when emerging genome editing technologies are initiated in HIC settings, and then researched and introduced in LMICs, which have a diversity of values, beliefs, social and cultural norms and governance systems. It will draw-out the common and distinct ethical issues between gene drive research and human genome editing research and assess what bearing the 'public' population-wide application of gene drive and the more 'private' application of human genome editing has on these issues.

Ethical issues associated with implementation are also within scope, for example, the concerns that the introduction of human genome editing will reduce population diversity or exacerbate existing

inequality if access is unequally distributed. Delaying debate on these issues leaves research largely unquestioned, with the effect that the technology, once realised, may seem to be inevitable and outside of societies control.[i] Research exists to serve the public good and so must be responsive to society's broad and diverse interests. Broad debate is necessary to understand whether, or under what circumstances, the technology would be acceptable and the conditions under which research can achieve its goals to benefit human health.

The GFBR has an opportunity to integrate international perspectives on genome editing research by:

1. Exploring what concerns of genome editing research are generalizable and which are culturally specific. Further, explore the questions which are endemic to genome editing and those systemic to transfer of an emerging technology from the global north to the global south.
2. Understanding how stakeholder engagement can provide insight into some of the ethical questions discussed, and if approaches need to vary according to the specific application of genome editing (e.g. whether the technology has a population or individual impact) or depending on which different societies, groups or countries are to be engaged.
3. Bringing guidance on genome editing research together, identify differences and gaps.
4. Identifying the resources, and expertise, required in LMICs for the ethical review and governance of genome editing research and its application. A clear mechanism for sharing current practice in regulating genome editing can reduce the resources required to regulate it in new settings.

This paper is being published with the call for case studies and proposals on guidance and policy issues. Case studies and proposals may relate to the issues below or other issues that present ethical challenges. Please note that the case studies should focus on research conducted in LMICs. They could address (but are not limited to) one or more of the following general questions:

Social acceptability:

- How might cultural or religious beliefs and norms impact on the social acceptability of genome editing research (e.g. in relation to the status of the embryos and/or beliefs about what it means to be human and making changes that will affect future generations or have an impact on the environment)?

Engagement:

- Whose responsibility is it to undertake engagement work when a new genome editing technology is being researched and introduced in a LMIC?
- What should this engagement look like, who should be engaged and for what purpose? Does it look different to engagement for non-genomic technologies?
- Does engagement for human genome editing look different to engagement for gene drive research (e.g. in relation to the methods and who or which groups should be engaged)?

Uptake:

- What does broad societal consensus look like? What level of community acceptance is needed before research using a genome editing technology can be undertaken? Is there a difference between the level of acceptability required for a technology that has a 'private' health impact (human genome editing) vs a public health impact (gene drive research)? Or is this a false distinction given that the both technologies present broad societal issues?
- What constitutes fair and legitimate authorisation for field trials of gene drive organisms?

Governance:

- What are the responsibilities on funders to promote equitable research collaborations/partnerships involving both HIC and LMIC researcher so research design and conduct is co-created and co-owned?
- How do you ensure that governance processes are appropriate and fit for purpose in LMICs (e.g. regulatory frameworks, funding mechanisms, institutional structures and policies etc.)?
- Are current governance structures sufficient for dealing with the long-term social risks of research or are other governance mechanisms required (e.g. an international or national advisory and monitoring group)?
- When introducing research that uses complex genomic technology in LMICs what are the obligations on funders to address gaps in systems e.g. regulatory gaps, Research Ethics Committee procedures etc.? How can this be managed in such a way that takes account of conflicts of interest?
- What would an anticipatory ethics framework for research on gene drive technologies and human genome editing, particularly in the context of LMICs, look like? Can it be drawn from past debates on biotechnological research e.g. synthetic biology and genetically modified organisms?

Section 1 <u>Human genome editing</u>

1.1 Background

Recent technical advances have improved the precision, cost and simplicity of genome editing and increased its potential to improve human health. The application of CRISPR-Cas9 is already having a significant effect on research intended to further understanding of the roles of specific genes and processes in human health and disease. In future it could be applied clinically to prevent or treat genetic diseases.[ii]

Editing can take place in either somatic cells – whose genomes are not transmitted to the next generation – or germline cells (i.e. sperm, egg or embryos) – whose genomes are transmitted to the next generation. The potential for somatic cell genome editing to address a multitude of genetic diseases, without the concern of creating heritable changes, has resulted in an expansion of research in this field. New initiatives, such as the NIH's Somatic Cell Genome Editing program, are developing high-quality tools to share with the research community with the aim of accelerating the translation of genome editing technologies to the clinic.[iii] One of the first targets of CRISPR-Cas9 mediated somatic genome editing is likely to be sickle cell disease, which affects 20 million people worldwide, in particular where malaria is prevalent, such as sub-Saharan Africa.[iv] While public approval of the technology may vary, consent and implementation are at an individual level and the technology may be accepted by sufferers if efficacy is proven.[v]

Germline editing came to attention in 2015 when a team of researchers led by Junjiu Huang at Sun Yat-sen University, China, used CRISPR-Cas9 to edit a human embryo.[vi] Although the embryos were non-viable, this was a world first for germline editing and called urgent attention to such technologies. Since then, the science has progressed rapidly with researchers in 2017 reporting[vii] repaired disease-causing mutations in viable human embryos for the first time. Later that year, a team at Oregon Health & Science University[viii], Portland, reportedly did the same but without the incomplete and off-target effects in previous attempts. Not only are we seeing rapid developments in the use of CRISPR-Cas9, but also in new techniques, or new RNA enzymes for the CRISPR system further testing existing regulatory systems.

The tension between the rapid developments of the science and the need for good governance of germline editing came to the fore in 2018. Jiankui He, a Chinese scientist, claimed he created twin girls with a modification using CRISPR-Cas9 to reduce the risk of HIV infection.[ix] The claim was met with international criticism, with its flaws cited as 'an inadequate medical indication, a poorly designed study protocol, a failure to meet ethical standards for protecting the welfare of research subjects, and a lack of transparency in the development, review, and conduct of the clinical procedures'.[x] The announcement added further weight to the call for ethical considerations to progress alongside the science rather than brought in later and on the need for better governance.[xi]

Progress and developments in genome editing were considered at Second International Summit on Human Genome Editing in November 2018. In a statement made after the Summit, the Organizing Committee said while they 'applaud the rapid advance of somatic gene editing into clinical trials, [they] continue to believe 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'.[xii]

1.2 Current ethical issues

The pace of the science has been matched by calls for consideration of the ethical implications. Below are some of the key issues raised. This is not exhaustive as discussions are still progressing and it is through exploring the issues, particularly in different cultural contexts, that further complexities will surface.

Many of the questions raised are not new, but they are brought together uniquely by human genome editing. Ethical concerns may vary over space and time, for example on the use or length of culture of embryos for research.

Risk assessments
As with any emerging technology there are questions over the safety and efficacy of human genome editing and its use as a new, alternative or replacement therapy potentially leading to unintended side effects. Although recent research has reduced off-target effects and mosaicism, the process of genome repair is still unknown. Clear measures to demonstrate that the technology is safe and efficacious enough in order to progress to first-in-man clinical trials will need to be established.

Risk assessments will need to take account of the potential harms associated with creating one improvement (i.e. making an edit to combat a specific disease) and increasing a person's susceptibility to another disease (e.g. sickle cell is protective against malaria, cystic fibrosis is protective of cholera).[xiii]

Heritable modifications
Genome editing has the potential to create heritable genetic changes. This raises concerns in terms of preservation of the human genome, and its diversity and poses questions related to human, and disability rights. There are moral arguments about right to life, and the value of biological difference. Further there are issues of the next generation being unable to give their consent. It is traditionally the preserve of the parents when judging treatment for children, but in this case consent at the point of treatment (in the research or clinical context) would need to cover infinite subsequent generations. In the longer term, how would consent work for the ongoing follow up of people who have received human germline editing in the research context and who is responsible for this monitoring (the research funders, governments etc.)? Such issues have resulted in some research funders, for example the US National Institutes of Health, adopting policies not to fund genome editing research that involves human embryos.[xiv]

Questions of germline modification imply a moral distinction between editing of germline and somatic cells; this distinction may be informed by cultural or religious views. For example, speaking at the Second International Summit on Genome Editing, Mohammed Ghaly explained that, 'from an Islamic perspective, somatic cell therapy is considered acceptable because it is a treatment for disease, has limited scope, and affects only an individual. Germline cell therapy is considered much more controversial in Islamic communities, because it goes beyond human authority in the universe, has an impact on offspring, and violates the notion that humans are trustees and not owners of their bodies'.[xv] These concerns may also be raised outside an Islamic or religious perspective.

Some have suggested that procedures such as preimplantation genetic diagnosis or somatic gene editing after birth would be preferable to genome editing of germline cells.[x]

Use of embryos – intrinsic concerns
Cultural and religious perspectives may also inform the ethical discussion on whether or not the use of embryos in research can be morally justified. Questions include, at what point (in time) does an embryo have the moral status of a person? However, even within religious groups, it is likely there will be a diversity of individual views.[xvi]

Use of embryos – practical concerns
There are practical issues that may inhibit human germline editing in low resource setting, including the limited availability of embryos for research and skills gaps in IVF clinics. This raises another important question – should only embryos left over from IVF be used in genome-editing research or can embryos be specifically created for research? For left over embryos, where and when should consent be sought and from whom? For example, from the patient undergoing IVF or the gamete donors when they attend the IVF clinic? Or, for abandoned embryos, consent by the IVF clinic or a decision on use made by a person appointed by the courts as a guardian *ad litum*[1]?

Enhancement
Research[xvii] has suggested a representative sample of the US public are more concerned with applying somatic or germline genome editing technologies for enhancement purposes rather than treating serious disease. Others have warned of "function creep" and the difficulty of limiting germline editing to particular medical purposes.[xviii]

The US National Academy of Sciences has acknowledged that distinguishing between treating or preventing disease and disability on the one hand, and a notion of enhancement on the other, is challenging; the lines between therapy, prevention, and enhancement are not fixed or easily discernible in all cases. This raises the issue of defining disease and disability, and the question of how and where to set appropriate boundaries for treatment and prevention of these conditions. [xix]

Social and cultural issues may impact on what is considered to be an acceptable risk and application of germline genome editing. For example, Jiankui He's research, which reportedly resulted in the birth of twins, sought to prevent the risk of HIV infection. Much of the international criticism related to the use of high-risk germline genome editing to solve a social problem (the high levels of stigma around HIV) – rather than to solve an unmet medical need.

[1] Guardian *ad litem* is used in child welfare legal proceedings and can represent a born or unborn minor. For a discussion of their role in consent for germline research see 'Ethical dilemmas in germline editing focusing on informed consent' presentation by Judith Daar at the Second International Summit on Human Genome Editing, November 2018. Available at: http://www.nationalacademies.org/gene-editing/2nd_summit/presentations

Equity

Early sequencing initiatives predominantly took place in high income countries, with the reference sequencing being derived from Western populations. Although subsequent initiatives have sought to enhance the representativeness of genomic reference sequences, there is still not much known about non-Western genomes. This situation gives rise to significant issue of equity as genomic tools and technology are based largely on Western populations meaning they are likely to be not as useful for other populations. Successful research will require representative data, and thus must reach all parts of society. For research to be applicable to all it must be inclusive.

Like most health interventions, the benefits of genome editing may not be distributed equally; affected by factors such as wealth, gender, ethnicity etc. There are concerns, particularly in LMICs, that applications may not reach all people and thus widen existing social divisions and inequalities. Most likely, genome editing research will take place in HIC first but there is a need to ensure a pathway towards LMIC translation. Such research could be used to address diseases that impact LMIC settings the most, including sickle cell, and could plausibly promote global health equity if research priorities and funding are set as such. For example, there may be an argument for focusing on heritable over somatic genome editing in LMICs given that it is one-off, and the benefits are long term. This could be a more sustainable way to treat health issues which then doesn't depend on the ongoing successful functioning of a health system. However, such treatment would rely on there being infrastructure to support germline modification (e.g. functioning IVF clinics).

Secondary to access there are concerns of exploitation in settings with isolated indigenous populations. This concern may have contributed to restrictive guidance from the Ecuadorian Health Ministry on genetic material management, which works from the assumption that all genetic studies are high-risk.

Section 2 Gene drive research to prevent disease transmission to humans

2.1 Background

Gene drive is a well-established field of research and is a naturally occurring phenomenon that has been the subject of investigation for many years.[xx] The technique works by altering the likelihood of offspring inheriting a specific gene and 'driving' the inheritance of the gene in future generations. It has been applied to animals like mosquitoes that reproduce sexually, have a short lifespan and produce many offspring. This ensures that the gene – and the trait it encodes – become increasingly common in the species over time.[xxi]

Gene drive research has applications in both health and conservation (for example to control invasive species). **Given the GFBR's global focus on human health this meeting will address gene drive research where it is intended to directly prevent the transmission of disease by vectors to humans (and will not address applications in conservation, food security or biosecurity).** For example, gene drive research is being assessed for its potential to prevent malaria, a public health priority with 216 million cases and 445,000 deaths attributed to the disease in 2016.[xxii] One such initiative, Target Malaria[2], is preparing to release a sterile (non-driving strain) of mosquito in Burkina Faso – the first release of a modified mosquito on the African continent. [xxiii]

[2] Target Malaria is a not-for-profit research consortium that aims to develop and share technology for malaria control. The consortium includes scientists, stakeholder engagement teams, risk assessment specialists and regulatory experts from Africa, North America and Europe. See https://targetmalaria.org/who-we-are/

Gene drive research can be used to suppress or modify a population. For example, a suppression strategy could be used to inactivate or knock-out genes involved in the mosquito's survival or reproduction (e.g. driving the gene that results in inheritance of the male chromosome, reducing the number of malaria-transmitting females). This will reduce the size of the vector population to such an extent it will not be able to sustain malaria transmission. Although it may not be required for the technique to be effective, the population may crash. Alternatively, a population modification strategy could be used to reduce the inherent ability of the individual mosquitoes to transmit the malaria pathogen (e.g. by inactivating a gene or genes that facilitate parasite survival in the mosquito).[xxiv]

2.2 Current ethical issues

Gene drive research has the potential to be a significant and beneficial tool for public health. However, the potential effect of gene drive on entire populations of species gives rise to issues about its impact on the environment broadly. Gene drive research involves many uncertainties that create significant challenges at every level of development of the technology, but may be particularly challenging for fair stakeholder engagement, for the development of appropriate risk assessment and regulatory paradigms, and impact and safety assessment.

Potential impact on the environment
A key features of gene drive research is that the genetic modification is designed to spread in the wild population. This has given rise to concern about how to limit the spread of genetically engineered mosquitoes to a defined geographical region, and what impact they might have on the existing ecosystems (e.g. on competitors, predators).[xxv] Questions have also been raised about how to stop the propagation of the gene if there is a loss of control of the technology. It is important to understand people's perspectives in relation to the environmental uncertainties associated with gene drive research and that such concerns for the environment may result in some people opposing the technology.

The National Academies of Science, Engineering and Medicine (NASEM) addressed these issues in its 2016 report 'Gene Drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values'[3]. The report recommended additional research to address the gaps in knowledge, particularly in regard to ecological and evolutionary considerations for the organism and its ecosystem.[xxvi] It will be important to identify these environmental risks, and assess if they can be managed or mitigated to an acceptable level.[xxvii] Mathematical modelling can play an important role in predicting the effects of gene drive under realistic transmission conditions.

An international, multi-disciplinary working group of experts in mosquito research have recommended a pathway for the safe and ethical testing of gene drive mosquitoes from discovery research to implementation. Progression through the testing pathway is based on fulfilment of safety and efficacy criteria, and is subject to regulatory and ethical approvals, as well as social acceptance. The working group acknowledged that the predicted ease of spread of gene drive mosquitoes calls for extremely thorough risk assessment and evaluation under careful confinement before release into a hospitable environment.[xxviii] For example, the initial malaria gene drive research is being conducted in the UK in contained laboratories. If there is any unintended release, the UK climate is too cold for the mosquitoes to survive and there is no native wild population with which they could mate. [xxix]

[3] Although gene drives have a number of potential applications e.g. militarisation, commercialisation, food security, biodiversity the NASEM report only addressed the last one. This is relevant to GFBR's focus on health.

While calling for extremely thorough risk assessment and evaluation, the international working group also called for the safety expectations to be proportionate to those of other vector control tools and that the risks of inaction (and maintaining the status quo) should be considered.

Potential benefits and harms for people

The NASEM report gives two clear examples of the potential human benefits of gene drive research:

- as an alternative to current dengue prevention strategies that rely on laborious removal of breeding sites and ultra-low volume spraying of insecticides, the efficacy of which is challenged by increasing resistance among targeted species. Theoretically, gene drive could provide enhanced sustainability for disease prevention, and might also provide a broader health benefit, since the *Aedes aegypti* mosquito also serves as a vector for a range of other viruses responsible for human disease, including yellow fever and zika.
- in the context of malaria, there is widespread and increasing resistance of mosquitoes to insecticides and the parasites have developed resistance to many first-line drugs. While malaria can be cured using drug therapy, therapy requires that the parasite be detected and that the infected person has access to health care. These requirements can be challenging in many settings where malaria is endemic. A gene drive intended to prevent mosquitoes from transmitting the protozoan parasite that causes malaria to human could have a significant public health impact. [xxx]

Release of a gene drive organism may have unintended effects that give rise to potential harms to human. For example:

- the mosquito may become more susceptible to hosting a different virus that is also harmful to human health
- the virus may evolve a new phenotype that poses a slightly different hazard from the one that the gene drive was meant to suppress
- there could be broader impacts on the ecosystem, with the suppression of the mosquito population paving the way for another disease vector. [xxxi]

As discussed above, consideration of gene drive research will require case-by-case investigation with modelling of possible outcomes. Technical, environmental and societal issues will need to be assessed and harms, benefits and uncertainties weighed. The challenge will lie in negotiating differing views on what constitutes a harm and what constitutes a benefit, and deciding what level of uncertainty is acceptable.

Consent in field trials

There is a lack of consensus on whether consent is required for field trials, at what level and from whom. For example, consent could be individual, at the level of the household or in certain contexts it may be culturally appropriate for traditional leaders to consent on behalf of the community. In this respect, gene drive research raises similar issues to cluster trials that are designed to assess a public health intervention: how can the research community acquire the necessary legitimacy and authority to proceed and how can the buy-in from the affected population be gained? This is particularly important given that individuals within the community cannot opt-out.

Individuals who live in or near a site where gene drive organisms are to be released will have a clear interest in the research and its impact, but are they research participants in the tradition (or legal) sense? Kolopack and Lavery[xxxii] argue that living in the vicinity of a release trial does not automatically render someone a research subject and therefore it is inappropriate to require informed consent from every individual in the vicinity. However, they identified circumstances in which individuals satisfy the conventional requirements to be considered human research subjects

and informed consent may be required.[4] They acknowledge that even in these cases consent may be waived or modified according to the judgment of research ethics committees (acting in accordance with regulations and guidelines). Importantly, any approach to informed consent should be properly justified and it should be part of a broader regulatory framework, informed by stakeholder engagement.

What constitutes fair and legitimate authorisation for field trials of gene drive?

Section 3 Engagement and uptake

- ***Whose responsibility is it to undertake engagement work when a new genome editing technology is being researched and introduced in a LMIC?***
- ***What should this engagement look like, who should be engaged and for what purpose? Does it look different to engagement for non-genomic technologies?***
- ***Does engagement for human genome editing look different to engagement for gene drive research (e.g. in relation to the methods and who or which groups should be engaged)?***

There have been calls for 'broad societal consensus' before any clinical use of germline editing could proceed, informed by broad participation and input by the public.[xxxiii] Likewise, there have been calls for any future use of gene drives to be preceded by public debate about the risks and benefits of gene drives and the relative desirability of using gene drives compared with alternative social, economic or technological solutions.[xxxiv] Such engagement is necessary given the potential societal implications of both technologies.

Multiple public engagement strategies could be employed to inform and elicit public views, e.g. film, surveys and drama, along with public talks, seminars, small group discussion and citizen juries. In general, engagement activities are funded or organised by either research funders (e.g. research councils, learned societies, individual funding organisations), researchers who work in the field, advocacy organisations or policy makers (e.g. government departments). The purpose of engagement may vary, for example, it can be used to help the public understand the science or used to promote dialogues which are intended to elicit public views and to directly influence policy decisions.

Human genome editing: The public engagement literature is dominated by HIC activities. For example, the UK National Centre for Public Engagement is undertaking a program that aims to synthesise learning and create tools to be shared to encourage high quality public engagement on the topic of genome editing.[xxxv] This is only one of many HIC initiatives[xxxvi] that aims to map past public engagement activities, identify best practice and discuss future approaches.

Engagement is also required with specific stakeholder groups e.g. patient organisations, researchers, bioethicists, regulators and policy-makers etc. Such stakeholder activities have taken place in a number of countries, for example:

- 'Getting the ethics of genome editing right: engaging multiple perspectives', Malaysia, 2019

[4] Situations in which informed consent may be required: (1) when blood and other forms of clinical data are collected from them, as will likely be the case in some studies involving epidemiological endpoints, such as the incidence of new infections with dengue and malaria; (2) when they participate in social science and/or behavioral research involving the completion of surveys and questionnaires; or (3) when their home or property is accessed and the location recorded as a spatial variable for the release or collection of mosquitoes because the precise location of the household is important for entomological reasons and these data constitute identifiable private information at the household level.

- ‘Symposium on the ethics of gene modifying technologies’, Singapore, 2018
- ‘International summit on genome editing’, USA, 2015 and Hong Kong, 2017
- ‘Fostering global responsible research with CRISPR-Cas9: Latin America workshop’, Argentina, 2016.[xxxvii]

The Centre for Genetics and Society has called for ‘democratic governance’ of human germline research that is informed by a range of perspectives and takes account of its potential social consequences – its impacts on communities (especially vulnerable groups), on cultural assumptions, and on societies – rather than only on individuals or couples.[xxxviii] They argue this will require engagement with civil society groups, artists and cultural producers, community-based organizations, rights and justice advocates, and social movements.

Gene drives: The Gene Drive Sponsors and Supporters’ Forum is an example of funders and others coming together to discuss the issues surrounding the introduction of a new technology.[5] They have strongly endorsed the need for stakeholder engagement and recognised the importance of ensuring transparency with all stakeholders, including researchers, local communities and other publics, national authorities and international agencies. They recommended that engagement should be integrated into gene drive research activities from an early stage to open an ongoing dialogue about research and development processes.[xxxix, xl]

The Forum has also recognised the need for empirical evidence to clearly identify what information various stakeholders – scientists, government officials, communities and other publics – want to receive.[xli] A standard terminology, a “common language”, with clear definitions, would help with communication in both technical and non-technical settings, and have potential benefits for engagement, policy making and regulation.[xlii]

Human genome editing and gene drive research both require broad engagement and transparent dialogue around both their potential benefits and risks, but does the more ‘public’ application gene drive research ethically demand a different approach? For example, does the ability of gene drive organisms to cross national boundaries demand engagement with regional and multinational bodies with authority to represent transnational sets of stakeholders?[xliii]

The potential of gene drive organisms to spread geographically also raises the question of how widely engagement activities should take place from the release site (e.g. the next town/village or within a set radius). And consideration is also needed for other potential cross-border issues (e.g. ethics approval in multiple potential neighouring countries, or informing neighbouring countries’ governments etc.).

At a more local level, individuals who live in or near a site where gene drive organisms are to be released will likely have a particular interest in the technology as they may be affected by it. The Target Malaria team in Uganda includes engagement and communication experts who work closely with communities. The team inform the community about the project objectives, activities and collects their feedback and knowledge to contribute to the co-development process of the approach. The local communities are involved at the collection sites, where they share their knowledge about

[5] The Forum has published principles for sponsors and supporters of gene drive research. They aim to develop a “consensus standard” designed to set an agreed level of good practice or quality to help establish confidence in gene drive innovations. This will include consideration of harmonized approaches to stakeholder engagement, regulatory oversight, transparency and data sharing to support the research, knowledge sharing, and public discourse on gene drive technology. For more information see: http://science.sciencemag.org/content/358/6367/1135.full

malaria mosquitoes and play a role to facilitate mosquito collections. [xliv] Local engagement teams are also working at Target Malaria sites in Burkina Faso and Mali.

In another study, social research was used to design an engagement framework tailored to the concerns, expectations, and socio-political setting of a potential trial release site in Vietnam.[xlv] Although this case did not involve genetically-modified mosquitoes – the mosquitoes were biologically-modified as a new dengue control method – the work may be informative for gene drive engagement strategies. Residents' desired level of engagement included regular updates and authorisation from government and at least one member of every household. In addition, they wanted to be informed and engaged about the science, the project, its safety, the release and who would be responsible should something go wrong. Similar social science research in the context of proposed gene drive research could inform an engagement approach that is targeted to the local community at the release site.

The Outreach Network for Gene Drive Research has described a role for such communities in the final decision on whether specific uses are acceptable or desirable – with the decision being made case-by-case by potential beneficiary communities, as well as the regulatory authorities.[xlvi] But in this scenario, who speaks for the community and how, practically, can the community's assent be attained?

For both human genome editing and gene drive research:

- ***What does broad societal consensus look like? What level of community acceptance is needed before research using a genomic technology can be undertaken? Is there a difference between the level of acceptability required for a technology that has a 'private' individual health impact (human genome editing) vs a public health impact (gene drive research)? Or is this a false distinction given that the uptake of both technologies presents broad societal issues?***
- ***How might cultural or religious beliefs and norms impact on the social acceptability of genome editing research (e.g. in relation to the status of the embryos and/or beliefs about what it means to be human and making changes that will affect future generations or have an impact on the environment).***

Section 4 Governance, guidance and best practice

Good governance can provide a system that offers a secure basis for trust in science: one that takes account of questions of equity and respect for participants and communities, including consideration of benefit, interests, and appropriate protections. Governance can include: regulation/laws; international, national or funder specific policies; ethical/normative guidance published by the World Health Organisation (WHO) and similar organisations and institutional policies that implement ethical norms. Governance of research is underpinned by formal and informal structures and processes for decision making and requires the action of many stakeholders, including researchers, RECs, funders, governments and regulators.

The governance of international partnerships for genome editing research can be a challenge given the multiple and sometimes conflicting mandates, goals and agendas for partners in a project who arrive with different perspectives (e.g. private, public, government, civil society). Funders play a critical role in these partnerships. They can provide enabling conditions for the introduction of genome editing technologies into LMICs and can have a significant impact on how the ethical issues are addressed. However, if funders have a minimalistic view of stakeholder engagement, or fail to

build flexibility and responsiveness into budgets and protocols to permit meaningful learning from stakeholders, then many of the ethical issues may end up not being identified or addressed.

Other forms of financing – such as private equity/professional investing – are likely to play a critical role in at least some genome editing technologies, especially as they move from research towards commercialization pathways. These may come with different claims about control of the technology and raise ethical issues in the way they shape the conditions and terms under which technologies are moved towards, and into, markets. These conditions and terms can create challenges for governance.

The issue of funding ties into questions around global justice and equity and the need for technologies to be funded and developed in a way that makes them available to LMICs. Jasanoff and Hurlbut have called for studies of the social dynamics of international collaborations — from setting research agendas to the allocation of intellectual-property rights — to help reveal the hidden power imbalances in science (cultural and institutional) that are likely to influence who benefits from genome editing research, as well as who does not.[xlvii]

- ***What are the responsibilities on funders to promote equitable research collaborations involving both HIC and LMIC researcher so research design and conduct is co-created and co-owned?***
- ***How do you ensure that governance processes are appropriate and fit for purpose in LMICs (e.g. regulatory frameworks, funding mechanisms, institutional structures and policies etc.)?***

Guidance for genome editing is diverse and inconsistent. Some organisations have recommended a moratorium on germline editing research (International Society for Stem Cell Research[xlviii]), whereas others suggest the door should be left open but only with broad consensus and answers to moral, ethical and scientific questions (European Academies Science Advisory Council[xlix]). More international guidance, such as UNESCO[l], is potentially self-contradicting, calling for a research moratorium but for progress to be owned by researchers. Gene drive research has faced a call for a moratorium on field releases, at the 14th Conference of the Parties of the Convention on Biological Diversity (CBD) in Egypt in November 2018. The idea was rejected with a call for case-by-case risk assessment.[li]

There is also diverse guidance on related but not specific issues, for example limits to embryo culture in research which may be legislative or guidelines, or sharing outputs of genetic technologies under the Nagoya Protocol[lii], which may or may not be ratified by a given country.

In 2018 the UK's Nuffield Council on Bioethics published its report on '*Genome editing and human reproduction: social and ethical issues'* concluding that 'the potential use of heritable genome editing interventions… could be ethically acceptable in some circumstances, so long as:

- it is intended to secure, and is consistent with, the welfare of a person who may be born as a consequence of interventions using genome edited cells; and
- it is consistent with social justice and solidarity, i.e. it should not be expected to increase disadvantage, discrimination, or division in society.'

The report makes a number of recommendations, including on the need for broad and inclusive societal debate; for governments to work with international human rights institutions to promote international dialogue and to develop a framework for international governance of heritable genome editing interventions. It also recommended the formation of an independent UK body to

promote public debate on the use of genomic and related technologies to respond to societal challenges; to help to identify and understand public interests at stake; and to monitor social, cultural, legal and health impacts.[liii]

- ***Are current governance structures sufficient for dealing with the long-term social risks of genome editing research or are other governance mechanisms required (e.g. an international or national advisory and monitoring group)?***

Other initiatives and publications include:

Human genome editing

- European Academies Science Advisory Council: 'Genome editing: scientific opportunities, public interests and policy options in the European Union' (March 2017)
- European Group on Ethics in Science and New Technologies, which is currently preparing an opinion on gene editing, to be complete by summer 2019[liv]
- Association for Responsible Research and Innovation in Genome Editing[lv]

Gene drives

- American National Academies of Sciences, Engineering and Medicine: 'Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values" (June 2016)
- Gene Drive Research Forum[lvi]
- Australian Academy of Science: 'Synthetic gene drives in Australia: implications of emerging technologies' (May 2017)
- Dutch National Institution for Health and Environment (RIVM) 'Gene drives: policy report' (2016)
- OECD Co-operative Research Programme on Biological Resource Management for Sustainable Agricultural Systems sponsored conference: 'Environmental release of engineered pests: building an international governance framework' (October 2016)[lvii]

However, these initiatives come from predominantly wealthy nations and are thus likely missing perspectives from developing settings. Often this overlooks the underlying problems in these areas such as baseline levels of mistrust in science or, in Latin America, a lack of infrastructure to store patient data. Without knowledge of systemic problems, it is challenging to tackle those additional and specific to genome editing.

The French National Institute of Health and Medical Research, alongside Wellcome have explored the ethics of human genome editing in other settings, notably Latin America and India. Discussion pointed to different concerns, particularly on access, malpractice or bogus claims, and the ability to enforce regulation. It is possible that existing guidance developed elsewhere is not appropriate in these settings. There is a worry that without more tailored guidance, efforts to reduce potentially unethical research may prevent all forms of research.

There is a need for consensus and clarity. The US National Academies of Science, Engineering and Medicine[lviii] have attempted to find one using shared principles. Their report outlines seven global principles for research and clinical use of genome editing: *promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational cooperation*. More specific recommendations are given for clinical use, including a potential framework for clinical trials in the US. The report makes excellence progress, but still frames the issue from a global north perspective.

Consensus may be more easily found with more diverse voices involved, as existing guidance is largely driven by the global north and may not reflect other cultures and systems. In the context of gene drive research, the gene-drive activity cannot be contained – this may have driven a more inclusive debate. Those exposed to threats, for example from malaria, have different perspectives on the ethics of action over inaction. However, cost-benefit analysis and regulatory leadership have traditionally been driven by Europe or the US. To date, engagement and communication appear to be substituting for more comprehensive governance strategies for genome editing technologies. To make sustainable progress more needs to be done to support regulatory leadership and capacity and the strengthening of governance systems in context.

International harmonisation on genome editing is unlikely to be possible or desirable. Governance will reflect the cultural setting and capacity in any given country. It is unclear what the most appropriate strategy for sharing 'good' practice is. Developing countries may look to existing frameworks in the US or Europe to see what can be applied to their setting, or may choose to develop completely new frameworks. Further communities, such as funders, researchers or ethicists, may prefer to rely on agreed principles or codes of practice rather than rigid frameworks. This field is evolving rapidly: in December 2018 the WHO announced the creation of an expert panel to develop standards for the governance and oversight of genome editing, both at the national and global level. This promises to be a significant contribution to the existing work in this field and one that will hopefully draw on a range of diverse voices.

Capacity strengthening

- ***When introducing research that uses complex genomic technology in LMICs what are the obligations – on researchers and funders – to address gaps in systems e.g. research capacity, regulatory gaps, Research Ethics Committee procedures etc? How can this be managed in such a way that takes account of conflicts of interest?***

Research capacity strengthening: Research capacity will need to be strengthened in LMICs in key disciplines that underpin genome editing technologies. Training of scientists from LMICs and their involvement in research design and deployment initiatives from the beginning will be essential for co-ownership. Training needs can be addressed through the programs of individual funding organisations as a way of promoting equitable partnership[lix] and should be followed by the transfer of technologies and infrastructure. For example, Target Malaria ran a 3-day short course on gene drive for malaria control in collaboration with the Pan African Mosquito Control as a way of engaging and training the next generation of researchers and has built a new insectary facility at the Uganda Virus Research Institute.[lx] Training will also be needed to support ethical reflection and review of the proposed research.

Regulatory capacity strengthening: Human genome editing and gene drive research pose issues that are new for regulators worldwide, and LMIC regulators should be involved from the outset in these discussions.[lxi]

The NASEM report on gene drives recommended that funders and researchers give careful consideration to the adequacy of regulatory systems in countries where field testing or environmental releases will be conducted. Organisations like The New Partnership for Africa's Development (NEPAD) Agency have an active role in capacity strengthening in the regulation of emerging technologies, including gene drives, at the national and regional levels.[lxii]

The Gene Drive Sponsors and Supporters' Forum has discussed the issue of regulatory strengthening and agreed that:

- sponsors of gene drive research have a responsibility to ensure thorough, well-informed and unbiased evaluation of research applications at multiple different levels, including strong regulatory review; this in turn implies a responsibility to support regulatory capacity strengthening. Conflicts of interest should be avoided by ensuring that regulatory capacity strengthening is carried out with strict separation between research proponents and regulatory authorities.[lxiii]
- regulatory capacity strengthening must be done through organisations with the appropriate mandate, such as intergovernmental agencies, but that others may be able to assist, for example with technical support. [lxiv]

These conclusions apply equally to the implementation of human genome research in LMICs.

Relevant International Ethical Guidelines

Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo Convention) at https://rm.coe.int/168007cf98	A framework Convention that aims to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. It sets out fundamental principles applicable to daily medical practice and is regarded as such at the European treaty on patient's rights. It also deals specifically with biomedical research, genetics and transplantation of organ and tissues. Article 18 addresses research on human embryos in vitro. Article 13 states 'an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aims is not to introduce any modification in the genome of any descendants'
Universal Declaration on Human Genome and Human Rights at http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/	
Convention on Biological Diversity at https://www.cbd.int/convention/text/default.shtml	The Convention has 3 main objectives: 1. The conservation of biological diversity 2. The sustainable use of the components of biological diversity 3. The fair and equitable sharing of the benefits arising out of the utilization of genetic resources
Nagoya Protocol at https://www.cbd.int/abs/text/default.shtml	This is a supplementary agreement to the Convention on Biological Diversity (CBD). It provides a transparent legal framework for the effective implementation of one of the three objectives of the CBD: the fair and equitable sharing of benefits arising out of the utilization of genetic resources
WHO Guidance Framework for testing genetically modified mosquitoes	Aims to foster quality and consistency among processes for testing and regulating new genetic technologies by proposing standards of efficacy and

https://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/	safety testing comparable to those used for trials of other new public health tools. Drafted by four different working groups (efficacy; safety; ethical, legal and social; and regulation)

References

[i] Jasanoff S and Hurlbut JM (2018) A global observatory for gene editing, *Nature* 555:435-437 https://www.nature.com/articles/d41586-018-03270-w (accessed 26 April 2019)

[ii] The Academy of Medical Sciences, AMRC, BBSRC, MRC, Wellcome (2015) Genome editing in human cells – initial joint statement https://acmedsci.ac.uk/file-download/37773-55e6b4e90f49c.pdf (accessed 26 April 2019)

[iii] National Center for Advancing Translational Sciences (2018) Somatic Cell Genome Editing https://ncats.nih.gov/somatic (accessed 26 April 2019)

[iv] Collins F (2018) Accelerating cures in the genomic age: The sickle cell example https://directorsblog.nih.gov/2018/12/11/accelerating-cures-in-the-genomic-age-the-sickle-cell-example/ (accessed 26 April 2019), Persaud A et al (2018) A CRISPR focus on attitudes and beliefs towards somatic genome editing from stakeholders within the sickle cell disease community, *Genetics in Medicine* https://www.nature.com/articles/s41436-018-0409-6 (accessed 26 April 2019)

[v] Ogaugwu, CE Agbo SO and Adekoya MA (2019) CRISPR in sub-Saharan Africa: applications and education, *Trends in Biotechnology* 37(3): 234-237 https://www.sciencedirect.com/science/article/pii/S0167779918302038 (accessed 26 April 2019)

[vi] Liang P et al (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, *Protein & Cell* 6(5):363-372 http://dx.doi.org/10.1007/s13238-015-0153-5 (accessed 26 April 2019)

[vii] Tang L, Zeng Y Du H, Gong M et al (2017) CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein, *Mol. Genet. Genomics* 292(3):525-533 https://doi.org/10.1007/s00438-017-1299-z (accessed 26 April 2019)

[viii] Ma H et al (2017) Correction of a pathogenic gene mutation in human embryos, *Nature* 548:413-419 doi:10.1038/nature23305 (accessed 26 April 2019)

[ix] The He Lab (2018) About Lulu and Nana: twin girls born healthy after gene surgery as single-cell embryos https://www.youtube.com/watch?v=th0vnOmFltc&app=desktop (accessed 26 April 2019) The claim has not been independently verified

[x] National Academies of Science, Engineering, and Medicine (2019) Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop-in Brief. Washington, DC: The National Academies Press. https://doi.org/10.17226/25343 (accessed 26 April 2019)

[xi] Li J et al (2019) Experiments that led to the first gene-edited babies: the ethical failings and the urgent need for better governance, *J Zhejiang Univ-Sci B (Biomed & Biotechnol)* 20(1):32-38

[xii] National Academies of Science, Engineering, and Medicine (2019) Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop-in Brief. Washington, DC: The National Academies Press. https://doi.org/10.17226/25343 (accessed 26 April 2019)

[xiii] Withrock IC et al (2015) Genetic disease conferring resistance to infectious disease, *Genes and Disease* 2(3):247-254 https://www.sciencedirect.com/science/article/pii/S2352304215000239 (accessed 26 April 2019)

[xiv] National Institutes of Health (2015) Statement on NIH funding of research using gene-editing technologies in human embryos https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos (accessed 26 April 2019)

[xv] National Academies of Science, Engineering, and Medicine (2019) Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop-in Brief. Washington, DC: The National Academies Press https://doi.org/10.17226/25343 (accessed 26 April 2019)

[xvi] Warmflash D, Genetic Literacy Project (2018) How religious beliefs shape our thinking on cloning stem cells and gene editing https://geneticliteracyproject.org/2018/11/09/cloning-stem-cells-gmos-religious-beliefs-shape-thinking/ (accessed 26 April 2019)

[xvii] Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D & Hard BW (2017) U.S. attitudes on human genome editing, *Science* 357(6351):553-554, DOI:10.1126/science.aan3708 (accessed 26 April 2019)

[xviii] Addendum to the Center for Genetics and Society's Response to the 2016 Call for Evidence (2017), Submission to the Nuffield Council on Bioethics http://nuffieldbioethics.org/wp-content/uploads/2017-Center-for-Genetics-and-Society-WEB.pdf (accessed 26 April 2019)

[xix] National Academies of Sciences, Engineering, and Medicine (2017) Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press. https://doi.org/10.17226/24623 (accessed 26 April 2019)

[xx] Outreach Network for Gene Drive Research (2018) Open letter: research on gene drive technology can benefit conservation and public health https://genedrivenetwork.org/open-letter (accessed 26 April 2019)

[xxi] Wellcome website: Emerging science and technologies https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)

[xxii] World Health Organisation (2017) World malaria report 2017 https://www.who.int/malaria/publications/world-malaria-report-2017/en/ (accessed 26 April 2019)
[xxiii] Toe LP (2018) Target Malaria blog, Burkina Faso is getting ready for its next stage of research – sterile male mosquito release https://targetmalaria.org/burkina-faso-is-getting-ready-for-its-next-stage-of-research-sterile-male-mosquito-release (accessed 26 April 2019)
[xxiv] James S et al (2018) Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: Recommendations of a Scientific Working Group, *Am. J. Trop. Med. Hyg*. 98(6):1–49 doi:10.4269/ajtmh.18-0083 (accessed 26 April 2019)
[xxv] James AA (2018) First opinion: Gene-drive technology must be developed in a safe, ethical way, *STAT* https://www.statnews.com/2018/07/10/gene-drive-technology-safety-ethics/
[xxvi] National Academies of Science, Engineering, and Medicine (2016) Gene Drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and (accessed 26 April 2019)
[xxvii] Burt A et al (2018) Gene drive to reduce malaria transmission in sub-Saharan Africa, *Journal of Responsible Innovation* 5(1):66-80 https://doi.org/10.1080/23299460.2017.1419410 (accessed 26 April 2019)
[xxviii] James S et al (2018) Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: Recommendations of a Scientific Working Group, *Am. J. Trop. Med. Hyg* 98(6):1–49 doi:10.4269/ajtmh.18-0083 (accessed 26 April 2019)
[xxix] The Royal Society (2018) Gene drive research: why it matters https://royalsociety.org/~/media/policy/Publications/2018/08-11-18-gene-drive-statement.pdf (accessed 26 April 2019)
[xxx] National Academies of Science, Engineering, and Medicine (2016) Gene Drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and (accessed 26 April 2019)
[xxxi] National Academies of Science, Engineering, and Medicine (2016) Gene Drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and (accessed 26 April 2019)
[xxxii] Kolopack PA and Lavery JV (2017) Informed consent in field trials of gene-drive mosquitoes, *Gates Open Res* 1(14) doi: 10.12688/gatesopenres.12771.1 (accessed 26 April 2019)
[xxxiii] National Academies of Sciences, Engineering, and Medicine (2017) Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press. https://doi.org/10.17226/24623 (accessed 26 April 2019)
[xxxiv] The Royal Society (2018) Gene drive research: why it matters https://royalsociety.org/~/media/policy/Publications/2018/08-11-18-gene-drive-statement.pdf (accessed 26 April 2019)
[xxxv] National Co-ordinating Centre for Public Engagement. Genome editing public engagement synergy https://www.publicengagement.ac.uk/nccpe-projects-and-services/nccpe-projects/genome-editing-public-engagement-synergy (accessed 26 April 2019)
[xxxvi] Sciencewise, a UK programme which supports government bodies to commission deliberative public dialogue, held a workshop in 2018 with researchers and policy makers to explore public engagement priorities. The briefing paper for the meeting provides a valuable summary of past work where the public engagement activities have focussed on either helping the public to understand the science or on promoting dialogues which are intended to elicit public views and to directly influence policy decisions. The workshop report made a number of suggestions about how to enhance the quality and robustness of intelligence gathering about public attitudes, which could be used to inform decision making and the design of future engagement activities. See: https://sciencewise.org.uk/wp-content/uploads/2018/07/Genome-Editing-for-Human-Health-Briefing-Paper-FINAL.pdf and https://sciencewise.org.uk/wp-content/uploads/2018/07/Genome-Editing-for-Human-Health-event-report-FINAL-1.pdf
The Nuffield Council on Bioethics hosted a workshop in 2016 on public dialogue for genome editing. The workshop brought together people with three distinctive kinds of interest in discussing genome editing: scientists and research funders who are involved in the developing and applying the techniques; policy makers who will have to set the conditions in which this takes place to protect and promote the public interest; and dialogue specialists who can offer advice on the different modes, benefits and limitations of public engagement. See http://nuffieldbioethics.org/wp-content/uploads/Public-Dialogue-on-Genome-Editing-workshop-report.pdf
[xxxvii] Inserm (2016) Fostering global responsible research with CRISPR-Cas9 - meeting presentations and report https://www.inserm.fr/en/research-inserm/ethics/inserm-ethics-committee-cei/ethics-committee-workshops/fostering-global-responsible-research-with-crispr-cas9 (accessed 26 April 2019)
[xxxviii] Addendum to the Center for Genetics and Society's Response to the 2016 Call for Evidence (2017), Submission to the Nuffield Council on Bioethics http://nuffieldbioethics.org/wp-content/uploads/2017-Center-for-Genetics-and-Society-WEB.pdf (accessed 26 April 2019)
[xxxix] Gene Drive Sponsors and Supporters' Forum – summary meeting report (December 7, 2017) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)
[xl] Gene Drive Sponsors and Supporters' Forum – summary meeting report (September 11-13, 2018) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)
[xli] Gene Drive Sponsors and Supporters' Forum – summary meeting report (September 11-13, 2018) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)

[xlii] Gene Drive Sponsors and Supporters' Forum – summary meeting report (September 11-13, 2018) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)
[xliii] James S et al (2018) Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in sub-Saharan Africa: Recommendations of a Scientific Working Group, *Am. J. Trop. Med. Hyg*. 98(6): 1–49 doi:10.4269/ajtmh.18-0083 (accessed 26 April 2019)
[xliv] Malaria Must Die Campaign, How Ugandan researchers are part of a bigger effort to combat malaria mosquitoes https://www.malariamustdie.com/researchers-combat-mosquitoes/
[xlv] McNaughton D and Huong Duong TT (2014) Designing a community engagement framework for a new dengue control method: a case study from central Vietnam, *PLoS Negl Trop Dis* 8(5) doi: 10.1371/journal.pntd.0002794 (accessed 26 April 2019)
[xlvi] Outreach Network for Gene Drive Research (2018) Mission and principle statement https://genedrivenetwork.org/resources/6-mission-principles-statement-july2018/file (accessed 26 April 2019)
[xlvii] Jasanoff S and Hurlbut JM (2018) A global observatory for gene editing, *Nature* 555:435-437 https://www.nature.com/articles/d41586-018-03270-w (accessed 26 April 2019)
[xlviii] International Society for Stem Cell Research (2015) ISSCR Statement on Human Germline Genome Modification http://www.isscr.org/professional-resources/news-publicationsss/isscr-news-articles/article-listing/2015/03/19/statement-on-human-germline-genome-modification (accessed 26 April 2019)
[xlix] European Academies Science Advisory Council (2017) Genome editing: scientific opportunities, public interests and policy options in the European Union, Halle, DE: German National Academy of Sciences https://www.easac.eu/fileadmin/PDF_s/reports_statements/Genome_Editing/EASAC_Report_31_on_Genome_Editing.pdf
[l] UNESCO (2015) UNESCO panel of experts calls for ban on "editing" of human DNA to avoid unethical tampering with hereditary traits http://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits
[li] Decision adopted by the Conference of the Parties to the Convention on Biological Diversity CBD/COP/DEC/14/19 on Synthetic biology https://www.cbd.int/doc/decisions/cop-14/cop-14-dec-19-en.pdf (accessed 26 April 2019)
[lii]The Nagoya Protocol on Access and Benefit-Sharing (2014) https://www.cbd.int/abs/ (accessed 26 April 2019)
[liii]Nuffield Council on Bioethics (2018) Genome editing and human reproduction: social and ethical issues http://nuffieldbioethics.org/project/genome-editing-human-reproduction (accessed 26 April 2019)
[liv] European Group on Ethics in Science and New Technologies website. An opinion on gene editing is due to be published summer 2019 https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/european-group-ethics-science-and-new-technologies-ege_en
[lv]Association for Responsible Research and Innovation in Genome Editing website: https://arrige.org. For background see Chneiweiss H, Hirsch, F, Montoliu, L et al (2017) *Transgenic Res* doi.org/10.1007/s11248-017-0028-z,
[lvi]Emerson, C, James S, Littler, K and Randazzo F et al (2017) Principles for gene drive research, *Science* 358(6367):1135-1136 http://science.sciencemag.org/content/358/6367/1135
[lvii] Environmental release of engineered pests: building an international governance framework (2016) *BMC Proceedings* 12(Suppl 8) edited by Carter L, Brown Z and Gould F https://bmcproc.biomedcentral.com/articles/supplements/volume-12-supplement-8
[lviii]National Academies of Sciences, Engineering, and Medicine (2017) Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press. https://doi.org/10.17226/24623 (accessed 26 April 2019)
[lix] Gene Drive Sponsors and Supporters' Forum - summary meeting report (December 7, 2017) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology (accessed 26 April 2019)
[lx] Burt A (2019) Target Malaria Blog, 2018 – key achievements https://targetmalaria.org/2018-key-achievements/
[lxi] Burt A et al (2018) Gene drive to reduce malaria transmission in sub-Saharan Africa, *Journal of Responsible Innovation* 5(1):66-80 https://doi.org/10.1080/23299460.2017.1419410 (accessed 26 April 2019)
[lxii] Glover B et al (2016) Strengthening regulatory capacity for gene drives in Africa: leveraging NEPAD's experience in establishing regulatory systems for medicines and GM crops in Africa, *BMC Proceedings* 12(Suppl 8):11
[lxiii] Gene Drive Sponsors and Supporters' Forum - summary meeting report (December 7, 2017) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology
[lxiv] Gene Drive Sponsors and Supporters' Forum - summary meeting report (September 11-13, 2018) https://wellcome.ac.uk/what-we-do/our-work/emerging-science-technology

This paper incorporates and builds on a shorter topic paper on human genome editing, written by members of Wellcome's Policy Team in 2017. The authors of the topic paper were Sam Alvis and Sarah Rappaport.

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