3 July 2020

# Human Genome Editing: A DRAFT Framework for Governance

*Please note this document is a work in progress. It is a living record of the ideas presented to and discussed by the Committee. It will evolve as the group's consultations continue. In its current form, it does NOT represent the final views or recommendations of the Committee.*



## Part 1. Introduction

1. The Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (the Committee) was tasked by the Director-General "to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell)" (Box 1), with a direction to advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for both somatic and germline human genome editing.

2. During the course of the work of the Committee, the world was faced with managing the SARS-CoV-2 pandemic. Genome editing has proven to be an important tool for addressing this crisis, by helping to develop animal models that better reflect the human experience of the disease, by pointing toward new diagnostics and avenues of therapeutic intervention, and by offering new tools for those developing vaccines. As with agricultural and environmental uses, none of these applications are within the scope of this report. But this new pandemic underscores our contingent vulnerability to sudden catastrophe, which, in turn, reinforces how important it is that we develop effective governance mechanisms, the task that lies at the heart of this Committee's work. And it demonstrates vividly the importance of using new tools and new methods to combat serious diseases, while also reminding us that unless these are developed carefully, with testing and quality assurance measures in place, they may do more harm than good. This balance between risk and benefit, speed and safety, and innovation and access is relevant not only to the pandemic, but also to all the possible applications of genome editing for human health.

**BOX 1: A spectrum of uses for human genome editing**

| BOX UNDER DEVELOPMENT – Text needed |
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3. The Committee held in-person briefings with relevant experts during all its meetings, two open-ended public online consultations, as well as a comprehensive series of online webinars with relevant experts. Throughout its work, the Committee actively sought input from institutions, organizations, communities, and peoples often under-represented in international science policy processes, including through a dedicated meeting, online sessions, and telephone consultations. The Committee also drew on past work on relevant topics, such as existing bioethical analyses of human genome editing (Box 2).

**BOX 2: Existing bioethical analysis of human genome editing**

BOX UNDER DEVELOPMENT – Text needed

4. Proposed human genome editing research and clinical care (and especially human germline and heritable genome editing) touch on deeply held political, spiritual and religious beliefs. Already, different countries are adopting different positions with regard to legality, funding and regulation of human genome editing (Box 3).

**BOX 3: Existing analysis of the regulatory status of human genome editing**

| WHO Region | No. of Countries | No. of Documents |
|---|---|---|
| Africa | 3 | 3 |
| Americas | 12 | 12 |
| Eastern Mediterranean | 5 | 4 |
| Europe | 43 | 44 |
| South East Asia | 1 | 3 |
| Western Pacific | 7 | 14 |
| **TOTAL** | **71** | **80** |

5. Human genome editing research and applications – clinical care (treatment and prevention) and enhancements – will transcend national borders, as will its possible societal effects. Therefore, governance for this technology is needed at national (domestic policy and regulation) and transnational levels (conventions and treaties; coordination of cross-border movement of researchers, clinicians, patients and social effects). Some of the necessary governance tools exist, but they may need to be amended. Any gaps in policy (such as laws, regulations, guidance or associated capacity) must be filled.

6. Some of the measures recommended in this report can be undertaken by WHO. Others should be undertaken by other authorities and entities of influence, but the WHO stands ready to offer advice and assistance.

7. Anticipated benefit to society should drive innovation in human genome editing. In turn, good governance of emerging technologies should ensure that adequate protections are in place for those most in need of the potential benefits of human genome editing and those most likely to experience the potential harms, who may or may not be the same people.

8. While not the focus of human genome editing research and applications, data on human genetic diversity and the role gene variants play in health and disease under many different genomic and external environments are foundational to human genome editing. Those, in turn, depend upon vast collections of human samples and genetic data, collected over many years with varying degrees of understanding and consent from the individuals. Such collections are not currently representative of the global population and the risk is that genome editing innovations making use of available data could be biased against many. In addition, particular distress has been expressed by those who have had little control over the use of biological materials and data drawn from them, especially when in indigenous or historically exploited communities or among individuals whose perspectives concerning the human body, privacy, or the risks of stigmatization, are significantly different from those collecting and using their data. This larger question of ethical collection and use of biological and genetic materials and genetic data is

outside the scope of this committee's scope but has been considered as a background to its deliberations and conclusions.

# Part 2. Generally Applicable Considerations for Good Governance of New and Emerging Technologies

9. The Committee has endorsed a UNESCO description of governance as:

> …structures and processes that are designed to ensure accountability, transparency, responsiveness, rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation. Governance also represents the norms, values and rules of the game through which public affairs are managed in a manner that is transparent, participatory, inclusive and responsive.[1]

## 2.1 Fundamental choices

10. As with many emerging technologies, certain fundamental choices must be made when developing or amending relevant regulatory regimes. First, it may be necessary to consider whether all potential applications of a technology should be regulated by a single system or whether sector-specific approaches are warranted. For example, in the early years of recombinant DNA research, each research use was reviewed (by requirement or on a voluntary basis) by a national committee. Alternatively, to the extent that regulation is based on a harm-benefit profiles and that this balance differs across sectors, there may be good reason to introduce different regulatory approaches for each sector. Thus, the use of an emerging biotechnology might be subject to fundamentally different regulatory regimes in the context of plant genome editing (where regulation might focus on ecological disruption) versus animal genome editing (where regulation might have an animal welfare focus) versus creation of new biologics (where regulation might focus on safety and efficacy for human health).

11. A second fundamental choice centres on the degree of oversight required:

a. If there is a broad understanding that the potential for harm from a technology is low, then a more permissive regulatory regime may be developed. For example, some parts of the world concluded that engineered foods were not intrinsically more likely to pose a threat to human health or the environment than their counterparts made through traditional methods, such as hybridization. As a result, the regulatory regimes introduced permitted these foods to enter the market with only minimal oversight. The system of oversight is friendly to innovation and to new or small industry actors, who may lack the experience or resources to deal with elaborate premarket regulatory demands. Notably, this kind of 'green light' approach risks fostering public distrust, given the absence of tight controls and independent review of safety claims by the producers.

[1] http://www.ibe.unesco.org/en/geqaf/technical-notes/concept-governance

b. If there is a broad understanding that the potential for harm from a technology is high, a more restrictive regulatory regime may be developed. For example, in many countries, new drugs are subject to a 'red light' system that halts entry to the market until premarket testing has convinced the regulatory agency to approve the product. Such a system slows market entry to provide more time for extensive testing to demonstrate safety and efficacy, which can improve both the quality of the products and consumer confidence. But it also can slow innovation by making premarket requirements too complicated for newer companies or too lengthy and expensive for smaller companies to manage. It can create consumer backlash when the system is perceived as denying patients needed medications.

12. A third fundamental decision may need to be taken as to the speed at which the technology may comfortably be adopted. There will likely be a tension between speed to promote innovation and caution to promote safety and efficacy. This has led to many efforts to find a 'yellow light' system that provides a better balance, including systems for conditional approval of new drugs, or options for fast track reviews. Most of these systems are limited to products where innovation is needed to address an unmet need, where there is reason to believe premarket barriers will be difficult to overcome in time to address that need, and where there is some means for predicting reasonably good odds the product will ultimately prove to be safe and efficacious. Specific tools can be the use of surrogate endpoints that appear to predict successful long-term outcomes, use of suboptimal data (e.g. from sources other than prospective randomized controlled trials), extrapolation from smaller test populations, and the imposition of special conditions on sale, such as special registries or limiting use to certain populations or practitioners. These systems only work if there is a commitment to following up over time, ensuring that the hoped-for successes have been realized. Merely assigning companies the responsibility for post-market research is insufficient in the absence of effective enforcement mechanisms, such as automatically sunsetting market authorization of post-market commitments are not fulfilled.

## 2.2 Good governance

13. Good governance is not limited to formal regulation pursuant to legislation or judicial opinion. Governance is a system of norms as well as influence, and it includes forces to shape the direction and conditions of research and applications, such as well-crafted public and private funding priorities and conditions. Good governance also includes professional and industrial best practices, peer review and ethics assurance by publishers, and health care insurance coverage decisions for instance. Possible liability for harmful research or clinical care is an indirect source of governance, mediated by liability insurance.

14. Good governance is an ongoing process. Countries, organizations, institutions and so on with formal approvals or prohibitions should include mechanisms for revisiting earlier policies (laws, regulations, guidelines, etc.) in light of technical, practical and ethical developments.

15. Good governance promotes public confidence, by ensuring public values and viewpoints are incorporated into policymaking, by making governance choices clear and transparent, and by including a means to hold policymakers accountable for those choices.

16. Good governance incorporates a variety of values, principles and goals. While the precise expressions may differ, and the meaning of these terms may vary among different cultures and political systems, in substance the following tend to be a feature of all good governance:

a. Clarity, transparency and accountability;
b. Responsible stewardship of resources;
c. Inclusiveness, solidarity, and the common good;
d. Fairness, non-discrimination, and social justice;
e. Respect for the intrinsic dignity of the person; and
f. Enforcement capacity.

# Part 3. Human Genome Editing Governance: Considerations for an Emerging Technology

17. In addition to the values, principles and goals common to good governance generally, human genome editing demands particular attention to additional specific values, principles and goals (Box 4).

**BOX 4: Values, principles and goals specific to human genome editing**

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| **Clarity, transparency and accountability** | A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. |
| **Inclusiveness, solidarity, and the common good** | A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. |
| **Responsible stewardship of science** | A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. |
| **Responsible stewardship of resources** | A commitment to expend available resources—financial and social (time and personnel)— wisely, recognizing that a meaningful commitment to |

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| | inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. |
| **Fairness** | A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. |
| **Social justice and non-discrimination** | A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. |
| **Respect for individual dignity** | A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. |

18. These specific values, principles and goals must be entrenched in appropriate policies (laws, regulations, and guidelines) and practices, and adequate resources must be available to enforce these policies (to detect and punish non-compliance) and to promote these practices (to educate, engage and empower members of the scientific and medical communities as well as the public). As with other aspects of the governance framework for human genome editing, the precise approaches and measures likely will depend upon the context.

19. Genome editing can be used on human cells as part of:

a. Laboratory-based basic science research;
b. Laboratory-based screening for drug targets;
c. Pre-clinical and clinical phases of research;
d. Clinical care (treatment and prevention) as an innovative or, eventually, a standard intervention; and
e. Enhancement.

An ideal governance system will address all these phases.

20. The science of human genome editing is rapidly evolving. Good governance must be responsive (able to adapt policies and practices) as needed, in response to new information and changing mores.

21. Human genome editing has been the subject of extensive public discussion in many societies, but often important differences between human genome editing in somatic cells and germ cells have been conflated; as well there has been conflation between genome editing in early embryos and other germline cells *in vitro* for research (sometimes referred to as germline genome editing) and genome editing of germ cells or embryos for reproduction (sometimes referred to as heritable genome editing). Good governance must specifically consider the challenges inherent in both germline and somatic human genome editing, as well as uses for both research and reproduction.

22. To improve decision-making and gain public trust, governance must make extra efforts to educate, engage and empower many publics. Of necessity, this will include efforts to inform, to listen, to incorporate a range of perspectives, and to be transparent about who is responsible for which policy choices, on the basis of which facts and values, principles and goals, and how they can be amended.

**BOX 5: Good practices in public education, engagement, and empowerment**

Public education, engagement and empowerment initiatives and activities: public education (where information flows in one direction using tools such as public service announcements and advertising campaigns); public engagement (where information flows in two directions using discussion-based tools); and public empowerment (through shared priority-setting and decision-making tools).

In some cases, efforts to foster a dialogue on emerging technologies, such as human genome editing, might be added into existing initiatives. In other cases, it may be necessary to develop new initiatives specifically for human genome editing.

Public education, engagement and empowerment may also be facilitated through the creation of a separate body, independent of government and

independent of existing regulatory agencies. This body could help to identify and produce an understanding of public interest(s) through promotion of public debate, engagement with publics and monitoring the effects of relevant technological developments. Relevant efforts might usefully consider ethical, social, and legal implications as well as technical work. They might need to address how to engage traditionally under-represented groups, such as indigenous peoples, different ethnic groups, or specific patient groups.

Efforts should be inclusive, with active consideration as to how best to include a range of perspectives including those who support and those who oppose the development and use of human genome editing, as well as those who are agnostic. There should also be careful consideration of how best social media and outreach to the traditional media may be used to further these aims.

23. At the national level, governance may have different areas of focus. For example, countries with an extensive research base may have robust regulations governing laboratory, pre-clinical and clinical research, while countries with a primary focus on the delivery of clinical care may have robust regulations on quality assurance and health care financing.

24. Countries will differ in their capacity to comprehensively govern human genome editing research and clinical care. Where the personnel or funding are insufficient, capacity building should be a priority. For immediate needs, provision should be made to draw on regulatory capacity in other countries or in international institutions.

25. Human genome editing is likely to be the subject of comprehensive regulation in some countries and weak or no regulation in others. The high level of excitement about the technology among some enthusiasts introduces two related risks – the risk that the technology will be oversold by unscrupulous entrepreneurs and clinics operating in jurisdictions without the capacity to oversee their operation, and the risk that patients will be enticed to explore unproven and possibly dangerous interventions of no potential benefit. Human genome editing governance must include measures to prohibit human genome editing travel or tourism and have disciplinary tools to deter unscrupulous behaviours.

## 3.1 Special Challenge: Heritable Human Genome Editing

26. Heritable human genome editing commonly refers to editing of nuclear DNA in a way that is heritable across generations. It also encompasses editing of mitochondrial DNA, which has different technical challenges and harm-benefit profiles. Good governance should have the capacity to evaluate both.

27. Human genome editing can be carried out on gametes and their precursor cells, or embryos in a fashion that has heritable (i.e. potentially transgenerational) effects. Heritable human genome editing is the subject of intense debate over its possible consequences for offspring and for society in general. Because it is associated with human reproduction, it evokes spiritual, religious or deeply personal issues for many. It is certain that there will significant differences in the policy directions taken by countries around the world regarding prohibition versus

permission (usually within a regulatory regime). Good governance must anticipate this and plan for these variations.

28. Heritable human genome editing, if approved for research and clinical applications, raises concerns with regard to fairness, social justice and non-discrimination, as well as potential disregard for the individual dignity of persons with disabilities. There is also the added complication of long-term follow-up over a longer timeframe than usual (and perhaps a lifetime and the next generation). Good governance must be particularly attentive to lessons from the past about how reproductive technologies have been used and abused at large scale, and whether those abuses would likely recur.

29. Technological alternatives to heritable human genome editing that allow both parents to have a genetically-related child are pre-implantation embryo testing (PGT-M/PGD), as well as prenatal testing followed by selective abortion. It is also possible to use donor gametes or embryos, although the genetic connection to one or both parents is not maintained. These alternatives are more or less acceptable to different individuals and different cultures. Adoption is a social alternative to heritable human genome editing. Good governance must make policy decisions about how much weight to give to the desire to have genetically related offspring and to whether the risks are tolerable in light of the available technological and social alternatives.

30. Good governance must pay attention to where the harms and benefits devolve. The prospective parents have the immediate benefit of satisfying their desire for a genetically related child while reducing the known risk of a serious disease or condition in the child. There is also a potential for harm to the prospective parents if their child is not as healthy (or perhaps worse off) than they would otherwise have been.[2] There are also potential benefits for the prospective new-born as they exist when they might not otherwise have been brought into existence. There are also potential harms from both unintended effects as well as potentially even having been brought into existence (such as in wrongful life cases). For the societies that surround the prospective parents and child there may also be harms (such as an added burden of care should the editing have undesirable affects) and benefits (such as removing the need for supporting a lifetime of care for child that would otherwise suffer from a serious genetic disease).

## 3.2 Special Challenge: *In Utero* Somatic Human Genome Editing

31. Editing of somatic cells of foetuses *in utero* has some potential benefits for children who would otherwise be born with systemic effects that cannot be properly addressed in postnatal somatic human genome editing. It may be medically justified when a disease has early onset and irreversible effects. *In utero* genome editing could be a middle ground between germline and somatic editing, provided that the *in utero* editing is not heritable. Little is currently known about the safety and efficacy of such procedures. Good governance needs to consider the possibility and acceptability of *in utero* somatic editing and ensure that permitted procedures are safe and effective.

[2] The Committee highlighted the importance of considering the background of spontaneous mutations and chromosome abnormalities that may have nothing to do with the editing.

## 3.3 Special Challenges: Human Epigenetic Editing

32. Human epigenetic editing offers the possibility of making usually short-term or reversible changes in gene expression, without impacting the sequence of the underlying DNA. While the editing components may act for only for a short time, depending on the gene being affected, this can have long term consequences. Because the DNA sequence is unchanged, there is little chance of gene or chromosome damage. Moreover, the epigenetic changes are unlikely to be heritable. As a result, the risk profile is different, but the possibility for using human epigenetic editing for "enhancement" is increased given that the risks would likely be lower and therefore more in proportion to the risks to the individual. Particularly if it were undetectable, human epigenetic editing will raise concerns about fairness and individual dignity, even if we tolerate all kinds of other biological and mechanical enhancements of our bodies. Good governance… [Text needed]

## 3.4 Special Challenges: Post-Natal Human Somatic Genome Editing

33. Many countries have existing regulations for somatic gene therapy, and these are generally considered to be adequate for methods that make use of genome editing in this context. However, while these may be sufficient to cover many aspects of a translational pathway, including those concerned with patient safety and efficacy, they may be insufficient with respect to details and they may not deal with broader issues of governance, including social justice, public engagement, and the range of possible applications.

34. 'Traditional' somatic gene therapy makes use of viral vectors to introduce additional copies of a gene encoding the missing gene product at random positions in the genome, hoping to provide enough gene product in the right place to give benefit. However, genome editing allows for much more precise targeted gene alterations, with several approaches currently being trialled or in preclinical research. These include:

a. Directly modifying one or more alleles of a gene in order to correct a genetic defect, with the advantage that the gene product will be regulated appropriately (e.g. correct the specific mutation in beta-globin leading to sickle cell disease; or promote exon skipping to give a slightly shorter version of Dystrophin, rather than a truncated non-functional protein, as a way to treat Duchenne Muscular Dystrophy).

b. Boosting the activity of another gene in order to give therapeutic benefit (e.g. for beta-thalassemia, increase fetal gamma-globin gene expression postnatally by deleting a repressor element from its regulatory region).

c. Inserting a functional copy of a gene in a 'safe harbour' site, which is an approach similar to traditional gene therapy, except the insertion is at a single site known to allow robust expression (e.g. for metabolic diseases).

d. Mutate the receptor for a virus to limit its propagation within the body (e.g. CCR5 for HIV).

It follows that the potential benefits are enormous, but in each case these need to be balanced by the potential risks. The latter could include incorrect on-target events, including unwanted insertions or deletions, chromosome damage, loss of heterozygosity (which could lead to inactivation of tumour suppressor genes), etc., as well as off-target events. When genome editing is carried out on single cells, such as a fertilised egg or a stem cell line from which single cells are expanded to give a clonally derived stem cell line, it is possible to test for such events, however, if the methods are being used on many millions of cells simultaneously, it will be very challenging to show that all are free of such potentially harmful events.

35. There are two general routes to somatic genome editing. The first, and one used the most to date in clinical trials, is ex vivo manipulation of cells, often stem cells such as those of the haematopoietic system (bone marrow), which are then reintroduced into the patient, with or without prior treatment to reduce endogenous (un-edited) stem cells. The second is in vivo somatic genome editing. These both have specific issues that are relevant to regulation and/or governance.

36. Ex vivo editing has the advantage in that it is theoretically possible (although challenging, as mentioned above), to verify that the cells only have the desired on-target alteration before the cells are introduced back into the patient. It also avoids issues about any immune response to the genome editing components. However, given the need for appropriate facilities and techniques to handle the cells in a clean and safe way while outside the body, it is a very expensive and labour-intensive route, which is currently possible to perform in only a small number of centres, most of which are in developed countries. Some of the first gene therapy protocols that have been licensed cost more than $500,000 per patient. Without considerable effort in capacity building and cost reduction, this makes the approach difficult to apply in countries which often have the greatest burden of genetic disease, such as sickle cell disease and beta-thalassemia.

37. Apart from a few potential treatments, where the target cells are in fairly accessible sites, such as the retina, skin or mucous membranes, and perhaps the liver, in vivo genome editing still has many technical challenges. These include how to introduce enough copies of the viral vector(s) carrying the genome editing components, preferably targeting only the desired cell type, in order to correct the genetic defect in a sufficient proportion of the cells to give clinical benefit, but in a way that does not lead to excess off-target or inappropriate on-target events, and does not lead to any adverse immune response to the genome editing components, including the viral vector. While there is a lot of promise, it will be critical to develop new reagents and methods, including ways to analyse the outcome in tissue taken from patient. There will be a need for a lot of preclinical research for each type of treatment. However, once developed and shown to be safe and clinically beneficial, and as long as methods are not too dependent on patient genotype, the costs of in vivo editing approaches should not be excessive.

38. There is also the potential for applications that go beyond therapy, e.g. forms of enhancement, such as for muscle mass or oxygen carrying capacity through boosting levels of erythropoietin (EPO), etc. Uses of the methods for non-serious conditions or for enhancement of body performance or features, should be discouraged because the potential benefits are at best marginal and cannot offset the risks, which are currently still uncertain.

39. In addition, because genome editing methods are often touted as being simple as well as accurate (even if neither are close to the truth for clinical applications), this opens up the possibility of abuse. This could include 'do-it-yourself' body hackers, or 'rogue' clinics offering direct to consumer treatments, with little chance of success. There are many clinics around the world, even some located within prestigious institutions, offering stem cell-based treatments, that have little basis in science, and no or minimal preclinical data, where there is little oversight or follow-up of patients. Some countries might even encourage such clinics as a source of revenue. These bad practices have led to patients being worse off or to them dying. They also lead to reputational damage for the field. Governance mechanisms for genome editing applications will need to discourage such clinics. Moreover, they need to ensure that jurisdictions do not succumb to pressure for compassionate use, except in the very clear cases, or to relax the usual requirements for clinical trials, oversight and follow-up of patients.

40. The financial and logistical obstacles for clinical use of somatic genome editing in low resource countries will require considerable attention. This will also need to be matched by efforts in public engagement and in ensuring appropriate ethical standards. It is critical to avoid past mistakes, such as exploiting the populations of such countries for data and resources, and instead to partner with them, including capacity building for infrastructure and expertise, to ensure maximum benefit and minimal harm.

## 3.5 Special Challenges: Enhancement

41. There is a substantial literature on the spectrum of human genome editing that includes curing or mitigating a life-threatening condition (treatment), preventing a disease (prevention), and enhancing an already typical and perfectly adequate capacity (enhancement). With heritable human genome editing, there is also the prospect of creating persons with or without certain traits– this could be the prevention of persons with so-called 'harmful' traits or the creation of persons with so-called 'beneficial' traits. Good governance needs to explicitly consider whether the use of genome editing technologies for enhancement purposes should be permitted.

42. With *in utero* and postnatal human somatic human genome editing, the harm-benefit balance to the individual for treatment, prevention and enhancement will vary. And, with human heritable genome editing, the harm-benefit balance to the potential future person, the prospective parents, and society for treatment, prevention and enhancement will also vary. Even in those instances where there is a favourable harm-benefit ratio, some governments may want to look more closely at societal concerns. The possibility that human genome editing interventions will be used for the enhancement of human traits is deeply controversial. The concern is that permitting such applications would aggravate social inequality. Governance decisions about the permissibility of using human genome editing for enhancement purposes therefore need to be subject to inclusive and transparent societal debate.

43. Societal concerns may differ, depending upon the context in which enhancement would be used, such as improving performance in sport, academic endeavours, or military, or space missions. Effective governance will need to be flexible enough to evaluate the proposed enhancements in different contexts. It will also need to consider and evaluate the possibility of enhanced individuals be they elite athletes or enhanced warriors changing careers. Governance

decisions about the permissibility of using human genome editing for enhancement purposes therefore need to take into account the dual-use dilemma.

# Part 4: Tools, Institutions and Processes for Human Genome Editing Governance

44. Governance of human genome editing will best be achieved by taking advantage of the full range of individuals and organizations able to influence or control the direction of the research and possible future applications. The best mix of these tools will depend on whether they are to be used for national and transnational governance, and, for the latter, upon the particular political system within a country. Similarly, identifying stakeholders in each context will depend on the roles played by national and regional governments, civil societies, professional and academic societies, research sponsors, insurers, payors, funders, and the general publics. What follows, then, is a description of many tools, institutions, and processes from which choices can be made.

## 4.1 Law: Declarations, Treaties, Conventions, Legislation and Regulations

45. Law governing human genome editing and related technologies can be created by a variety of mechanisms. Some of this law is broad and human genome editing simply comes to fall within its large scope, while in other cases law is created specifically for this technology.

46. For human genome editing, the most likely sources for international law will be declarations, treaties and conventions (often with a requirement for ratification at a national level by signatories). In this context, the stakeholders are usually state actors who negotiate terms of the agreements, albeit with each state actor subject to its own domestic political system. An example of this is the Council of Europe's Oviedo Convention, which prohibits any intervention aimed at modifying the genome of any descendent. International organizations are often aided by dedicated ethics and policy committees, such as UNESCO's International Bioethics Committee or the Council of Europe's Committee on Bioethics, which help to analyze technological developments and prepare positions for meetings on international agreements and international funding agencies. Their work on human genome editing complements other broad international instruments such as the Declaration of Nuremburg on research ethics and the World Medical Association's declarations of ethics and professional standards in care.

47. At the domestic level, legislation is a common tool, often supplemented by enforceable regulations or influential guidance, issued by an arm of government such as a ministry or department, in order to provide more detail on both substantive rules and procedural mechanisms. Examples include:

a. The Assisted Human Reproduction Act in Canada, which prohibits knowingly altering “the genome of a cell of a human being or *in vitro* embryos such that the alteration is capable of being transmitted to descendants";

b. In Algeria, Law 18-11 limits access to assisted reproduction to married couples unable to procreate naturally and prohibits the donation, or sale of gametes, embryos, or sperm, the collection of embryos for research, as well as prohibiting sex selection or human cloning;

c. In the U.S. general legislation governing FDA marketing of certain biological products is supplemented by guidance that sets out special screening rules to prevent spread of infectious disease when using donated gametes in assisted reproduction; and

d. In China, He Jiankui, who performed the first known human embryo edits resulting in live births, was prosecuted under the Criminal Laws of the Chinese People's Republic Code.[3]

48. Domestic legislation may also have indirect impacts on good governance of human genome editing. For example, South Africa's 'Choice on Termination of Pregnancy Act' (CTOPA) is about the right to obtain an abortion, but has implications for any debate surrounding heritable human genome editing, which may in practice rely on availability of abortion as a safeguard in the event of adverse effects on the developing embryo and foetus. Similarly, developing or testing the technology for germline or heritable genome editing depends on creating embryos for research. This is actively permitted in very few countries and is actively prohibited in many more.

49. Regulations can add detail to both substantive rules and procedural mechanisms of their authorizing legislation. For example:

a. In Egypt, the Professional Ethics Regulations of the Egyptian Medical Syndicate covers assisted reproduction and specified that sperm, egg and embryo donations are not permitted, that gestational surrogacy is illegal, prohibits the creation of egg, sperm, or embryo banks, and bans the trade in human embryos;

b. In Japan in 2019 regulations on gene therapy were revised to address genome editing, explicitly prohibiting germline modification;

c. In Turkey, updated regulations on assisted reproduction therapeutic applications and assisted reproduction therapy centers were adopted in March 2010. They clarify the rules of access and use of infertility treatments, for stipulating that "only married couples that cannot have a child in natural ways, can benefit from the services of assisted reproduction. The use of eggs, sperms, and embryos out of the married couples is banned and the utilization of donors is prohibited. The new regulation also stipulated that the storage of the reproductive cells is prohibited with some exceptions in strict cases of medical obligations"; and

[3] The Committee recalled that He Jiankui was convicted of "illegal medical practices", rather than a specific offence involving human genome editing.

d. In the United Kingdom, the Human Fertilisation and Embryology Authority was created pursuant to acts of Parliament, and it details permissible and impermissible forms of embryo research and assisted reproduction, as well as approving personnel and facilities for this work.

50. Legislation and regulation are subject to public control via mechanisms such as testifying at legislative and regulatory rulemaking hearings, lobbying by interest groups, commenting on proposed rules, bringing judicial challenges to unwanted policies, and elections. The strength of public control varies according to the particulars of the political system and the power of its various interest groups as well as the voting public. In Italy, for example, street demonstrations by patients and members of the public demanding access to stem cell therapy led the government to fund clinical trials of an unproven, prohibited intervention. The policy was then reversed following a focused campaign by physicians and scientists concerned about its safety. The promoter of the intervention was later criminally prosecuted for continued actions taken to evade the prohibition.

51. In many countries, advisory committees play an important role in formulating law and regulating of life sciences technologies. Examples include in Saudi Arabia, the Standing Committee for Research Ethics on Living Creatures, in France the Consultative Committee on the Ethics of Health and Life Sciences, in Germany, the Ethics Council, in Argentina the National Committee of Ethics in Science and Technology, in the UK the Nuffield Council on Bioethics, and many more. Their functions vary, depending upon the branch of government they are tasked with advising, the degree of public participation in their deliberations, the methods for selecting members, and the scope of life sciences research and clinical care within their remits. They provide an important source of extended deliberation, often accompanied by publications laying out evidence-based analyses of a technology's current and expected future capabilities and their probable effect on individuals and society at large. In some cases, they make recommendations for laws and regulations, which have varying degrees of force on governmental bodies.

## 4.2 Judicial rulings

52. At times, law can be developed by courts, in their role as interpreters of constitutional guarantees or legislative language, or more indirectly by virtue of setting precedents in their decisions on individual criminal and civil cases. For example, in the immediate aftermath of the He Jiankui debacle, some observers attributed the reckless experiment to a regulatory vacuum in the People's Republic of China. Others pointed to administrative regulations and ethical norms that, in their view, clearly prohibited this kind of experimentation. The 2003 "Ethical Principles for Human Assisted Reproductive Technology and Human Sperm Bank," for example, makes explicit reference to the principle of protecting future generations and stipulates that "[i]f there is evidence that the implementation of human assisted reproductive technology will cause serious physical, psychological, and social harms to future generations, medical professionals have an obligation not to implement the technology." But it is not clear whether this document played a role in the decision of the Chinese court. In December 2019, the Nanshan District People's Court in Shenzhen found that He and two others were guilty of "deliberate violence of China's relevant regulations and medical ethics" and of violating Article 336 of the Criminal Laws of the

Chinese People's Republic Code, which prohibits engaging in medical activities without a license.

53. Civil cases concerning dispositional authority over gametes and embryos have been brought in many countries, often between former spouses or by survivors, where the deceased has left unused reproductive materials. Genome editing of human gametes or human embryos would, with current technology, probably take place outside the body and be affected by these rulings.

54. Civil cases can also be brought to assert malpractice, as in a number of countries when genetic screening or counseling was done negligently. Malpractice is understood as falling below the generally accepted level of care, which is measured by general practice among similarly situated providers, compliance with legislative and regulatory standards, and conformity with guidelines offered by professional societies.

55. While in these cases the immediate stakeholders are only those who are party to the litigation, the precedents set by decisions in their cases can serve to solidify consensus concerning a standard of practice, which in turn may affect the availability and affordability of liability insurance, and this directly impact on decision-making. Because insurers engage in risk assessment to determine coverage, they not only reflect the standard of practice but also help to enforce it, by making it more difficult for non-conforming practitioners to offer services and by influencing coverage by private and public health care and insurance services.

## 4.3 Ministerial decrees

56. In 2019, Russian geneticist Denis Rebrikov made a series of public statements about his plan to follow in He Jiankui's footsteps and to attempt the use of heritable genome editing to provide resistance to HIV infection in resulting children. Specifically, Rebrikov announced that he planned to enrol couples where the female partner was HIV positive and the offspring were at risk of vertical transmission of HIV. (He Jiankui's experiment involved couples where the male partner was HIV positive, offering potential sperm washing.) When Rebrikov was unable to identify willing research participants he said he would look at other targets and named "dwarfism, deafness, or blindness" as possible alternatives. In October, the Ministry of Health of the Russian Federation noted that the use of germ cells and embryos is regulated by a 2012 Ministerial decree that lists contraindications and restrictions on the use of assisted reproductive technologies. The Ministry also announced that heritable genome editing research was premature and that it would then not approve Rebrikov's plans.

## 4.4 Conditions on Research Funding

57. Human genome editing is funded from both private and public sources, and one powerful source of governance comes from decisions about priority setting and funding rules. Particularly in the public sphere, decisions about funding priorities can speed or slow development of whole areas of basic science or pre-clinical and clinical research. Priorities may be set to reflect unmet need in the population, to reflect areas of anticipated progress toward difficult problems, or simply to reflect the interests of individual members of the government or lobbyists. Funding

may be denied, reflecting a dominant or particularly powerful viewpoint. In many countries public funding of research using human embryos is prohibited.

58. Rules governing the funding of private and public research may impose a range of conditions that function as a governance tool. Among them are rules concerning provenance of the gametes or embryos (especially with respect to payment to and consent from the providers); limits on the degree of development or length of time an embryo or embryo model[4] may be maintained in vitro; rules concerning creation of chimeric or hybrid embryos; rules concerning ownership of, and dispositional authority over, the gametes and embryos; and rules about intellectual property ownership as well as data and materials sharing. Depending on the availability of alternative resources, a single large-scale national funder may effectively govern almost the entire field of research within the country.

59. Funding for pre-clinical and clinical research phases in human genome editing will be subject to general research rules adopted by many countries. They tend to focus on ensuring independent review of risks and possible benefits to society and most particularly to individuals enrolled in the clinical trial; informed consent (on the part of persons with decision-making capacity); and monitoring for adverse events. Human somatic genome editing clinical trials are still very new, and assessment of risks - necessary both for informing potential research participants and for drafting inclusion or exclusion criteria - may be difficult for the immediate future.

60. Many countries ensure independent review of protocols by creating local research ethics oversight boards, but with human genome editing both relatively new and rapidly evolving, some discussion has arisen about the need to create centralized research ethics review bodies with deeper expertise in the science, or centralized fora for exchange of information and debate about possible uses. In the past, the Recombinant DNA Advisory Committee in the US performed both these functions, for federally funded work and, when asked, for all other recombinant DNA clinical trials as well. The UK has both regional ethics committees and centralised specialised review bodies, such as the Medicines and Healthcare products Regulatory Agency and the Human Fertilisation and Embryology Authority. These bodies then either have, or can co-opt, the necessary expertise.

## 4.5 Moratoria

61. Moratoria on one or more aspects of human genome editing have been the subject of significant discussion, most especially with respect to heritable human genome editing. By definition, a moratorium is a temporary prohibition of an activity. To be effective, it requires either voluntary compliance by all relevant actors or some form of external discipline, such as governmental regulation with enforcement powers. It is improved by clear articulation of the reasons for the temporary prohibition and specific milestones that must be reached for the moratorium to be partially or fully lifted.

[4] Embryo model refers to what some call synthetic embryos

62. Currently, there is a moratorium on human genome editing in the Council of Europe Convention on Human Rights and Biomedicine (the Oviedo Convention). This binding international treaty, ratified by 29 nations, stipulates in Chapter IV – Human genome Article 13 – Interventions on the human genome: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is *not to introduce any modification in the genome of any descendants*." (italics added)

63. For those countries that are not party to the Oviedo Convention, the possibility of a moratorium on heritable human genome editing has been discussed largely as a voluntary time-limited mechanism to provide time for informed public discussion and decision-making about a range of individual and societal issues.

64. In practice, regulatory systems in which heritable human genome editing is legal but only permitted after meeting specific conditions is functionally similar to a moratorium. Until the conditions can be met, heritable editing remains impermissible, and subject to civil (and in some cases, criminal) penalties. But the very fact of having conditions that might be met is sometimes viewed as signalling an expectation that research on heritable human genome editing will someday fulfil these criteria. By contrast, calls for a moratorium generally take either an open view or imply that research will never be sufficient to meet conditions. In some cases, calls for such a moratorium include a ban on basic research making removing the possibility of ever meeting such conditions.

## 4.6 Accreditation, registration or licensing

65. In addition to regulating what can be done with human genome editing, governance can focus on who may do it, where it may take place, and how it will be monitored. An example of this in the general medical sphere is the common approach to licensing medical practitioners, who are required to undergo training and demonstrate competence before being allowed to treat patients. Similarly, facilities may be required to meet conditions for staffing, hygiene and manufacturing practices. In the realm of assisted reproduction, the UK's Human Embryo and Fertilisation Authority imposes conditions in this way, allowing it very close control over who may perform procedures and where. Monitoring is facilitated by requiring registration of persons and facilities providing a service, so that inspections may take place.

66. Such an effort already exists for clinical trials, where national and regional registries are indexed by the World Health Organization's International Clinical Trials Registry Platform. In the context of human genome editing, the WHO Registry, discussed in more detail in (link to report needed), will make it possible to track and inquire about research involving human genome editing.

## 4.7 Professional self-regulation

67. In the absence of government regulation, or as a supplement to government regulation, professional societies can establish their own guidelines on human genome editing, as well as requisite credentialing and best practices for facilities management, recruitment of research participants and treatment of patients. Professional guidelines can be an important tool when

formal policy found in legislation, regulation or judicial decisions does not address potential uses of a technology or require additional detail. Professional self-regulation can be done by guideline committees made up entirely by those actively pursuing research and patient care, or it can be done with committees that invite others to participate, including social scientists, ethicists, lawyers and clergy. It may also include representatives of interest groups, such as disease-oriented groups, and of civil society organizations. The quality of professional self-regulation and the degree of public confidence in their contribution to good governance is enhanced by these broader consultations.

68. Professional guidelines may also become a useful resource or reference point if lawmakers undertake the task of drafting legislation and regulations. This has been the case, for example, in the field of stem cell therapy, in which guidelines produced by the U.S. National Academies of Sciences, Engineering and Medicine committee and the International Society for Stem Cell Research became a powerful influence on the legal conditions later developed for federal funding of this research in the United States.

69. Because the process of amending professional guidelines can be less onerous than the processes for amending legislation and regulations, professional self-regulation, like other forms of 'soft-law', can also serve to keep best practices up to date with a rapidly evolving area of science. However, there is a potential conflict of interest as the same groups within society setting the best practices are those with a vested interest in pursuing the research.

70. Different from professional self-regulation but still within the realm of professional self-reflection are the various national science and medicine societies. These serve both as honorific societies and, for many, as a center for evidence-based analysis of technologies and development of recommendations for funding and regulation. They can also serve as organizers of public events aimed at bringing greater attention to a technology and to helping the field maintain a dense network of professional connections and to developing norms for ethical uses. Prominent examples in the field of human genome editing include:

a. The collaboration between the Chinese Academy of Sciences, the Academy of Science of Hong Kong, the UK Royal Society and the US National Academies of Medicine and of Science, to host international summits in 2015 and 2018, both primarily composed of scientific presentations but with dedicated sessions on ethics and societal impacts;

b. The Association for Responsible Research and Innovation in Genome Editing (ARRIGE), which is open to a broad membership beyond scientists and health professionals, and which hosts active on-line information exchange and face-to-face meetings; and

c. The Science Council of Japan's recommendation on Genome Editing Technology in Medical Sciences and Clinical Applications in Japan.

## 4.8 Research Ethics Guidelines

71. Complementary to government regulation and professional self-regulation, existing ethics systems can play an important role in the good governance of human genome editing. This can involve both operational guidelines to help shape good practice and associated review bodies designed to ensure that good practices are implemented in research design and execution.

72. As with professional self-regulation, ethics guidelines may be more readily amended than government legislation and regulation helping to keep pace with relevant technical and sociological developments.

73. Research ethics efforts can be institutional or national but they can also be international. They can address a broad range of issues or focus in on a specific topic. For example, the proposed Global Observatory for gene editing that would: act as a clearing house for ethical and policy response; track and analyse significant conceptual developments, tensions and emerging areas of consensus; and serve as a vehicle for convening periodic meetings, and seeding international discussion informed by insights drawn from data collection and analysis.

## 4.9 Collaboration with Publishers and Conference Organizers

74. Journal editors have the ability to influence ethical norms by choosing to make compliance with applicable law and professional standards a condition of publication. This practice has already been adopted by leading journals with respect to clinical trial registrations aimed at protecting research participants, and authors typically must provide documentation of compliance, pursuant to recommendations from the International Committee of Medical Journal Editors. It is also one of the means used to address concerns about papers that present "dual-use" dilemmas, that is, where the science of human genome editing may raise concerns about biosafety and biosecurity.

75. The degree of control journal editors can offer, however, has diminished somewhat in recent years by the increasingly frequent phenomenon of publication on early release pre-print platforms like bioRxiv and, even more problematic, publication by press release. There are, however, indications that some pre-print servers are increasingly carrying out ethics checks on materials they host. There are also external efforts to address these issues, such as PubPeer and retraction watch.

76. For human genome editing, requiring documentation of compliance with applicable laws and regulations and with any accepted professional standards would deter noncompliant research by scientists interested in recognition from peers. Similarly, conference organizers could insist on evidence of compliance before accepting abstracts for poster sessions and presentations.

## 4.10 Education and Training of Researchers and Clinician-Scientists

77. Ethics education and training is already a part of the medical school curriculum in most countries, but its content and intensity vary widely. For graduate training in fields for which human genome editing is becoming a commonly used tool, and for medical specialties that may

eventually use human genome editing, adding modules on research integrity and ethics relevant to human genome editing is a means to encourage a culture of responsibility and to create a shared, global norms concerning contested uses, such as heritable modifications, aesthetic enhancement or use in the context of competitive sports. Modules might include information on varying national policies, history of genetics research and engineering, updates on gene transfer / gene therapy, and a survey of relevant areas of philosophy, law, sociology and other science-technology studies. This would supplement, not supplant, basic training in the ethics of clinical trials and clinical care, and the safe conduct of basic science research.

### 4.11 Interest Groups and Public Influencers

78. While it is common to refer to "the" public and its role in setting policy, there are many different publics, a number of which are represented through organized interest groups. In the field of genetics and in some countries, civil society groups have sprung up to collect information and express viewpoints, whether through publications, organizing lobbying campaigns, or developing teaching materials. These groups span the range of ideology and perspectives on human genome editing and have had an effect on the construction of public debate. Other interest groups organize on the basis of common experience of a particular disease that might be amenable to treatment or prevention with human genome editing, or around religious, spiritual or historical identities associated with particular value systems that support or resist some applications of human genome editing. Funding for these groups also varies, in some cases coming from those funding or pursuing the research, in other cases from philanthropic sources, and sometimes from popular campaigns.

79. As well, there are interest groups made up of futurists, transhumanists, artists or philanthropists, each with some capacity for entering the general public debate and the governmental policymaking arena in order to express views on whether and how this technology should be developed. Influencing public attitudes, though often without the intent to explicitly engage in policy debate, are the creative artists such as science fiction writers, in books and screenplays, who find in the possible applications of genetic technologies a rich backdrop for developing stories about the transformations they may cause in the fabric of social life. Dystopian films such as Gattaca and Jurassic Park, and more bio-optimistic science fiction such as Star Trek, can have a profound influence on the wider public's instinctive reaction to news of new technological developments and possible applications of human genome editing.

## Part 5: Scenarios

80. These scenarios are intended to demonstrate how the various elements discussed in this governance framework come together in practice. They illustrate the types of practical challenges that might be encountered when implementing good governance for human genome editing.

81. Each scenario explores a different facet of the governance puzzle. It begins with a short narrative description of a possible future event. Relevant components from the governance framework are then identified, including the values, principles and goals discussed in Part 3, as

well as the questions to be considered (Annex). There follows a discussion on possible actions to be taken using the tools, institutions and processes discussed in Part 4.

## 5.1 Scenario 1: Clinical Trials Involving Somatic Human Genome Editing for Sickle Cell Disease

82. Scenario:

> *An international research team wants to begin a clinical trial of somatic human genome editing to treat sickle cell disease. Because the condition is most prevalent in West Africa, the team proposes to do the research there. Due to resource limitations, patients in West Africa generally only receive the standard hydroxyurea therapy when available and often are not supported and managed through specialist clinics as would be the case in other parts of the world. If the somatic human genome editing for sickle cell disease is successful, and safe and effective therapies become available, it is expected that these will be affordable primarily in wealthier countries and too expensive for all but the wealthiest individuals in the country where the research will be conducted.*

83. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in the Annex to this report. (Table 1)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, Transparency and Accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *Is clinical research on somatic human genome editing permitted in the host country?* |
| | *Are there laws/regulations that permit or prohibit enrolling citizens in research with little prospect of yielding a therapy that will be financially accessible to them?*<br>*How might the answers to these questions differ if there was a commitment on the part of the foreign research team to promote capacity building and benefit sharing?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *Will there be public opinion polling, public education, public engagement, or efforts at public empowerment in relation to the proposed research?* |
| | *Will there be an opportunity for the public to influence decision-making about the permissibility of the proposed research involving somatic human genome editing, and if so, in what manner?* |
| | *If the research is permissible, will there be an opportunity for the public to contribute to priority setting, and if so, in what manner?* |
| | *If the research is permissible, will the public have an ongoing opportunity to revisit domestic policy on funding, permissibility and conditions of somatic human genome editing, and if so, in* |

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| | *what manner?*<br>*Should patients with sickle cell disease and patient groups that represent their interests be provided with discrete opportunities to inform the research agenda or not?* |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *What mechanism is in place to ensure the use of good scientific practices?* |
| | *If the research is not permitted, what are the penalties (civil, criminal) for undertaking such research and how will violations be identified; for example, are there mechanisms to allow individuals or institutions to report violations?* |
| | *If the research is permitted, is this within an existing regulatory framework for research involving humans or an independent regulatory framework specific to human genome editing?* |
| | *If the research is permitted, is there adequate capacity to manage the technical review of the research proposals and to follow-up on results?* |
| | *If developing a new regulatory framework, how will this coordinate with other domestic regulatory bodies?* |
| | *If the permitted research is a randomized controlled trial, will the control arm be best available therapy (YY) or "locally" available therapy (XX)?* |
| | *How will long term follow-up be managed?* |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | *What are the opportunity costs associated with the investment of time and personnel in this research as compared with other research that might yield affordable therapies?* |
| | |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *If the proposed research is permitted, and local capacity to initiate and run a clinical trial is limited, what conditions should the government impose regarding capacity building for local health professionals and research oversight systems?* |
| | *What conditions should the government impose to ensure future access to safe and effective somatic human genome editing therapy?* |
| | *What remedies exist in case of injury to research participants?* |
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be | *What support should be provided to local organizations to promote capacity building and benefit sharing?* |

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| made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | *Is there adequate provision of genetic counselling?*<br><br>*Are there regulations in place about rights to privacy? With respect to anonymity, will the wishes of patients undergoing the clinical research be respected?* |

**TABLE 1: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on clinical trials of somatic human genome editing.**

84. Possible actions that might be taken as a result could include:

a. Permit research only if the control arm includes the standard hydroxyurea therapy (despite it being unavailable to many in the country) along with specialized care;

b. Approve the research only if it includes a wraparound component allowing those in control arm to obtain the investigational therapy if it is proven safe and effective;

c. Approve research if it includes an obligation for the sponsor to train and equip local specialists who will remain in the country once research is concluded;

d. Invoke the TRIPS agreement or negotiate with the research sponsor, and permit in-country research in exchange for free or discounted access to any patented materials and for financial assistance to provide the therapy if/once approved; and

e. If the therapy looks promising, conduct an economic assessment of long-term costs and savings, and adjust domestic budget priorities or obtain financial assistance from international finance organizations to cover short term costs that permit long-term savings.

## 5.2 Scenario 2: Clinical Trials Involving Somatic Human Genome Editing Research for Huntington's Disease

85. Scenario:

*Researchers are interested in somatic human genome editing as a possible future treatment for Huntington's Disease, a late on-set condition. Because it would take years to determine if an edit was successful in slowing or preventing onset, the researchers propose using surrogate markers as endpoints. A clinical trial's endpoints measure the outcomes in the trial. Clinical outcomes directly measure whether people in a trial feel or function better, or live longer. The benefit or likely benefit of a therapy, as measured by clinical outcomes (e.g., improvement in symptoms), is assessed to determine whether it outweighs any adverse effects. Surrogate endpoints may be used instead of clinical outcomes in some clinical trials. For example, surrogate endpoints are used when the clinical outcomes, like determining whether a disease that strikes late in life has been prevented or delayed, might take a very long time to study. Surrogate endpoints may be molecular, histologic, radiographic, or physiologic biomarkers that are expected to correlate with longer-term clinical outcomes.*

86. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in Annex to this report. (Table 2)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *Should clinical research on somatic human genome editing be permitted for late onset conditions?* |
| | *How will the surrogate markers be determined, and how might this be driven by commercial interests?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *Will there be public opinion polling, public education, public engagement, or efforts at public empowerment in relation to the proposed research?* |
| | *Will there be an opportunity for the public to influence decision-making about the permissibility of the proposed research involving somatic human genome editing, and if so, in what manner?*<br>*If the research is permissible, will there be an opportunity for the public to contribute to priority setting, and if so, in what manner?*<br>*If the research is permissible, will the public have an ongoing opportunity to revisit domestic policy on funding, permissibility and conditions of somatic human genome editing, and if so, in what* |

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| | *manner?*<br>*Should patients with Huntington's disease and patient groups that represent their interests be provided with discrete opportunities to inform the research agenda or not?* |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *What mechanism is in place to ensure the use of good scientific practices?* |
| | *If the research is permitted, does the regulatory system have the capacity for long-term follow-up of research participants, and will this obligation rest with the research team, the research sponsors, the government or some other entity?* |
| | *If the research is permitted, what means are available to ensure research participants continue to be available for study while not interfering with their personal autonomy?* |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | *If the research is permitted, who will pay for pre-symptomatic testing to determine eligibility for research participation? The prospective research participant, public or private health care plans, or the research sponsor?* |
| | *Until the surrogate endpoints have been confirmed to predict clinical outcomes, the intervention is still research. Should research participants have to share the cost of the somatic human genome editing?* |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *Should research priority be given to early onset conditions?* |
| | *Should research priority be given to lethal conditions regardless of the age of onset?* |

| | |
|---|---|
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | *What support should be provided to local organizations to promote capacity building and benefit sharing?* |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | *Is there adequate provision of genetic counselling?* |

**TABLE 2: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on somatic human genome editing.**

87. Possible actions that might be taken as a result could include:

a. Developing a plan for long-term follow-up to validate the surrogate endpoints by confirming their predictive value with respect to clinical outcomes, and ensure there are financial resources sufficient to support the plan for the years or decades needed;

b. Fostering collaboration in research participant recruitment, protocols, data sharing and interim data analysis among patient groups, private and public research sponsors, private and public clinical care insurers, researchers and clinicians in order to get broadest possible view of the value of the surrogate endpoints;

c. Taking particular care in understanding the family culture in each research site because Huntington's is a familial disease, and arranging to provide counseling as needed on topics such as information sharing within families, reproductive planning and mental health care; and

d. Ensuring local review boards and regulators have the capacity to monitor the research and to identify points at which it should be stopped (due to adverse effects or lack of efficacy) or should be moved out of research and into clinical care.

## 5.3 Scenario 3: Somatic Human Genome Editing and Unscrupulous Entrepreneurs and Clinics

88. Scenario:

*Somatic human genome editing has entered clinical trials for a limited number of diseases. Advertisements have sprung up on the internet for clinics offering somatic genome editing 'therapies' for a number of conditions.*

90. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in Annex to this report. (Table 3)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *How will results and data from the clinic be made available to others and in a form that allows detailed scrutiny?* |
| | *How much awareness is there among consumers of medical evidence for human genome editing?* |
| | *How will compliance with laws, regulations or guidelines be assessed?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *Does the country where the clinics operate have the means to prevent false or misleading advertising?* |
| | *Are there rules stopping clinics from offering somatic human genome editing "therapies" when the technology has not been proven safe and effective?* |
| | *If the clinics are not in the country, what enforcement mechanisms exist to stop nationals from travelling to purchase unproven, potentially harmful interventions?* |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *What mechanism is in place to ensure the use of good scientific practices?* |
| | *What measures are in place to pre-empt the exploitation of vulnerable patients?* |
| | *Who will pay for experimental treatments? Will this be the clinic (desirable)?* |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources— | *What rules are in place to shutter fraudulent businesses?* |
| | |

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| financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *Is there a need for bilateral agreements to protect patients from charlatans encouraging medical travel?* |
| | |
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | *Are there regulations in place about rights to privacy?* |
| | *With respect to anonymity, will the wishes of patients undergoing the clinical be respected?* |

**TABLE 3: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on clinical care of somatic human genome editing.**

91. Possible actions that might be taken as a result could include:

a. Determining if there are formal or informal mechanisms to control domestic exposure to the internet advertisements, whether through regulatory authorities or by voluntary action of the platforms;

b. With assistance from the medical and research communities, developing accurate information about the current state of the field and the effectiveness/safety of various interventions, and posting the information in ways most likely to reach those who need it, whether by programming platforms to provide this information alongside any advertisements for unapproved therapies or by collaborating with patient groups to distribute to members of otherwise;

c. Considering use of consumer protection laws or medical therapy development laws to discipline advertisers of unproven therapies;

d. Working with medical licensing authorities, clinic licensing authorities and professional societies to discipline professionals and entities offering unapproved therapies; and

e. Establishing independent efforts to identify unscrupulous entrepreneurs and clinics, such as the bloggers working in the field of stem cells.

## 5.4 Scenario 4: Enhancement to Improve Athletic Ability

92. Scenario:

*Athletes have been showing interest in use of somatic human genome editing to increase muscle strength.*

93. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in the Annex to this report. (Table 4)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *The World Anti-Doping Agency prohibits gene and cell doping. Is this a relevant consideration?* |
| | *Do international sporting organizations (such as the International Olympic Committee, and the International Paralympic Committee) also prohibit gene and cell doping? Is this a relevant consideration?* |
| | *Does the country have a formal national position on the use of various methods to attain competitive advantage in sports, such as high-altitude training, nutritional supplements, advanced equipment and materials, or pharmaceutical aids? If so, does somatic human* |

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| | *genome editing fit within this scheme?* |
| | *What information is provided to the other athletes in the competition, to the judge, and to the public?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *Anti-doping rules are motivated in part by concern for the health and well-being of athletes. How might efforts at enhancement harm athletes? In particular, how might they harm athletes who are under the age of majority?* |
| | *If gene and cell doping is, or will be, permitted, how might this harm competitive sport? How might it harm amateur sport?* |
| | |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *What mechanism is in place to ensure the use of good scientific practices?* |
| | *Is there an appropriate mechanism for carrying out a risk/benefit analysis?* |
| | *What is known about the potential harmful effects of somatic human genome editing for enhancement, and do these potential harms include the risk of inadvertent germline genome editing?* |
| | *Is there provision of genetic counselling?* |
| | *What information is provided to the athlete to enable informed consent?* |
| | *How is any increase of performances provided by the treatment being measured?* |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | *"Available resources" include – time, money and personnel. Should somatic human genome editing for the purpose of enhancement in sport take precedence over the need to invest time, money and personnel to develop therapies for patients? Are there any conditions under which this would be considered a "wise" investment of available resources?* |
| | |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *If somatic human genome editing to increase muscle strength is not, or will not be, permitted, will it be possible to detect it at all, and if so, how might this be done without unduly invading the privacy or civil rights of athletes?* |
| | *If somatic human genome editing to increase muscle strength is (or will be) permitted, how will equitable access be assured?* |
| | *If somatic human genome editing to increase muscle strength is (or will be) permitted, how will it be possible to protect athletes from subtle (or overt) coercion to avail themselves of enhancements they do not want?* |

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| | *Who should pay for the treatment? Are there opportunities to raise revenue to support other uses of somatic human genome editing?* |
| | *Could 'enhancement' become mandatory to ensure fairness among athletes? Who would make such a decision?* |
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | *If somatic human genome editing to increase muscle strength is (or will be) permitted, and there is inequitable access how will this not further exacerbate economic inequality (by providing inequitable access to the economic benefits of success in sport)?* |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | *Are there regulations in place about rights to privacy?* |
| | *With respect to anonymity, will the wishes of patients undergoing the clinical be respected?* |

**TABLE 4: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on enhancement.**

94. Possible actions that might be taken as a result could include:

a. Working with domestic and international sports organizations (amateur and professional) to develop a policy on whether such editing would be disqualifying in the various athletic competition contexts;

b. Working with sports medicine professional societies to ensure accurate understanding of benefits and risks of such editing, and encouraging societies to include statements about the wisdom of such use in its public documents and practitioner educational materials;

c. Working with insurers on a policy regarding coverage for elective editing interventions and any adverse events they may cause; and

d. Working with schools and universities on policies for athletic scholarships and participation that address whether such editing is ever acceptable.

## 5.5 Scenario 5: International Considerations: Expanding Assisted Reproduction Services

95. Scenario:

*A clinic outside the country has been advertising heritable human genome editing to "rescue" embryos that would go unused following IVF and PGD.*

96. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in the Annex this report. (Table 5)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *In countries where research involving heritable human genome editing is prohibited, may a research team evade this prohibition by advertising and recruiting research participants within the country, but conducting the research outside the country, in a jurisdiction where (i) this research is permitted, (ii) the research is also prohibited but there is no oversight (or only lax oversight)or (iii) where the law is silent?* |
| | *If heritable genome editing research is prohibited, is this for practical, technical, financial, ethical, societal or other reasons? And are these reasons known and endorsed by the public?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *What obligations does a country have to ensure that members of their research community do not exploit vulnerable persons who might be enticed to travel abroad to access research that is prohibited at home?* |
| | *Have religious perspectives been canvassed?* |
| | *Have indigenous groups been consulted?* |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential | |
| | *What assessment will be used to ensure the benefits are greater than unintended effects?* |
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| benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | *If people go outside their country to participate in heritable human genome editing research (which is a prohibited intervention in their country), what effect (if any) should this have on their eligibility for private or publicly funded health care if the offspring shows any adverse effects?* |
| | *How much time, talent and treasure should be spent on developing heritable human genome editing to change the traits of future people when there are people living among us who might better benefit from somatic human genome editing?* |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *Who will pay? Would it be a government, health insurer or the patient?* |
| | *Are there domestic rules in place regarding residents who go to another country to receive somatic human genome editing applications that would be illegal in their home country? If so, what are they? If not, are there plans to develop any?* |
| | *Are there plans to welcome or to discourage people from other countries to travel to access somatic human genome editing clinical trials or therapies?* |
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | *Does the proposed research fit with (support) national research priorities?* |
| | *Is the research to be privately or publicly-funded? If privately funded what measures can be put in place to ensure equitable access to the fruits of research?* |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons | *How will the interests of future generations be taken into account?* |
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| while satisfying the needs and desires of those today. | |

**TABLE 5: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on international considerations.**

97. Assuming such editing is not permitted domestically, possible actions that might be taken as a result could include:

a. Investigating whether there are means to prohibit such advertising within the country:

b. If the embryos are currently held in a domestic laboratory, clarifying border control rules governing export of biological materials (to the country where editing would take place) and import of biological materials (when shipping embryos back). (Note - if the prospective mother has the editing embryo transferred to her while she is out of the country, the import controls will not be relevant);

c. Working with authorities in the country where the editing would take place to determine if such action is, or should, be permitted there, and if it is, whether it is permitted to offer the service to people outside the country (i.e., whether this may now become an editing "haven" that attracts people from many other countries);

d. If needed, clarifying kinship and citizenship rules to ensure that regardless of permissibility, no child will be legally disadvantaged solely because of the editing done at the embryonic stage;

e. Consulting with professional societies on best means of long-term monitoring the health of any resulting children; and

f. Evaluating the potential for, and likely impact of, the development of a assisted reproductive services industry.

## 5.6 Scenario 6: Heritable Human Genome Editing

98. Scenario:

*A maverick researcher proposes using heritable human genome editing to alter traits such as sexual orientation, stereotypically "racial" features, and personality or cognition. The research will progress through preclinical and clinical research phases in embryos prior to any attempt to try this with people already born.*

99. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in the Annex to this report. (Table 6)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability** | *Are there any rules that affect funding or* |

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|---|---|
| A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *permissibility of this research?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | *If heritable human genome editing is permitted, what restrictions would apply if it were attempted on people now alive?*<br>*Have religious perspectives been canvassed?*<br>*Have indigenous groups been consulted?* |
| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *What mechanism is in place to ensure the use of good scientific practices?* |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | |
| **Fairness**<br><br>A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | |

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| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | *Does the proposed research fit with (support) national research priorities?*<br><br>*Is the research to be privately or publicly-funded? If privately funded what measures can be put in place to ensure equitable access to the fruits of research?* |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | |

**TABLE 6: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on heritable human genome editing.**

100. DISCUSSION OF POSSIBLE ACTIONS THROUGH TOOLS, INSTITUTIONS, AND PROCESSES – Text Needed

## 5.7 Scenario 7: In Utero Somatic Human Genome Editing

101. Scenario:

> *A research team wishes to try prenatal (in utero) somatic human genome editing for cystic fibrosis, in order to forestall the systemic effects of the disease, but diagnosis and editing could not take place until well into the second trimester.*

102. The scenario highlights the central role of the values, principles and goals identified in Box 4, as well as illustrative questions to be considered when developing governance measures, based on those detailed in the Annex to this report. (Table 7)

| Values, principles and goals | Questions to be considered when developing governance measures |
|---|---|
| **Clarity, transparency and accountability**<br><br>A commitment to share accurate, evidence-informed, accessible and timely information about the relevant science (including sources of funding, access and outcomes), guiding ethical principles, and proposed or approved policies for human genome editing so that individuals, organizations, nations and publics may hold each other to account. | *Is in utero therapy currently available? If so, under what regulatory or professional society regime?* |
| | *What rules apply to abortion in the second trimester, and would those rules permit abortion if an attempt at heritable human genome injured the fetus in a manner that would affect the length or quality of life for the child?* |
| | *What are the rules about the decision-making role of the genetic father of a fetus? Of the intended rearing partner? Are these rules clear with respect to the decision-making role of non-marital partners, who may or may not be the same sex as the pregnant person?* |
| **Inclusiveness, solidarity, and the common good**<br><br>A commitment to draw on the full contributions of all parts of global society, and to consider diverse points of view, different social, cultural, and religious beliefs and moral values, skill sets, additional methods of program management and measurement, and governance. Also, a commitment to live and work in harmony, to share the benefits and burdens, to minimize the risk of exploitation and to promote the common good. | |
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| **Responsible stewardship of science**<br><br>A commitment to pursue rigorous, high quality science with appropriate caution for uncertainty and risk, to follow ethical practice in scientific and clinical conduct (with particular attention to issues of integrity and conflict of interest), to maximize the potential benefits of research while minimizing the potential harms, to adopt good practise, and to obey the law. | *Are there local and/or national oversight mechanisms adequate to manage technical review of risks and possible benefits particular to in utero human genome editing, including risk to pregnant women's health from use of viral vectors; risk of introducing new disease or disability; risk of unintended changes to fetal gametes; and risks of the timing of the application resulting in loss of opportunity to make decisions concerning pregnancy termination?* |
| | *What mechanism is in place to ensure the use of good scientific practices?* |
| | |
| **Responsible stewardship of resources**<br><br>A commitment to expend available resources—<br>financial and social (time and personnel)—wisely, recognizing that a meaningful commitment to inclusiveness can be very resource intensive. As concerns financial resources, this means an equitable return on investments not only for research institutions and research sponsors, but also for taxpayers who are often the venture capitalists. | |
| | |
| **Fairness** | *If a child were born following an unsuccessful attempt at heritable human genome editing,* |

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| A commitment to fair dealings in relation to all individuals, organizations, nations and publics. Also, a commitment to ensure equitable access to opportunities and potential benefits. This includes access to support for research and for the development of medical interventions that are appropriate and feasible for the widest possible range of populations. | *would the research team be responsible for the costs of rearing and medically managing the child's condition throughout his or her lifetime?* |
| **Social justice and non-discrimination**<br><br>A commitment to ensure that human genome editing research and applications are developed and used in ways that will reduce socio-economic inequality. Efforts should be made to develop human genome editing so as to promote global health equity and avoid unjust discrimination, for instance by prioritising the health and research needs of the global poor and by making emerging technologies more affordable. Also, a commitment to celebrate and promote diversity by rejecting concepts of enforced eugenics or patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and physical ability. | |
| **Respect for individual dignity**<br><br>A commitment to avoid harm or stigmatization because so many applications touch on things that affect the human body or human reproduction, both of which are the subject of strongly held yet widely divergent perspectives among cultures, religions and populations. The capacity for human heritable genome germline editing suggests a particular need to protect the interests of future persons while satisfying the needs and desires of those today. | |

**TABLE 7: Values, principles and goals, as well as questions to be considered when developing governance measures connected to the scenario on in utero somatic human genome editing.**

103. Possible actions that might be taken as a result could include:

    a. Working with professional societies and patient groups to develop a guide to most reasonable indications and best practices for *in utero* editing;

    b. Ensuring that consent includes thorough discussion of all available alternatives;

    c. Determining whether the research intervention poses risks to the pregnant woman as well as the fetus, and possible benefits to the pregnant woman as well as to the future child. With this in mind, clarify whether consent must be obtained from the male progenitor (who may or may not be the intended rearing father) and/or from the intended rearing father;

d. Clarifying whether pregnancy termination would be permitted if the intervention proves to be harmful to the pregnant woman or the fetus;

e. While unlikely, planning to determine if there is any unintended editing of gametes, and if so, whether this has implications for the resulting child's own reproductive rights once grown into an adult; and

f. Consulting with professional societies on best means of long-term monitoring the health of any resulting children.

# Part 6: Implementation, metrics, and review

104. The Committee identified a number of relevant considerations for the successful implementation of oversight and governance measures for human genome editing. These included metrics for assessing impact as well as processes for reviewing and updating the framework

## 6.1 Implementation of the governance framework and associated measures

[Text needed]

## 6.2 Metrics

[Text needed]

## 6.3 Reviewing and updating the governance framework

[Text needed]

ANNEX

# Questions to be considered when developing governance measures

When developing a policy on human genome editing, some basic questions should be addressed, both by reference to what the policy position will be (for example where to fall on a spectrum between prohibitive or permissive approaches) and how and by whom it will be implemented using one or more of the tools identified above.

Questions that should be considered when developing the overall governance architecture:

a. How should genome editing technologies be used - what are the rationale, objectives and anticipated consequences?

b. What are the interests of the broader community and how will they be served by this new and emerging technology?

c. How will the values, principles and goals specific to human genome editing (Box 4) be considered?

d. Is there a means to revisit such values, principles and goals over time?

e. How would a lack of consensus on such values, principles and goals managed?

f. How will social justice be ensured?

g. What are the health economics implications, considering the costs of both taking action, and not taking it?

h. What are the implications for governance efforts of the depth of knowledge of human genetics and genetic variation?

i. Will genetic councillors be needed, and if so how will they be recruited and trained?

## Post-Natal Somatic Human Genome Editing

Relevant questions include:

a) Will basic science research on somatic human genome editing be permitted?

   i. If so, will pre-clinical and clinical research on somatic human genome editing be permitted?

   ii. If not, what are the penalties (civil, criminal) and how will violations be identified; for example, are there mechanisms to allow individuals or institutions to report violations?

iii. If so, will pre-clinical and clinical research on somatic human genome editing fit within an existing regulatory framework for research involving humans? If using an existing regulatory framework, does it need specific amendments to capture somatic human genome editing?

iv. If so, is there adequate capacity to manage the technical review of proposals for pre-clinical and clinical research on somatic human genome editing and to follow-up on results? What remedies exist in case of injury to research participants?

b) How will the cost of clinical trials and therapies be shared as among patients, researchers, insurers, and third-party (private and public) sources?

c) If the existing regulatory framework governing research involving humans is not adequate, are there plans to create a new framework or rely on regulatory review and approvals from an external body? Which one?

d) If developing a new regulatory framework, how will this coordinate with other regulatory bodies in the country?

e) Do questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, inform individual decisions on a particular proposal?

## Future Post-Natal Somatic Human Genome Editing Clinical Care

Relevant questions include:

a) How will decisions be made regarding access to clinical care involving somatic human genome editing once this is proven safe and effective?

b) Are there domestic ethical standards regarding access to care that relate to this question, and, if so, how are they enforced?

c) What role could be played by liability insurers, health care coverage rules, clinics and professional licensing societies and medical journals?

d) Is control exercised at the executive, legislative, judicial, or administrative/medical society level? Central or regional? Or is this at the discretion of the provider?

e) Is control focused on eligibility for funding, permissibility of marketing, or permissibility of any use at all? Are there any distinctions about permissibility in private versus public clinics or with use of public versus private funding?

f) Do questions of equitable access to safe and effective treatment across domestic populations and communities, affect an individual decision on access to care?

## *In Utero* Somatic Human Genome Editing – Special Considerations

Relevant questions include:

a) Is *in utero* therapy currently done in your country? Under what regulatory or professional society regime?

b) Are existing local and/or national oversight mechanisms adequate to manage technical review of risks and possible benefits particular to in utero human genome editing research, including risk to pregnant women's health from use of viral vectors; risk of introducing new disease or disability; risk of unintended changes to fetal gametes; and risks of the timing of the application resulting in loss of opportunity to make decisions concerning pregnancy termination?

c) If in utero human genome editing is done, will this have any effect on rules governing rights of pregnant women to continue or terminate pregnancies, to make decisions about management of their pregnancies, or to make decisions about management of neonates born with extreme prematurity or disorders?

d) d) Is there clarity in current rules about the decision-making role of the genetic father of a fetus? Of the intended rearing partner? Are these rules clear regarding the decision-making role of non-marital partners, who may or may not be the same sex as the pregnant person?

## Germline Human Genome Editing Research (basic science research)

Relevant questions include:

a. Will non-heritable basic science research on germline human genome editing that involves gametes, embryos or embryo models be permitted?

   i. If not, what are the penalties (civil, criminal) and how will violations be identified; for example, are there mechanisms to allow individuals or institutions to report violations? There may be international considerations too (see the section on international considerations).

   ii. If so, will this research fit within an existing regulatory framework for research involving humans? If using an existing regulatory framework, does it need specific amendments to capture germline human genome editing?

   iii. If so, is there adequate capacity to manage the technical review of proposals for germline human genome editing?

   iv. If so, will this research be subject to any special rules regarding funding or limits on research past a particular developmental stage of embryo or embryo model?

   v. If the research requires the creation of embryos, is this permitted?

vi. If research is not permitted, are researchers able to carry out research in another jurisdiction where it is permitted? Are they allowed to return? Will the research they carried out in a permissive jurisdiction count towards their employment prospects (hiring, promotion, etc)?

b. If the existing regulatory framework governing research involving humans is not adequate, are there plans to create a new framework or rely on regulatory review and approvals from an external body? Which one?

c. If developing a new regulatory framework, how will this coordinate with other regulatory bodies in the country?

d. How will human gametes and embryos be obtained, and with informed consent from whom?

## Heritable Human Genome Editing (for reproduction)

Relevant questions include:

a. Will basic science research on heritable human genome editing that involves gametes, embryos or embryo models be permitted?

b. Will pre-clinical and clinical research on heritable human genome editing be permitted?

i. If not, what are the penalties (civil, criminal) and how will violations be identified; for example, are there mechanisms to allow individuals or institutions to report violations? There may be international considerations too (see the section on international considerations).

ii. If so, will pre-clinical and clinical research on heritable human genome editing fit within an existing regulatory framework for research involving humans? If using an existing regulatory framework, does it need specific amendments to capture heritable human genome editing?

iii. If so, is there adequate capacity to manage the technical review of proposals for pre-clinical and clinical research on heritable human genome editing and to follow-up on results? What remedies exist in case of injury to research participants?

c. Are there any domestic ethical rules and standards that govern heritable human genome research? If so, how are they enforced?

d. If the existing regulatory framework governing research involving humans is not adequate, is there a plan to create a new framework or rely on regulatory review and approvals from an external body? Which one?

e. If developing a new regulatory framework, how will this coordinate with other regulatory bodies in your country?

f. Will domestic policy on research or use of 'human genome editing for enhancement' be different for heritable human genome editing than it is for somatic human genome editing?

g. Do questions of equitable access to research participation across domestic populations and communities, affect an individual decision on a particular proposal?

## Heritable Human Genome Editing Clinical Care

Relevant questions include:

a) How will decisions be made regarding general permissibility and specific conditions of clinical care involving heritable human genome editing?

b) For heritable human genome editing, what capacity exists for long-term, possibly multi-generational follow-up on health and safety of offspring? For monitoring of effects on society at large?

c) Are there any pertinent ethical rules and standards in your country that govern or relate to this question, and, if so, how are they enforced?

d) What additional role is being played or could be played by your liability insurers, health care coverage rules, clinics and professional licensing societies and medical journals?

e) Is control exercised at the executive, legislative, judicial, or administrative/medical society level? Central or regional? Or is it located at the level of provider discretion?

f) Is control focused on eligibility for funding, permissibility of marketing, or permissibility of any use at all? Are there any distinctions about permissibility in private versus public clinics or with use of public versus private funding?

g) Do questions of equitable access to research participation, as well as safe and effective treatment across your populations and communities, affect an individual decision on a particular proposal?

## Role of the publics – Special Considerations

Relevant questions include:

a) What role does the general public have in determining permissibility and conditions of somatic human genome editing?

b) Is there any formal effort at public education, engagement, and empowerment, or public opinion polling?

c) Is there any opportunity for public control or influence over the rules that will be adopted? If so, in what way?

d) Will the public have an ongoing opportunity to revisit the domestic policy on funding, permissibility and conditions of somatic human genome editing, and if so, in what manner?

## International Considerations

Relevant questions include:

a) Are there conventions, treaties, declarations or other international instruments addressing somatic human genome editing that have been signed or would be signed?

b) What is the relevance of professional society guidelines from international bodies or from national societies in other countries? Would violation of such guidelines have a material effect on domestic decisions regarding research funding, investigator discipline, physician licensing, clinic licensing or liability for medical malpractice?

c) Are there laws, regulations, or judicial rulings in place regarding residents who go to another country to perform research that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any?

d) Are there domestic rules in place regarding residents who go to another country to receive somatic human genome editing applications that would be illegal in their home country? If so, what are they? If not, are there plans to develop any?

e) Are there plans to welcome or to discourage people from other countries to travel to access somatic human genome editing clinical trials or therapies?

f) If there are no plans to regulate research in human genome editing, are there plans to regulate foreign researchers travelling from other countries to conduct research?

g) If there is limited oversight capacity or no regulation, what means are available to prevent unproven and possibly dangerous applications from being marketed and provided by clinics in your country?

## Prevention, therapy and 'enhancement' – Special Considerations

89. Relevant questions include:

a) Will the rules differentiate between preventive, therapeutic and 'enhancement' applications, or is each proposal reviewed strictly based upon its individual risks and possible benefits?

b) How will distinctions be drawn between disease/disability prevention and therapy? How will "enhancement" be defined - e.g., beyond ordinary human capacity and health?

c) If such distinctions will be made, are there existing rules about how to evaluate technologies used to enhance rather than to prevent/treat disease and disability?

d) What kind of preclinical research will be required before use in humans, including for "enhancement"? Will use in humans require legislation, regulations, or judicial rulings? What are the penalties for premature use in humans, or for uses that go beyond those permitted?

e) Do questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, affect an individual decision on a particular proposal?