Somatic genome editing governance approaches and regulatory capacity in different countries.

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This research was undertaken at the request of the Royal Society to help inform the Third Human Genome Editing Summit. The research was undertaken during December 2021 and January 2022. An initial analysis was carried out during February 2022. A set of preliminary findings were presented on 9 March 2022 at the online event Looking Ahead to the Third Human Genome Editing Summit.[1] Additional information was added throughout 2022 and revised set of findings were presented on 8 March 2023 at the Third Human Genome Editing Summit.[2]

[1] https://2022humangenomeeditingsummit.royalsociety.org/

[2] https://royalsociety.org/science-events-and-lectures/2023/03/2023-human-genome-editing-summit/

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Part 1: Overview and key findings

1.1 Statement of Work

The project aimed to survey, document, catalogue and analyse empirical information regarding regulatory capacity and governance approaches for somatic genome editing research interventions in different countries. The survey and analysis encompassed national and regional laws and regulations, research ethics guidelines, governance frameworks, key institutions, informal policies, and where applicable, approaches and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption. The methodology used to analyse national capacity was to be written up, along with lessons learned from the project, to provide an initial model for use in other countries in the future.

Due to timing and budget constraints, the scope of the project was limited to up to ten jurisdictions (Brazil, China, India, Mexico, Nigeria, Singapore, South Africa, South Korea, Uganda, Ukraine). These were identified by the research sponsor as being representative jurisdictions based on higher levels of genome editing and/or health biotechnology activity. Research in each of these countries was contingent on being able to identify a local collaborator within the jurisdiction.

1.2 Research Collaborators

This report and the research it described was the result of an international collaboration of experts from around the world. Each member of the team contributed equally to this work.

- **Network Coordinator**: Piers Millett, International Biosecurity and Biosafety Initiative for Science
- **Brazil**: Daiane Priscila Simão-Silva, Cancer Research Institute, Brazil
- **China**: Zhaochen Wang, Zhejiang University
- **India**: Shambhavi Naik, Takshashila Institution
- **Mexico**: Maria Mercedes Roca, Institute on Science for Global Policy, Mexico
- **Singapore**: Kostas Vavitsas, Singapore Consortium for Synthetic Biology
- **South Africa**: Bonginkosi Shozi, University of KwaZulu-Natal
- **Uganda**: Geoffrey Otim, SynBio Africa, Uganda
- **Ukraine**: Oksana Piven, Institute of Molecular Biology & Genetics, Ukraine

Additional information on each of the researchers can be found in Annex A.

1.3 Research summary

Each of the national collaborators carried out an assessment of their own country's governance and oversight capacity. This provides a useful benchmark on what an aware, engaged researcher can reasonably be expected to know about the rules and governance capacity in these countries. National collaborators were tasked with identifying and recording national and regional laws and regulations, research ethics guidelines, governance frameworks, key institutions, informal policies, and where applicable, approaches

and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption. They were able to use their own knowledge, personal and professional connections, institutional experts and support, as well as carry out desk research. National collaborators were also tasked with recording how they found out about the capacities they recorded. National collaborators were then tasked with identifying 5-6 lessons or insights about oversight and governance capacity in their country (Part 3). Following the national assessments, a series of cross-cutting themes were identified by the group.

A more detailed description of the research methodology is in Part 2 of this report.

1.4 Cross-cutting themes

Based upon the experiences in conducting national assessments of oversight and governance capacity for somatic human genome editing, a number of cross-cutting themes were identified:

1. **Every national collaborator was able to identify governance measures relevant to somatic human genome editing.** Not all national collaborators were able to identify measures in each of the areas they were asked to review. Most national collaborators felt that somatic human genome editing was governed in their country.

2. **Gaps in national assessments do not necessarily mean there are gaps in national capacities.** It is entirely feasible that there were measures the national collaborator failed to identify. This is not a shortcoming in this research but provides valuable insights. National collaborators were operating in their own country and were all familiar with the regulatory and oversight measures relevant to somatic human genome editing. Their efforts may, therefore, also represent what could be reasonably expected from a researcher or company wishing to carry out clinical trials in these countries. If there were relevant national measures that national collaborators failed to identify, greater efforts to raise awareness of them may be needed.

3. **Some countries have robust prohibitions on embryonic research.** These effectively prohibit clinical trials involving somatic human genome editing. Further research may be useful to consider how readily these rules may be revisited or revised, should there be widespread demonstration of the safety and efficacy of somatic human genome editing therapies.

4. **Most rules and ethical guidance identified did not focus specifically on somatic human genome editing.** In many cases, relevant rules and guidance focused on other issues, such as gene therapy, human subjects research, clinical trials, or medical oversight. In some cases, these rules and guidance have been updated to take into account advances in biotechnology, such as somatic human genome editing.

5. **There were examples of governance measures more closely aligned to, or partially capture, somatic human genome editing.** In some countries, there were rules and guidance that addressed the use of human embryonic stem cells, CAR-T, and Innovative Precision Improvement Techniques.

6. **There were no governance measures specifically targeted at somatic human genome editing.** Several national collaborators reported that there were new rules and regulations under development in their country. In some cases, they believed that new rules and regulations would specifically address human genome editing.

7. **How governance is implemented differed from country to country.** There was notable diversity in who was involved in governance and how responsibilities were distributed. In general, at the national level ministries of health, and science and technology tended to play a leading role. They were supported by a wide range of national agencies and institutions. In at least one case, there was a specialist national committee (i.e. India's Gene Therapy Advisory and Evaluation Committee).

Institutional committees (including those responsible for biosafety, or research ethics) were widely considered to be playing important roles. There was little evidence of non-governmental governance tools and approaches playing important roles in the countries assessed.

1.5 Challenges & potential shortcomings

During the national assessments, several challenges and potential shortcomings were identified:

1. **Key definitions are often absent or not well enough understood**. Several national collaborators noted that there was a lack of clarity as to the scope of the governance measures they identified. Of particular note, was a need for greater clarity or differentiation between somatic human genome editing and heritable human genome editing, as well as between research and treatment.

2. **Greater public(s) consultation is desirable.** A number of national collaborators highlighted shortcomings in public consultation procedures, these included the information being made available making it hard to provide relevant input, the timelines being set making it difficult to respond in time, a general lack of awareness from the public(s) that there are consultation processes in which they can participate, and in some cases a perceived lack of interest in collaborative agenda setting and policy development.

3. **A lack of information on enforcement.** In many cases, national collaborators were unable to identify if an organization was actively monitoring for non-compliance with the governance measures they identified. This suggests that even if there are somatic human genome editing measures that exist in theory, the practice may be different.

Part 2: Methodology

From the outset, this research was envisioned as a collaborative effort with national research using a standardised approach to review governance capacity in their own countries. In general, a 3 stage process was developed: (1) to gather factual information about a set of representative countries; (2) distil what we learned about governance in those countries and the methodologies we used to find that information; and (3) build on that factual information drawing conclusions and making any relevant recommendations.

Research design and identification of collaborators took place during three weeks in December 2021. National research collaborators had about a month to carry out their assessments during January 2022. February 2022 was used to distil insights from the national assessments, and to draw an initial set of findings. A preliminary presentation on the research and its findings was made on 9 March 2022 during the online event *Looking Ahead to the Third Human Genome Editing Summit*. Additional information was added during the remainder of 2022 and the results of the study were shared at the *Third International Summit on Human Genome Editing* in March 2023.

As part of the research design, the network coordinator worked closely with the Royal Society and experts in somatic human genome editing and its governance to define (i) the types of governance measures to be included, (ii) agree on a process for recruiting national research collaborators, and (iii) to develop a standardised template to record the governance and oversight capacity identified. To assist them, national research collaborators were provided with some useful background information, drawn from recent publications and reports. National research collaborators were then given just under a month to use their own knowledge, personal and professional connections, institutional experts and support, as well as carry out desk research to identify relevant governance and oversight measures. National research collaborators were also tasked with recording how they found relevant information. Their experiences have provided a series of lessons which could usefully be employed in future efforts to assess governance capacity in other countries or to repeat assessments recorded here.

It was a stated hope of this project that detailing the methodology used, and lessons learned, would form an important first step in standardising a research methodology for conducting assessments of national governance and oversight capacity. This in turn should improve our ability to associate disparate assessments and draw insights and conclusions from across the work of multiple groups and over time. The authors recognise that there will be room for improvement in the methodology used here but hope that these efforts form a firm foundation on which others may build.

2.1 Governance measures to be assessed

The different types of governance measures to be covered by the research were detailed in the statement of work and included:

- Laws and regulations;
- Ethics best practices, codes of ethics, research review processes;
- Other governance measures;
- Key institutions;
- Non-governmental measures; and
- Broader oversight approaches and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption.

2.2 Identifying research collaborators

As an initial step, the network coordinator, in collaboration with the Royal Society and associated experts outlined a desirable profile for national research collaborators:

> The ideal candidate will be a post-doc familiar with gene therapy, genome editing, and the national governance and oversight frameworks. They may be a practicing scientist or clinician with an interest in oversight, regulation, and governance. Alternatively, they may be a policy or legal specialist comfortable with modern biotechnology. They will need to work in English and will be expected to be able to answer a structured set of questions. An established set of national contacts in both the technical and policy domains would be a bonus. Candidates should be prepared to explore what happens in practice in their country. In addition to identifying which rules, regulations, or guidance exist (or is being developed), they will have to determine who the key players will be, what other efforts may be relevant, and how broader engagement and empowerment activities contribute to governance efforts. Finally candidates will need to record what they had to do to find out the answers to these questions – so experience in developing and recording research methodologies would be an advantage.

For each country included in the statement of work, a suitable point of contact was identified. These were more senior individuals who had been directly involved in international science policy processes involving biotechnology. In some cases, these individuals were identified by the research network coordinator. In other cases, potential points of contact were identified by the Royal Society and associated experts. In one case, experts inside the World Health Organization worked with their country offices to identify a suitable point of contact. National points of contact were identified for 9 of the 10 countries included in the statement of work. We failed to identify a suitable point of contact in South Korea. Points of contact were provided the model profile and asked to help identify possible candidates. In 8 of the 9 countries with a point of contact, a suitable national research collaborator was identified – someone who fit the profile and had the time, resources, and expertise to undertake the research on short notice. During the available time, it was not possible to recruit a suitable national research collaborator in Nigeria.

2.3 Developing a standardised template to record national governance and oversight capacity

The research network coordinator, in collaboration with the Royal Society and associated experts, developed a standardised template for use by the national research collaborators. This focused on the six types of governance measures to be assessed and prompted the researchers to record both the measures they identified and how they found out about it. A short set of instructions was developed, as well as explanatory text to assist the user in understanding *why* they were being asked to record things, as well as *what* they were being asked to record. The template used in this research is included in Annex B.

2.4 Useful background information

To assist them in identifying relevant governance measures, three sets of background information were made available to national research collaborators.

2.4.1 Scenarios for clinical trials involving somatic human genome editing

National research collaborators were asked to envisage that someone was planning clinical trials involving somatic human genome editing in their country. They were then tasked with finding the governance measures that would apply. This was intended to help the national research collaborator explore a practical application, rather than a broad hypothetical future use. It was hoped that this would also assist in identifying the broader groups of people and organizations (especially outside of government) that might need be engaged within governance efforts.

National research collaborators were encouraged to make use of one of the three scenarios involving somatic human genome editing developed by the WHO as part of its governance framework.[3] These included clinical trials for sickle-cell disease (scenario 1), Huntington disease (scenario 2), and Prenatal (in utero) trails for cystic fibrosis (scenario 7).

2.4.2 Laws and regulations

National research collaborators were provided lists of laws and regulations identified by *Baylis et al* as relevant to human genome editing.[4] There was no guarantee that these laws and regulations were relevant for somatic human genome editing but we hoped they will be a useful start.

2.4.3 Ethics best practices, codes of ethics, research review processes

National research collaborators were provided list of human subjects research standards compiled by US Department of Health and Human Services.[5] There was no guarantee that these guidance and codes will be relevant for somatic human genome editing but we hoped will be a useful start.

2.5 Conducting national assessments

Each national collaborator gathered information on relevant governance approaches and regulatory capacity in the way that made most sense to them and in a national context. Collaborators had a month to gather information. They were reminded that this was intended as desk research and encouraged to make use of their own knowledge, personal and professional connections, institutional experts, and institutional support. In practice, different national collaborators adopted different approaches. All national collaborators reported their findings using the standardised template found in Annex B.

Each national collaborator recorded how they found information on governance approaches and regulatory capacity. In addition to using the background materials provided, approaches used included:

- Prior knowledge of the measure, including from prior research, institutional onboarding and training, membership of relevant working groups or advisory bodies, etc.;
- Institutional expertise, including colleagues working on issues connected to somatic human genome editing;
- Identifying and interviewing scientists involved in relevant research, such as in clinical trials, stem cell therapy, or working on therapies for diseases like HIV or Sickle Cell Disease;
- Online research of government websites, including databases of laws, regulations, guidance, budget information, registries of clinical trials, etc.;
- Personal connections with other researchers, experts, or those involved with drafting or revising rules and regulations;
- Asking queries on science forums, such as WhatsApp groups;
- Interviews or discussions with regulators or other experts from relevant national centres, such as centres for drug evaluation, Bioethics Advisory Committee, National Biosafety Committee, etc.;
- Online search engines;
- Reading book chapters, congress proceedings, conferences, symposia, etc.;

[3] https://www.who.int/publications/i/item/9789240030060 Part 5.
[4] https://doi.org/10.1089/crispr.2020.0082
[5] https://www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html

- Medical applications fora, including those focusing on the human genome, gene therapy, stem cell research, assisted human reproduction and bioethics; and
- Participation in conferences and workshops connected to somatic human genome editing or the governance of emerging technologies.

2.6 Lessons learned

In general, some national collaborators already had access to much of the relevant information. Others had to contact national experts or government employees to find the details. In some cases, much of the relevant information was available online. In other cases, specific guidance was needed to locate relevant information. In all cases, national collaborators were able to go beyond the text of regulations and provide information on how these rules would work in practice. National collaborators were often able to identify key individuals and organizations (sometimes inside government and sometimes outside) and speak with them to add to an understanding of the national context. National collaborators were also instructed that a null return (failing to identify one or more type of governance measure) was also a useful finding. These results, at worst, highlight potential gaps in current governance approaches and regulatory capacity, and at best highlight a need for improved communication in certain national contexts (should such measures actually have existed but were not readily found by researchers).

A number of more specific lessons were distilled from the experiences of national collaborators, including:

- In many contexts, there were few, if any, governance approaches or regulatory capacity focused specifically on somatic HGE. National collaborators needed to think (and research) more broadly about measures which could be tangentially relevant.
- There may be specific measures focused on areas such as CAR-T which are of direct relevance to national capacity to govern or regulate somatic HGE.
- Discussions with regulators or members of relevant national commissions and committees were particularly useful for leads towards relevant information.
- It was not always possible to identify non-governmental governance measures or groups that may readily play a role in policy development or implementation. Such groups are rare in some countries.
- Where it was possible to identify non-governmental groups, their main interests were not obviously connected to somatic human genome editing. Their primary focus was on other areas, such as patient groups for specific diseases.
- In some countries, it was difficult to identify other policy statements, efforts to capture values and principles, rulings, judicial findings, etc. This was particularly notable in countries with comprehensive formal rules.

Part 3: National findings

3.1 Brazil

In Brazil, there are a set of laws and commissions that deal with broader normative issue in which the use of gene editing technology can fit. For example, Article 1 of Law nº 11.105/2005, also known as "Brazilian Biosafety Law", establishes "safety norms and regulations of genetically modified organisms – GMOs". Article 6 of this law prohibits genetic engineering in human germ cells, human zygotes, and human embryos.

Thee are also laws that govern key technologies. For example, Normative Resolution No. 16 of January 15 2018 (RN16), may be the most important Brazilian legal instrument dealing with gene editing techniques. Passed over a decade later than the Brazilian Biosafety Law, RN16 includes the first specific mention of Innovative Precision Enhancement Technologies (TIMP), including CRISPR Cas9. RN16 distinguishes genome editing technologies from GMOs. RN16 allows the issuance of safe-conducts for commercial products resulting from TIMP, including CRISPR-Cas 9 based systems and relevant variations, such as gene drives.

Brazilian laws and commissions have been adapted over time as new technologies and techniques have become available. For example, TIMPs were not known at the time of the enactment of the original law in 1995. Neither were they incorporated into later revisions, which discussed, among other things, the use of embryonic stem cells in research. In this sense, the focus of the law and the debate that followed were restricted to traditional recombinant DNA technologies and techniques. Advances, such as CRISPR-Cas9, came later and are much more recent. The task of incorporating such advances into rules and regulations ended up being self-delegated by the National Biosafety Technical Commission – CTNBio. Their work resulted, two decades later, in RN16, which deals specifically with TIMP.

RN16 Resolution defines products from TIPM as not being equivalent to GMOs. This differentiation between GMOs and products from TIMP is different than in other parts of the world, such as in the EU. R16 exempts research that make use of TIMPs but are not intended to produce GMOs (according to the concept established in the law), from the rules and requirements of Law nº 11.105/ 2005. Thus, at least in theory, research with human cells, tissues, and organisms, under these conditions, is not subject to the afore mentioned law, nor to the supervision of CTNBio.

All clinical trials conducted in Brazil, with an advanced therapy product, require prior authorization from Anvisa, as provided in Collegiate Board Resolution (RDC) no. 260, of December 21, 2018, or its updates. All research involving human beings must be submitted to the CEP-CONEP system which oversees human research ethics evaluation. The National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa (CONEP)) is the ultimate deliberative and supervisory body for the system and below it there is a wide network of commissions based in institutions and research centres. These commissions evaluate, authorize, and monitor all research with human beings, especially health research, with the exception of research which falls directly under the oversight of CONEP. Thus, all research involving human genome editing, regardless of the cell lineage involved, is covered by the CEP-CONEP System. It should be noted that CONEP does not have a seat on the CTNBio's deliberative council, there is an institutional distance between technical and biosafety oversight (provided by CTNBio) and ethical oversight (provided by CEP-CONEP).

The governance measures in place in Brazil and the set of bodies involved, although existing, at least in theory, may not be able to cover all circumstances and phases of the research associated with somatic human genome editing. Possible regulatory and integration gaps in the performance of regulatory and supervisory bodies require attention. Current arrangements may need to be reviewed and eventually

adapted, in light of the new challenges presented by TIMP, in particular by CRISPR-Cas9 or others editing tools.

The full results of this national assessment are contained in Supplementary Materials 1.

3.2 China

There were at lease 10 laws, regulations, and ethical rules in China that in some way may relate to somatic human genome editing. These included laws, regulations, and rules addressing personality rights under the Civil Code, the practice of medicine under criminal law, the administration of human genetic resources, the clinical application of new biomedical technologies, drug control, oversight of clinical trials, oversight of human embryonic stell cell research, oversight of human assisted reproductive technology, and oversight of biomedical research involving human subjects.

In many cases, these laws, regulations, and rules are not specific or exclusive towards somatic human genome editing. They can provide general norms that could be applied for somatic human genome editing, such as those relating to the rights to life, body or health, general requirements for clinical trials, or medical research involving human subjects.

Several of the laws, regulations, and rules focus more specifically on somatic human genome editing or are closely aligned to this topic. For example, the Ethical Guiding Principles on Human Embryonic Stem Cell Research, December 24, 2003 focuses on embryonic stem cells and relatively old, but it may still be referred once somatic human genome editing involves the use of embryonic stem cells. In addition, the rules overseeing CAR-T have been developing quickly. It is likely that there will be clinical trials of CAR-T relevant to somatic human genome editing trials in China, and perhaps globally. In the future, it may be really hard to distinguish CAR-T from other forms of somatic human genome editing.

Of note, there is an example of differentiation between heritable use and somatic human genome editing. For example, Article 336 of Amendment to Criminal Law of the People's Republic of China, March, 1, 2021, is not specific to somatic human genome editing but draws the distinction between the non-heritable use and reproductive use of these technologies.

A number of different institutions are involved with implementing these laws, regulations, and rules. They help translate these measures into effective action, including the National Health Commission, the State Administration for Market Regulation, National Medical Products Administration, as well as the Ministry of Science and Technology.

There are also at least five sets of technical guidelines of relevance to somatic human genome editing. These cover areas such as research and evaluation of cell therapy products, non-clinical research and evaluation of gene therapy products, non-clinical research of gene-modified cell therapy products, long-term follow-up clinical studies of gene therapy products, and clinical trials of human stem cells and their derived cell therapeutics.

There is also a draft Guidance on strengthening ethical governance of science and technology, released for consultation. These will set out the framework for overseeing scientific and technological activities with a higher ethical risk, such as involving people and experimental animals. Such activities will need to be examined and approved by a scientific and technological ethics review committee.

The full results of this national assessment are contained in Supplementary Materials 2.

3.3 India

India has developed specific guidelines to regulate somatic gene editing in humans. The National Guidelines for Gene Therapy Product Development and Clinical Trials, 2019 were developed by the Indian Council of Medical Research (ICMR) in collaboration with Department of Biotechnology (DBT). These guidelines allow for development of somatic gene editing therapies, while banning germline gene editing therapies. In addition, the National Guidelines for Stem Cell Research, 2017 mandate the use of gene editing of stem cells only to *in vitro* studies.

The decision to formulate guidelines, not a law is by design. Regulation was developed in this format so that changes can be fast-paced, keeping in line with the development of the technology. However, this nature of regulation also makes legal enforcement difficult. It appears that India is trying to achieve a balance in staying apace with technology, while ensuring there is regulation in place to monitor its applications. Guidelines may work relatively better in India, because a majority of research in life sciences remains led by public funding. Public bodies will fund only those projects which will follow the guidelines.

The formulation of the guidelines shows India's readiness to adopt certain applications of gene editing technology. The guidelines allow for somatic gene editing where it is of therapeutic benefit. However, neither therapeutic benefit nor somatic gene editing is well-defined. For example, there is no clear indication that somatic gene editing is only non-heritable gene editing application. Similarly, the lack of clarity over "therapeutic benefit" creates ambiguity over which application of gene editing will be allowed. While targeting of diseases such as sickle cell anemia or thalassemia are easy to classify, the ambiguity also leads to grey areas, where the use of gene editing may become controversial. An example is the potential use of gene editing for skin lightening – while darker skin colour is not a disease, lightening may be of therapeutic benefit to the mental health of those harassed for their colour.

A laudable feature of the guidelines is the prescription of a core regulatory committee and the appointment of consultants specific to the disease being treated. This indicates that the guidelines recognize that a one size fits all approach to gene editing may not work and specific applications require specific working guidance.

Including the core committee, Gene Therapy Advisory and Evaluation Committee, up to 8 committees may be involved in the complete approval process for somatic gene editing. However, there is little discussion on the normative ethics of gene editing in the guidelines and this key aspect requires further attention of policymakers. Even the National Ethics Guidelines for Biomedical and Health Research Involving Human Participants, 2017 do not address the ethical aspects of gene editing in depth and exhaustive public engagement remains to be performed to gain this critical understanding.

The full results of this national assessment are contained in Supplementary Materials 3.

3.4 Mexico

No specific regulation has been developed yet for somatic human genome editing, yet Mexico has in-house technical and regulatory capacity to undertake such research and governance in the near future. Three laws regulate human biotechnology and genomic medicine and research, including assisted human reproduction: Law of General Health, Law of Biosafety of GMOs (but confusingly, it specifically leaves out human health), Penal Code. Laws operate at the Federal and State Level. Mexico has appropriately trained professionals in human genetics, molecular biology, genetic engineering, bioethics, regulatory sciences, clinical trials, law and other related fields to develop the field. What Mexico lacks at present is the political will and the instructions to develops governance, from a government that has cut the science and innovation budget since 2018.

CONACYT, the equivalent to the US National Science Foundation regulates and coordinates activities that would fall under HSGeD. COFEPRIS is the equivalent to the US-FDA and issues permits

No clinical trials for HSGeD have been reported but there is in-hose capacity to conduct clinical trials (with private capital). The national Bioethics Comission regulary issues guidelines on a number of topics.

"Medical tourism" and the first mitochondrial replacement ("3-parent baby") occurred in Mexico in 2016, performed by foreign scientists (Dr. J. Zhang – the rogue scientists) without approval. Dr. Zhang was quoted saying that "there are no rules in Mexico" and one can presume this is the reason he set up a subsidiary branch of his New York fertility clinic in Guadalajara, Jalisco. Dr. Zhang's remarks upset many people locally, especially scientists and regulators. Local and international legal experts in the field have studied the case in detail and consider that Dr. Zhang broke the law, but without further repercussions, because regulation has loopholes and voids. Parallel worlds exist in Mexico: one that conducts research and develops products and has to follow regulatory guidelines; and one that may act outside legality if enough interests (especially monetary) are generated.

Bioethical activities are widespread and well-coordinated since 1998 with many international, regional and national partners. The main institution is the National Bioethics Commission. Mexico regularly conducted international and regional conferences on bioethics and trained professionals from other Latin American countries. Such activities seem to have stopped in 2018, and during the pandemic.

A new government came into power in 2018 that has shifted research priorities and budgets away from biotechnology, including somatic human genome editing.

There are many parallels between the governance and regulatory frameworks for genome editing for human applications and genome editing for agriculture and environmental applications. Laws and regulations exist for GMOs (for agriculture and the environment) and for assisted human reproduction, while no specific regulation has been officially announced yet for genome editing for any application. Public perception of the risks of biotechnology in general and genome editing in particular are often heard from activist groups for GMOs and from academics for human genome editing. It is unclear yet if somatic human genome editing will be treated with the hostility of many other biotechnologies. Embracing the OneHealth approach may help bridge gaps between fields and share experiences and resources in developing appropriate science-based regulatory frameworks. Definitions of terms and concepts need to be adopted using international guidelines and standards to harmonize policies and avoid medical tourism and rogue scientists taking advantage of voids and loopholes in the regulation.

The full results of this national assessment are contained in Supplementary Materials 4.

3.5 Singapore

In Singapore the research and applications of genome editing is strictly regulated by central government legislation and guidelines from the Ministry of Health and the Bioethics Advisory Committee. Research institutions are required to adhere to the national guidelines and restricted research (including embryonic research) needs approval from government authorities.

The national collaborator did not locate any advocacy, consultation, pressure groups, lobbying, or other official and unofficial organisations outside this framework.

In the case of somatic human genome editing, any research would need approval from the Institutional Advisory Boards and detailed consent from the participants. There is no regulation strictly forbidding research and a potential clinical trial (after reviewing the resources available), however the researchers and the clinicians would need to argue their case, receive approvals, and maintain the approval throughout the duration of the research/trial.

The full results of this national assessment are contained in Supplementary Materials 5.

3.6 South Africa

There are no laws, guidelines, or institutions that specifically relate to somatic human genome editing in South Africa. There are, however, numerous rules and guidance that indirectly regulate somatic human genome editing. For example, research on somatic human genome editing must comply with the relevant policies on removal of human biological material, genetic health research, and research involving human participants. Considered together, all these policies form a fairly comprehensive regulatory web.

Based on these governance measures, it is apparent that research and clinical applications of somatic human genome editing are legal in South Africa, so long as they have the relevant permissions and follow existing regulations and guidance. In practical terms, the use of somatic human genome editing would ultimately be determined by the various research ethics committees and medicines regulator. The onus is on researchers and institutions involved in relevant activities to ensure compliance.

At present, there is little authoritative guidance on how to effective exercise oversight. Relevant sources are arguably insufficient, confusing and can be hard to find. For example, the Health Professions Council of South Africa, in its General Ethical Guidelines for Biotechnology Research In South Africa has clarified "Somatic cell gene therapy is allowed under the National Health Act" (Para 13.3.1). This document, however, is not currently on the website of the Health Professions Council of South Africa (which during the research linked to the wrong document). This increases the likelihood that policy decision makers and researchers would also struggle to find correct document.

In conclusion, the fragmented nature of the regulatory framework makes being properly appraised of all relevant rules a challenging task for researchers. This is why scholars have failed to find any authority that clearly speaks to SHGE – as the example above shows, even where such authority does exist, it can be difficult to fund. Thus, it is suggested that researchers avail themselves of resources that endeavour to present all this information is summary form, such as academic articles and the studies published by ASSAf – though it should be noted that even these resources have at times proven to be misdirected about the status of the law. For these reasons, there is a clearl need for the government to develop a policy that harmonises the various sources of law and ethical guidance.

The full results of this national assessment are contained in Supplementary Materials 6.

3.7 Uganda

- The general perception that genome editing, and gene therapy are not regulated in Uganda is wrong.
- SHGE is provided for in existing regulations of research in Uganda.
- Regulators do not feel any specific urge to develop specific regulations to this field.
- However, human germline genome editing is prohibited in the country following a moratorium that was signed by Uganda National Council for Science & Technology.
- There are almost no non-governmental measures or guidelines for research.

The full results of this national assessment are contained in Supplementary Materials 7.

3.8 Ukraine

In generally any clinical trial conducted in Ukraine are regulated by specific Laws and Directives, which are harmonized with respective EU Directives and Guidelines. The Ministry of Health of Ukraine and Local Ethic Committees from relevant healthcare institutions (such as hospitals or clinic) would play an important oversight role for any such trials. They would impact the way any new medicines, or protocols for clinical trials, are developed and approved, including for somatic human genome editing.

At present, specific regulations or guidance on somatic human genome editing is absent. The national collaborator was unable to identify key definitions, for example for "gene therapy" or instruments for gene therapy (i.e., ZFN, TALENs or CRISPR). No specific oversight or governance measures were found.

Perhaps of greatest relevant, is the 2005 Directive of Ministry of Health of Ukraine № 426, (№ 426, 26.08.2005), revised in 2015 (№ 460, 23.07.2015), which regulates expertise and clinical trials of the active pharmaceutical ingredient including high-tech (biotechnological) medicines such as:

- genetic engineering, cell engineering, etc.;
- genetically engineered drugs – such as drugs obtained through the use of recombinant DNA technology; and
- provides guidelines for products expertise, clinical trials and registrations.

The full results of this national assessment are contained in Supplementary Materials 8.

Annex A: Biographies of research collaborators

Piers Millett

Piers provided substantive support to the WHO in developing its Governance Framework on Human Genome Editing. He has over a decade of experience in providing research support on science policy issues to academies of science, including the Royal Society, US NASEM, IAP: Global Network of Science Academies, and the German National Academy of Sciences Leopoldina. Piers has consulted and worked for a wide range of international and intergovernmental organizations on the implications of emerging biotechnology. Piers has an extensive network of international contacts across government, academia, industry, and citizen science.

Piers is the Executive Director of the International Biosecurity and Biosafety Initiative for Science, a new organization that works collaboratively with global partners to strengthen biosecurity norms and develop innovative tools to uphold them. Previously he was Vice President for Responsibility at the iGEM Foundation which runs the world's largest synthetic biology competition. He is also a Senior Research Fellow at the Future of Humanity Institute, University of Oxford. Piers co-founded Biosecure Ltd, a UK-based consultancy dedicated to safeguarding the bioeconomy.

Shambhavi Naik

Dr. Naik is Head of Research at the Takshashila Institution, an independent public policy think tank in Bengaluru, India. She works on health and life sciences-related policies, with a strong focus on genome editing, public health, and biosecurity. She has coauthored papers on gene editing governance in India, measures for India to tackle biowarfare threats, and steps for India to become a biotechnology leader. Dr. Naik received a PhD in Cancer Biology from University of Leicester, UK and a PGP in public policy from Takshashila Institution.

Geoffrey Otim

Geoffrey is a Molecular biologist, and a science policy advocate with strong interests in synthetic biology, biosecurity, Global catastrophic biological risks and biotechnological innovations. He is the Founder and CEO of SynBio Africa, legally incorporated in Uganda, an entity for science enthusiasts to convene and develop successful pathways for harnessing and integrating synthetic biology and biotechnology applications for sustainable solutions to great challenges in health, agriculture, and environment in Africa.

Geoffrey has been very active within synthetic biology arena, he received; Biosecurity Fellowship from Johns Hopkins Center for Health Security to attend the Global synthetic biology conference organized by SynbioBeta in 2018, in San Francisco; PGRIP Scholarship to attend and present at the UN Convention on Biodiversity (CBD) in Egypt, in 2018; Global community biosummit Fellowship to attend and present at the Global community biosummit at MIT Media Lab, Boston, MA in 2019; and Global South Biosecurity Diplomacy Fellowship to attend and present at the Global South Biosecurity conference in Geneva, Switzerland, in 2019.

Oksana Piven

Dr. Oksana Piven is a PI researcher at the Institute of Molecular Biology and Genetics of the National Academy of Sciences in Kyiv, Ukraine. She is a Doctor of Science in Molecular Genetics, Lecturer at the Kyiv Academic University and at the Biology Faculty of Institute of Molecular Biology and Genetics. Dr. Piven finished the Cold Spring Harbor Course on Mouse Engineering Virtual Minicourse and - Jackson Laboratory Certificate Program: Introduction to CRISPR/Cas9 and Cre-lox Technologies. MiniCourse Cre-

lox technology in Mouse Modelling. Dr Piven has held Fellowships from the EMBO: ASTF 518-2015 and ASTF 223.00-2011. She is a member of Ukrainian Biochemistry Society and Ukrainian Society of Genetic. She recently wrote the book for the Master and PhD students "Modern genome editing tools with the basics of molecular genetics" (in Ukrainian). At the present Dr Piven is carrying out research in the field of Molecular genetics of the heart, namely focusing on canonical Wnt signaling in heart development and maturation as well as homeostasis.

Maria Mercedes Roca

Dr. Maria Mercedes Roca is a Bolivian, Colombian and British national. She has a B.Sc. in Microbiology from King's College London and a Ph.D. in Plant Pathology with a specialization in Virology from University College London, UK. She has a diploma in Risk Analysis from USDA and Texas A&M University, and is editor and co-author author of a Risk Assessment Guide for Genetically Modified Organisms published in English, Spanish, Portuguese and French. She recently published a book chapter (Springer) on the regulatory challenges for genome editing in Latin America. She was a member of the Consejo Consultivo Científico (CCC, Scientific Advisory Board) of CIBIOGEM, Mexico, advising the Mexican Government on issues related to Genetically Modified Organisms and a member of the AHTEG for Risk Assessment of the Cartagena Protocolo n the Convention of Biological Diversity.

Dr. Roca was a lecturer and researcher for 17 years at Zamorano University in Honduras, and an advisor and lecturer for the Biotechnology Depratment at the School of Medicine of the Tecnológico de Monterrey, Campus Guadalajara. She is currently a senior fellow at the Institute for Science on Global Policy (ISGP), Executive Director of BioScience Think Tank, and sectorial advisor for biotechnology for Angel Ventures Pacific Alliance Fund II and Carabela Fondo Semilla - Angel Ventures, Mexico.

At Zamorano she founded the Biotechnology Program and was part of the National Biosafety Committee of Honduras charged with the release of GM maize in 2003. She has been a country delegate to UN summits of the Cartagena Protocol and the Convention on Biological Diversity.

Maria is passionate about working with young people to find science-based solutions to bioeconomy challenges. She believes in the power of young leaders with vision, commitment, and big dreams. She has coached several iGEM (international synthetic biology competition) teams and is co-founder of Youth Biotech, a non-profit organization dedicated to biotechnology policy development.

Bonginkosi Shozi

Dr Bonginkosi Shozi holds the degrees of Bachelor of Laws (LLB), and Master's of Laws (LLM) in Constitutional Law, Theory and Human Rights Litigation, and Doctor of Philosophy (PhD), all obtained from the University of KwaZulu-Natal. He is currently a postdoctoral research scholar at the Institute for Practical Ethics, at the University of California San Diego. He is also an Honorary Research Fellow at UKZN's School of Law, affiliated with the Health Law and Ethics Research Interest Group.

Dr Shozi's conducts research on the legal, ethical and human rights implications of novel technologies. This includes biotechnological innovations — such as CRISPR — as well as assisted reproductive technologies, and pharmaceutical products. He currently serves in a number of institutions aimed at providing input on the governance of genetic technologies. In 2021, Dr Shozi was elected as a Board Member of the Association for Responsible Research and Innovation in Genome Editing (ARRIGE). He was also invited to serve as a member of the South African Medical Research Council's (SAMRC) Bioethics Advisory Panel working group on gene editing.

Daiane Priscila Simão-Silva

Daiane is currently working with colleagues on an article analysing the Brazilian legislation for Innovative Precision Improvement Techniques. She is the president of the Brazilian society of bioethics in the state of Paraná, Brazil and actively participates in discussions on governance and biotechnology.

Kostas Vavitsas

Konstantinos (Kostas) Vavitsas is the consortium manager of SINERGY, the Singapore Consortium for Synthetic Biology. He holds a BSc in Biology from the University of Athens, Greece, a MSc in Applied Biotechnology from Uppsala University, Sweden, and PhD in Biotechnology from the University of Copenhagen, Denmark.

Kostas has conducted biotechnology research in Greece, Australia, Denmark, and Sweden. He has also worked as a science writer and consultant on synthetic biology, biotechnology, communications, and branding. He has previously served at the boards of Synthetic Biology Australasia and the European Synthetic Biology Society.

Zhaochen Wang

Zhaochen is lecturer on bioethics and medical law in the School of Medicine at Zhejiang University.

Annex B: Template for recording national governance and oversight capacity

Instructions

This research makes use of the WHO Human Genome Editing: A Framework for Governance.

In answering the questions below, we would like you to imagine that somatic human genome editing research is being undertaken in your country using one of the clinical trials scenarios in the WHO report (provided in a separate PDF) or using a scenario of your choosing. Your country may be undertaking the research, may be receiving foreign researchers undertaking the research, or both.

When you have a clear idea of the scenario you are exploring and have documented it in this template, we want you to identify relevant regulatory capacity and governance approaches in your country. We are asking you to identify: (1) laws and regulations; (2) ethics best practices, codes of ethics, research review processes; (3) other governance measures (including values and principles, rulings, judicial findings, processes for the engagement and empowerment of communities that may be affected by somatic human genome editing, as well as the integrations of the views of groups commonly excluded from policy making); (4) key institutions; (5) non-governmental measures; and (6) broader oversight approaches and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption. There is a separate section of the template dedicated to each of these 6 different governance measures. Please include regulatory capacity and governance approaches that are well established, those that have been created recently, as well as any recent or ongoing processes to revise, create or update them.

We understand that many countries may not have all the different regulatory capacity and governance approaches – recording that you were unable to identify any relevant measures in any of the six categories is a valid result.

We also realise that the timeframe is limited, as are your resources. We are not asking you for a definitive list of measures but rather what you can find in a dedicated effort using your existing resources and contacts. It is possible that there are relevant national measures that you simply could not find. This is also a valid outcome. Given your experience and expertise, if you could not find them in 6-8 weeks, they may also be inaccessible for those who may wish to carry out somatic human genome editing research in the future.

Finally, we are also asking you to record how you found out about the different governance measures. We will compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries. There is a dedicated space in each section of the template to record this information. We are interested in governance measures you already know about as well as those you identify during your research. Please provide as much detail as possible when recording how you found out about a measure as this will help us identify approaches that future researchers may want to adopt.

Research collaborator and scenario details

Country:	
Name: (as you wish it to appear publications, etc.)	
Affiliation: (as you wish it to appear publications, etc.)	
Email:	
Scenario: (if using one of the 3 scenarios developed by WHO for somatic clinical research, just note the scenario number and name. If using your own scenario, please describe it here)	

1. Laws & regulations

Please record relevant laws and regulations that you identify as relevant, including those that have been created recently. We are also interested in ongoing processes to revise, create or update relevant laws and regulations. As a starting point, we have provided you with a list of laws and regulations identified by Baylis *et al*.[6] While we encourage a focus on new laws and regulations, we understand that nothing may have changed for some years and would appreciate information about existing laws and regulations.

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Law or regulation,	**Date of entry into force** (inc. planned)	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these laws and regulations; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Law or regulation	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

[6] There may be relevant details in this publication, or there may not as many details were included in policies about assisted human reproduction.

2. Ethics best practices, codes of ethics, research review processes

Please record relevant ethics documents and processes you identify. As a starting point, we have provided you with a list of human subjects research standards by US HHS. In this section we are looking for ethics documents and processes that apply nationally. We are especially interested in recent ethics documents and processes, or recent or ongoing efforts to revise, create or update them. While we encourage you to identify recent documents and processes, we understand that nothing may have changed for some years and would appreciate information about these long-standing documents and processes.

Ethics documents and processes	**Date of entry into force** (inc. planned)	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these ethics guidelines; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Ethics documents and processes	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

3. Other governance measures

Please record details of any other national approaches, rules, or structures which will govern how somatic human genome editing is researched in your country. These measures may include other types of policy statements, efforts to capture values and principles, rulings, judicial findings, etc. It might also include regional networks or rules. **We are also interested in processes for the engagement and empowerment of communities that may be affected by somatic human genome editing, as well as how the views of groups commonly excluded from policy making will be integrated** (such as patient groups, indigenous people, etc.). Please think carefully about different measures which might be relevant. Different tools, institutions, and processes are discussed in Part 4 of WHO's Human Genome Editing: A Framework for Governance (pp28-39).

Governance measure	**Date of entry into force** (inc. planned)	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these governance measures; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Governance measure	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

4. Key institutions

Please record details of institutions that will play a key role in governing how somatic human genome editing is researched in your country. These may be found inside or outside of government. For example, there may be a national bioethics council, or a team working in the Ministry of Science or Technology, alternatively, there may be a body that oversees clinical research. Please think carefully about different institutions which might be relevant. We are interested in institutions that have been created recently, or about processes to revise, create or update institutions. Different tools, institutions, and processes are discussed in Part 4 of WHO's Human Genome Editing: A Framework for Governance (pp28-39).

Institution	**Parent department, agency, or organization**	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these institutions; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Institution	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

5. Non-governmental measures

Please record details of any other policies relevant to how somatic human genome editing is researched in your country. These measures may include laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education. It can include measures developed by groups other than governments. This might include community codes, institutional rules, or guidance from professional bodies. We are interested in recent non-governmental measures, or about processes to revise, create or update relevant non-governmental measures. Different tools, institutions, and processes are discussed in Part 4 of WHO's Human Genome Editing: A Framework for Governance (pp28-39).

Non-governmental measure	**Date of entry into force** (inc. planned)	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these non-governmental measures; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Non-governmental measure	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

6. Broader oversight arrangements

In addition to specific governance measures for somatic human genome editing, we are interested in approaches and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption in your country. Please record details of any measures, approaches, or practices relevant to how somatic human genome editing is researched in your country. These may include clinical research oversight arrangements, bodies involved with promoting or regulating the application of scientific advances to clinical research, or policies or statement encouraging, or discouraging, the use of certain technologies.

Oversight arrangement	**Institutional affiliation**	**Brief description of how it relates to somatic human genome editing** (inc. a link if possible)

Please record how you found out about these oversight arrangements; include as much detail as possible (such as keywords used to search, databases or search engines you used, the job titles and department of institutional specialists you consulted, etc.). If you knew about it already, please take a few moments to reflect on how. Perhaps you learned of it through your professional training (if so, please record what course, etc.). Perhaps it was the result of a professional membership or newsletter (please record this too!) We are aiming to compile the different approaches used by all our national collaborators into a methodology guide. This will be an important output from the research and is intended to help standardise future efforts to research governance capacity in other countries.

Oversight arrangement	**Details of how you found out about it** (feel free to use *ibid* and *op cit* to reduce repetition)

7. Additional remarks

What else can you tell us about the governance of somatic human genome editing in your country? What didn't we ask that we should have? What should future researchers know to help them find out about governance measures in their country?

Additional remarks