

TOWARDS A HUMAN RIGHTS FRAMEWORK FOR THE REGULATION OF HUMAN GERMLINE GENOME MODIFICATION

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Abstract: This is an excerpt from Andrea Boggio, Cesare P.R. Romano, Jessica Almqvist (eds.), Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies, Cambridge University Press, 2019. It is the version sent to the publisher, before editing. Please, cite to the published book. This chapter is the conclusions of the book. It gives the reader a summary of the current national regulatory standards in the 18 States discussed in the book, and asks to what extent they meet international human rights standards, and, in particular, the five foundational principles that a reading of international bioethics law combined with international human rights standards suggests: i) freedom of research; ii) benefit sharing; iii) solidarity; iv) respect for dignity; and v) the obligation to respect and to protect the rights and individual freedoms of others.

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TOWARDS A HUMAN RIGHTS FRAMEWORK FOR THE REGULATION OF HUMAN GERMLINE GENOME MODIFICATION

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This book presents eighteen national regulatory regimes for human germline genome modification, as well as the international legal framework within which they exist. Had this been our only aim, it would have been a worthwhile and thorough update of existing scholarly works, but hardly a novel endeavor. However, what no one has so far done is looking at the existing national and international regulations through the lens of international human rights standards and in particular through the lens of two sets of internationally-recognized human rights: the ‘right to science’ and the ‘rights of science’.

We believe international human rights standards ought to be central to the development of germline engineering law and policies for various reasons, the most cogent of which is that these rights are legally binding on states, at a minimum because they are written in treaties that have been widely ratified, or because they have become part of customary international law. No matter how technical or specific legislation regulating germline engineering is, governments cannot depart from their international human rights obligations in developing regulatory frameworks. It is not just a matter of legality. It is also a matter of legitimacy. International human rights standards are the legal articulation of widely agreed upon values. They are expression of an internationally-negotiated consensus. National regulatory frameworks cannot be consistent only with some human rights obligations while neglecting others. They need to be consistent with all of them.

We are aware our claim will surprise many. The ‘right to science’ and the ‘rights of science’ have been rarely invoked in the context of the discussion of the regulation of human genome modification. Moreover, the collective understanding of the normative content of the right to science – that is, what exactly are states’ specific obligations generated by these rights – is limited,

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if compared to other human rights. Nonetheless, it is time to take a hard look at current national regulatory standards to ask whether they meet international human rights standards, in particular the ‘right to science’ and the ‘rights of science’. This is the goal of this final chapter. Here, we analyze current national regulatory standards of the selected eighteen countries in light of the five foundational principles that a reading of international bioethics law combined with international human rights standards suggests. They are: i) freedom of research; ii) benefit sharing; iii) solidarity; iv) respect for dignity; and v) the obligation to respect and to protect the rights and individual freedoms of others.

We identified these principles by looking at key international bioethics instruments, and in particular the three UNESCO declarations — on the human genome and human rights (1997), human genetic data (2003), and bioethics and human rights (2005)) — while also taking into account the key provisions of the International Bill of Rights that concern science, including Article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) and Article 27 of the Universal Declaration of Human Rights (UDHR).¹ Whether current national regulatory standards respect these five principles, and thus meet international human rights standards, is the key question we raise in this final chapter.

This chapter is divided in three sections: I) evidence, where we summarize what emerges from a legal and comparative analysis of the national chapters included in this volume; II) analysis, in which we discuss the extent to which the current national regulatory standards are consistent with the five foundational principles we identified; and, III) recommendations, where we offer our vision of an international governance framework that promotes science and technological development while being mindful and respectful of international human rights standards as well as the different sensitivities with which citizens from different parts of the world approach this complex problem.

As the readers will notice, our analysis focuses mainly on the first two principles: freedom of research and benefit sharing. This is because the evidence gathered in the first section points to

¹ See, in this book, Ch. 2, Sec. 2.1 and Sec. 3.

problems precisely with these two principles, which reflect the primary goals of the right to science and the rights of science. We present a short discussion of the other three — solidarity, respect for dignity, and the obligation to respect and to protect the rights and individual freedoms of others — in the recommendations section. Of course, we hasten to say that the views expressed in this chapter do not necessarily reflect the views of the authors who contributed the national chapters to this book.

I) EVIDENCE

1) Basic Research

In this study, we defined ‘basic research’ as *in vitro* or *ex vivo* studies of germline tissue of humans, animals or of the two in combination, done to understand the biological mechanisms of germline genome modification. Basic research on germline genome modification can be done using either gametes (sperm and oocytes) or embryos.

a) *Basic research using gametes*

Among the countries we studied, the regulation of research using gametes is relatively underdeveloped. Very few have rules that apply specifically to the use of sperm and oocyte in basic research. In this regard, the Swiss Federal Constitution is an exception. It prohibits any “interference with the genetic material of human reproductive cells”, including gametes.² In Singapore, regulations provide that research with oocytes must be treated in the same way as research with embryos.³ Protocols of research on oocytes are subject to the full ethical review and the preapproval of an institutional review board.

None of the countries surveyed in this book prohibits the *in vitro* modification of gametes for research purposes. This includes ‘gametogenesis’, the *in vitro* derivation of gametes from iPSCs using gene-editing techniques. Japan and the United Kingdom are among the few countries

² See in this book, Ch. 15, p. [INSERT].

³ See in this book, Ch. 19, p. [INSERT].

in the world that have enacted specific regulation for gametogenesis.⁴ In both, the regulations permit gametogenesis and basic research involving germ cells derived from stem cells but prohibit the fertilization of iPSCs-derived gametes.⁵ Several countries (e.g., Australia, Germany, Spain, and Singapore) expressly prohibit clinical applications with gametes used in research.⁶

b) Basic research using embryos

The situation is more complex when basic research is done on embryos. Technically, CRISPR-based interventions are more efficient if a CRISPR/Cas9 tool is injected at the time of fertilization. This way, the likelihood of ‘mosaicism’ in the resulting edited embryos⁷ or off-targets mutations is lower than when CRISPR/Cas9 tools are used at later stages of development. The second-best option is to intervene on one-cell embryos (zygotes). Although off-target mutations may still occur, mosaicism is relatively under control. After cell divisions or ‘cleavages’, controlling how CRISPR-based interventions affect the embryos is more arduous.

Currently, basic research with CRISPR-based interventions at fertilization stage and one-cell stages is possible only in a handful of countries that permit the creation of ‘research embryos’, that is to say, embryos that are intended to be used only for research but not reproductive purposes. Of the 18 countries surveyed in this book, only seven permit the fertilization of an egg for research purposes (i.e. Belgium, China, Israel, Singapore, Sweden, the United Kingdom, and several jurisdictions in the United States). Of the other countries, 10 prohibit scientists to create embryos for research (i.e. Canada, France, Germany, Italy, Japan Mexico, the Netherlands, South Korea, Spain, and Switzerland). One, Australia, has restrictions so extensive that amount to a *de facto* prohibition.⁸

⁴ See in this book, Ch. 16, p. [INSERT], and Ch. 7, p. [INSERT].

⁵ See in this book, Ch. 16, p. [INSERT], and Ch. 7, p. [INSERT].

⁶ See in this book, Ch. 20, p. [INSERT]; Ch. 8, p. [INSERT]; Ch. 13, p. [INSERT]; Ch. 19, p. [INSERT].

⁷ The term “mosaicism” describes a situation in which different cells in the same individual have different numbers or arrangements of chromosomes.

⁸ Australia’s regulatory framework is very complex. In her chapter, Dianne Nicol concludes that there are “very limited avenues for legitimately creating and using embryos for the purpose of clinical and basic research.” See, in this book, Ch. 20, p. [INSERT].

It is important to note that, even where producing research embryos is permitted, research with gametes and embryos is still tightly regulated. All countries surveyed have adopted in some way (law, regulation or guideline) the so-called 14-day rule, which prohibits experimenting on embryos fourteen days after fertilization. In addition, scientists must obtain approvals from a regulatory agency or an independent body. These approvals are granted only upon showing that the statutory requirements are met.

In Belgium, research embryos can be produced only as a last resort, that is, when the research goal cannot be achieved by other means, including resorting to supernumerary embryos.⁹ Additionally, basic research must pursue a therapeutic objective; be based on the most recent scientific knowledge; meet the requirements of a correct methodology of scientific research; and be carried out in an approved research facility and under the supervision of a person who possesses certain credentials.¹⁰ The statutory regulator is the Federal Commission, which preapproves and oversees basic research with research and supernumerary embryos (and with gametes used to derive embryos).¹¹

In Singapore, research embryos can be produced only if scientists demonstrate “strong scientific merit” and “potential medical benefit” of the research, the lack of acceptable alternatives to achieve the research goals, and obtain approval from a regulatory agency.¹² Similar standards must be satisfied in Sweden for basic research that uses gametes or embryos that can be traced back to a living or deceased donor: respect human dignity; human rights and fundamental freedoms; promotion of new knowledge; scientific value of the research; alternative ways to achieve the intended outcome; data protection issues; and researcher’s credentials.¹³

In the United Kingdom, basic research on human germline genome modification can be carried out only after the regulatory authority has issued a license, contingent upon meeting various

⁹ See in this book, Ch. 9, p. [INSERT].

¹⁰ Ibid, p. [INSERT].

¹¹ Ibid, p. [INSERT].

¹² See in this book, Ch. 19, p. [INSERT].

¹³ See in this book, Ch. 10, p. [INSERT].

statutory requirements.¹⁴ These include: informed consent of tissue donors; showing that the use of human embryos is necessary and not merely desirable; an independent research ethics committee's approval of the research; inspection of the research facilities; and a positive review of the research proposal by peers.¹⁵

In the United States, the situation is more complex because of its federal system. The creation of research embryos is regulated both federally and at state level, with important differences. While some states allow the creation of research embryos, others prohibit it.¹⁶ Federal law does not prohibit the creation of research embryos *per se*, but federal funds cannot be used to support research where scientists edit the genomes of human embryos.¹⁷ Preapproval of research by a review body that assesses the risks and benefits of the research is typically needed. Yet, independent scientists and fertility clinics that refuse federal funds are not bound by these federal requirements. They are only subject to the rules of the specific state/s in which they operate.¹⁸

Of the eleven remaining countries discussed in this book, Australia, Canada, France, Japan, South Korea, Mexico, the Netherlands, and Spain permit research on supernumerary IVF embryos, that is, embryos that were produced during an assisted reproduction procedure and are no longer wanted, or cannot be implanted because not viable. Unsurprisingly, the six countries that permit the creation of research embryos allow also research with supernumerary IVF embryos (i.e. Belgium, Israel, Singapore, Sweden, the United Kingdom, and several jurisdictions in the United States).¹⁹ Research with supernumerary embryos is subject to limitations similar to those discussed above for research embryos: informed consent of tissues donors; need for research protocols to be preapproved; ethical oversight; need to show scientific rationale for the use of embryos; meeting research standards; and compliance with the 14-day rule.

¹⁴ See in this book, Ch. 7, p. [INSERT].

¹⁵ *Ibid.*, p. [INSERT].

¹⁶ See in this book. Ch. 4, p. [INSERT].

¹⁷ *Ibid.*, p. [INSERT].

¹⁸ *Ibid.*, p. [INSERT].

¹⁹ See in this book, Ch. 4, 7, 9, 10, 19, and 21.

Some countries have set up additional requirements that limit research with supernumerary IVF embryos further.²⁰ For instance, in Australia, embryos can be used in research only when they are “unsuitable” for assisted reproduction.²¹ This means that an embryo must have undergone a sufficient number of cell divisions to determine that it cannot be used for reproduction. As Dianne Nicol notes in her chapter, those embryos are not particularly useful for gene editing research “given how damaged these cells need to be declared unsuitable for implantation.”²² In South Korea, supernumerary embryos can be used only in research that targets certain rare or incurable diseases enumerated by law.²³ In Mexico, supernumerary embryos can be used in research that benefits a particular embryo (e.g., to eliminate or improve disease of the embryo) but without altering the embryo’s genotype. In France, the requirements for using IVF supernumerary embryos are so stringent that Blasimme, Caminiti, and Vayena report that, “as of 31 December 2015, out of the 20,000 embryos offered by couples to research, less than 10% have been made available for research.”²⁴

Of the countries surveyed, those with the most restrictive laws are Germany, Italy, and Switzerland. They prohibit research with embryos. However, research bans are not absolute. In Switzerland, embryos can be used *in vitro* to derive hESCs, but not to do experiments. As Blasimme, Caminiti, and Vayena report, embryos cannot be edited, and not even tested, for non-medical reasons.²⁵ “Given such rules”, the authors conclude, “it is not possible to perform genome editing of embryos in Switzerland for basic research purposes.”²⁶ In these three countries, as well as in Mexico, embryos can be manipulated, but only as long as the purpose is a therapeutic benefit for the specific manipulated embryo. What these countries seem to permit are *in vivo* and *in vitro* manipulations of embryos²⁷ to correct genetic variations that would determine the birth of a child

²⁰ In this case, the regulation of research with gametes is not relevant because the gametes were procured according to the rules regulating assisted reproduction.

²¹ See in this book, Ch. 20, p. [INSERT].

²² See, in this book, Ch. 20, p. [INSERT].

²³ See, in this book, Ch. 18, p. [INSERT].

²⁴ See, in this book, Ch. 14, p. [INSERT].

²⁵ See, in this book, Ch. 15, p. [INSERT].

²⁶ *Ibid.*

²⁷ With the exception of Switzerland where only *in vivo* manipulations are permitted. See, in this book, Ch. 15, p. [INSERT].

carrying a genetic disease.²⁸ However, at this point, scientists are still far from being able to engage in these sorts of germline interventions with confidence, and it is unclear how they can hone their skills if they cannot practice. Besides, it is unclear whether these statutes truly permit research aimed at editing the variations present in that embryo and, if so, what standard scientists would have to satisfy before their research is approved. As the authors of the chapters point out, the conclusion that this research is possible is merely speculative, since there are no reports of governmental authorities having permitted it, nor of scientists having engaged in this kind of research without sanction.²⁹

That being said, the regulatory framework of most countries neither prohibits nor permits germline genome modifications expressly, creating uncertainties for researchers that we will discuss later in this chapter. In some cases, while silent as to whether researchers can modify gametes and embryos, the regulatory frameworks prohibit using modified gametes and embryos to achieve reproduction. If one follows the general legal principle by which everything-which-is-not-forbidden-is-allowed, the conclusion can be drawn that since the regulators excluded *some* goals of germline engineering, particularly clinical research and applications, they did not exclude *other* goals of germline engineering, particularly acquiring knowledge and basic research. This is the conclusion that was reached by the authors of chapters on the six countries that allow the creation of research embryos (Belgium, Israel, Singapore, Sweden, the United Kingdom, and several jurisdictions in the United States).

Overall, the picture that emerges from our comparative analysis of the regulation of basic research with embryos and gametes is that this is an area filled with prohibitions and restrictions. In the second part of this chapter, we will discuss whether these regulations are excessively restrictive given that states must ensure the freedom indispensable for scientific research and the right of everyone to enjoy the benefits of scientific progress. However, before we move to that analysis, we need to address two more issues: the regulation of clinical research and applications.

²⁸ See, in this book, Ch. 8, p. [INSERT]; Ch. 12, p. [INSERT]; and Ch. 15, p. [INSERT].

²⁹ It is not clear how these exceptions must be interpreted. We invite readers to read the respective sections of the national chapters for more nuanced arguments about the meaning of these clauses.

2) Clinical Applications

Because the regulation of clinical applications is comparatively easier to navigate than that of clinical research, let us address first the end of the translational pipeline. In this book, we defined ‘clinical application’ of human germline genome modification as the use of these techniques on patients in a clinical setting. Most countries surveyed in this book prohibit unequivocally the provision of germline engineering therapies in a clinical setting. There are statutory prohibitions in Australia, Canada, France, Germany, Israel, Japan, the Netherlands, South Korea, Spain, Sweden, Switzerland, and the United Kingdom. Other countries have achieved the same result through regulatory mechanisms. For instance, in Singapore, clinical research and applications are not allowed as a result of a moratorium issued by the Bioethics Advisory Committee in 2005.³⁰ In China, a technical specification of standards for assisted reproduction, issued in 2003 by the Ministry of Health, prohibits “gene manipulation of human gametes, zygotes or embryos for reproductive purposes.”³¹ In the United States, while no federal law expressly prohibits clinics from providing germline-editing services, the federal legislature has prohibited the federal agency from accepting applications to begin clinical research.³² This also means that no gene-editing applications can be offered to patients in a clinical setting, since the regulators’ pre-market approval is a prerequisite to offering clinical applications.³³

A few regulatory frameworks leave the door open, intentionally or accidentally, to the possibility that, in some cases, germline engineering might be used in a clinical context. This is the case of Belgium, and also, counterintuitively, of Italy and Mexico.³⁴ This conclusion is reached if one keeps in mind the rationale of those national regulatory frameworks, which is to prevent embryos from being ‘harmed’ during research. Arguably, interventions that improve the well-being of the embryo are lawful. This interpretation of the Belgian, Italian and Mexican statutes has

³⁰ See in this book, Ch. 19, p. [INSERT].

³¹ See in this book, Ch. 17, p. [INSERT].

³² See in this book, Ch. 4, p. [INSERT].

³³ *Ibid.* Yet, we have seen that independent scientists and fertility clinics that refuse federal funds are not bound by these federal requirements.

³⁴ See in this book, Ch. 19, p. [INSERT]; Ch. 12, p. [INSERT]; Ch. 5, p. [INSERT].

not been tested in courts, so the extent to which clinical applications are actually permitted is unclear, but the possibility is intriguing.

Similarly, France permits the study of germline engineering techniques whose primary aim is therapeutic (e.g. preventing a genetic disease) rather than altering the descendants of the treated embryo. “If that is correct,” Blasimme, Caminiti, and Vayena conclude, “the use of genome editing technologies on human embryos that will likely result in germline modifications may not be a priori forbidden”.³⁵

Singapore and Israel appear to leave room for some procedures as long as their safety and effectiveness is demonstrated. Specifically, Singapore seems open to certain types of genetic germline modification technologies to prevent the transmission of mitochondrial diseases, including ooplasmic transfer, pronuclear transfer, and maternal spindle transfer.³⁶ De Miguel Beriain and Casabona argue that Spanish law does not ban clinical applications nor basic and clinical research using germline modification technologies as long as no new genetic material is introduced intentionally into the genome of the embryos.³⁷

3) Clinical Research

The regulation of clinical research is less clear-cut and, although in the translational pipeline it comes before clinical application, we present it after the discussion on clinical applications because, in some countries, the ban on clinical research is the corollary of a ban on clinical applications. Clinical research involves experimenting on a living person, testing therapies on patients. Clinical research on human germline genome modification would involve modifying germline tissue of the research subject *in vivo*, or transferring to a research subject gametes or embryos that were modified *ex vivo* (i.e., by transferring a modified embryo in the uterus), to test the safety and efficacy of germline genome engineering. All countries surveyed in this volume prohibit clinical research. In some countries, the ban is blank or absolute. In other countries,

³⁵ See in this book, Ch. 15, p. [INSERT].

³⁶ See in this book, Ch. 19, p. [INSERT].

³⁷ See in this book, Ch. 13, p. [INSERT].

exceptions to the prohibition are contemplated expressly, or are revealed by statutory interpretation.

The countries with blank or absolute prohibitions are: Canada, Japan, Singapore, South Korea, Switzerland, the United States,³⁸ and the European Union. In these countries, all clinical research involving human genome germline modifications is prohibited. In others, the ban is not absolute. For instance, in Israel, the Minister of Health could authorize, through regulations, clinical research on and clinical use of genetically modified germline cells, as long as it does not violate human dignity and may have therapeutic benefit.³⁹ According to Ravitsky and Ben-Or, the exception was designed as “a simpler and more efficient solution than subsequently trying to modify the Law” in the event germline-based therapeutic options become available.⁴⁰ Mexico permits clinical applications that have a positive therapeutic effect for the embryo.⁴¹ It follows logically that clinical research testing the safety and effectiveness of a procedure that is lawful should also be lawful. While this is a reasonable interpretation, the fact that the relevant statutes authorize clinical applications but not research cannot be ignored. What the legislator may have envisioned is that clinical applications that have been tested and approved in a different jurisdiction may then be offered to patients in their country. Or it might be simply an accidental omission caused by hasty legal drafting.

Limits to the bans can also be identified by means of statutory interpretation. For instance, in Australia only clinical applications of germline modification technologies that cause modification that are “intended to be inherited” are prohibited.⁴² Can germline modifications be tested on humans if there is no intent to pass on the modifications to the offspring of the research subject? This could be the case when the research subject has agreed to terminate the pregnancy after data for the clinical trial are collected. However, in her chapter, Dianne Nicol proposes a

³⁸ In the United States, clinical research is not possible not by virtue of a legislative ban, but rather because the legislative branch has barred the FDA from receiving any application for clinical research using germline genome modification. See in this book, Ch. 4, p. [INSERT].

³⁹ See in this book, Ch. 21, p. [INSERT].

⁴⁰ *Ibid.*, p. [INSERT].

⁴¹ See in this book, Ch. 5, p. [INSERT].

⁴² See in this book, Ch. 20, p. [INSERT].

more restrictive reading of the statute: the prohibition of clinical applications “could also apply in the research context,” Nicol argues, “where the intention for the genetic manipulation to be passed on to future generations is absent, but the intention to modify the genome in a way that *could* be inherited is present”.⁴³ In South Korea, since the law prohibits clinical research with a therapeutic goal, one could surprisingly argue that clinical research without a therapeutic goal (e.g. enhancement or aesthetic reasons) is allowed.⁴⁴ In Japan, although clinical research using germline genome editing is largely prohibited, editing that does not involve “the administration of a gene or cells” is not prohibited. Acutely, Ishii points out that this could be done if editing is performed using a messenger RNA (mRNA) rather than by inserting a plasmid harboring a gene of template DNA.⁴⁵

In China, clinical trials involving human genome germline modifications seem to fall in a legislative vacuum, and therefore there is some uncertainty as to what is prohibited. Research with human subjects is subject to regulations that have incorporated the main international standards for biomedical research. The *Guiding Principles for Human Gene Therapy Research and Quality Control of Preparation* allow only genetic therapy using somatic, but not germline, cells.⁴⁶ However, it is unclear whether the *Guiding Principles* allow gene therapy on human embryos and whether germline genome modifications can be clinically tested on humans. In the wake of Dr. He Jiankui’s controversial revelations, the Chinese regulatory and funding agencies and various professional bodies issued statements condemning Dr. He’s actions. In a joint statement, the Chinese Society for Stem Cell Research and the Committee of Genome Editing, Genetics Society of China concluded that “we believe the research led by He is strongly against ... the Chinese regulations”.⁴⁷ An investigating task force set up by the Health Commission of China in

⁴³ Ibid., p. [INSERT].

⁴⁴ See in this book, Ch. 18, p. [INSERT].

⁴⁵ See in this book, Ch. 16, p. [INSERT].

⁴⁶ See in this book, Ch. 17, p. [INSERT].

⁴⁷ Committee of Genome Editing, Genetics Society of China and Chinese Society for Stem Cell Research, Statement “Condemning the Reproductive Application of Gene Editing on Human Germline”, 27 November 2018. <<http://www.cscb.org.cn/news/20181127/2988.html>> accessed 11 December 2018.

Guangdong Province released a preliminary report on January 21, 2019, stated that He had violated government bans.⁴⁸

The situation in Europe is even more complex due to the stratification of regulatory instruments. First, of the nine European states surveyed in this book, three (France, Switzerland and Spain) are bound to prohibit interventions to modify the human genome for the purpose of introducing modifications in the genome of any descendants by virtue of their ratification of the Oviedo Convention.⁴⁹ Then, eight out of nine are members of the European Union. Currently, EU Regulation 536/2014 includes a blank prohibition under which EU member states cannot approve clinical trials involving the modification of the human genome germline.⁵⁰ However, before 2014, clinical trials were prohibited by a directive. As a general rule, directives are not self-executing, and member states must adopt their own laws to reach the policy goals set by a directive. As a result, some EU countries had no national legislation or had adopted national laws prohibiting clinical research. The Netherlands is the only European country surveyed in this book without a statute prohibiting clinical research on germline editing.⁵¹ The key Dutch statute prohibits “deliberately modifying the genetic material of the nucleus of human germ cells with which a pregnancy will be established”.⁵² As van Beers, de Kluiver and Maas note, “these words suggest that human genetic modification is prohibited only for reproductive purposes, and only where nuclear DNA is concerned”.⁵³

All other countries have statutes, some of which contain language that may be interpreted as granting certain exceptions to the pre-2014 EU-mandated ban on clinical research on germline modifications. The German and Swedish statutes expressly prohibit germline interventions that

⁴⁸ XINHUA, Guangdong Releases Preliminary Investigation Result of Gene-Edited Babies, 21 January 2019, <http://www.xinhuanet.com/english/2019-01/21/c_137762633.htm> accessed 25 January 2019.

⁴⁹ See in this book, Ch. 13, 14 and 15, p. [INSERT].

⁵⁰ See in this book, Ch. 6, p. [INSERT].

⁵¹ See in this book, Ch. 11.

⁵² *Ibid.*, p. [INSERT].

⁵³ *Ibid.*, p. [INSERT].

are therapeutic.⁵⁴ The authors of those chapters point out that certain human germline genome editing interventions without a therapeutic purpose might fall outside the scope of the statute.⁵⁵

On the opposite side of the spectrum, Belgium, France, and Italy permit only germline interventions that are therapeutic. Belgium and Italy have statutory language similar to Mexico, that is, they permit clinical applications that have a positive therapeutic effect for the embryo. As we have seen, one could reasonably argue that clinical research testing clinical applications that are beneficial to the embryo is permitted.⁵⁶ The French Civil Code includes an exception to the ban on clinical research allowing for research activities aimed at preventing or treating genetic diseases and not at modifying the genetic traits of a person.⁵⁷

In the United Kingdom, which soon might be no longer part of the European Union, the key statute does not set up a mechanism to evaluate and possibly authorize the clinical research on new technologies or treatments. To address this legislative void, Lawford Davies draws a parallel with the 2017 approval of the clinical use of mitochondrial donation using a pronuclear transfer. Thirteen years after the submission of the proposal for clinical research, the regulators authorized the research, but under the strict oversight of the agency and with the obligation that researchers apply for permission for each patient and monitor patients' health scrupulously in follow-up sessions. "Should clinical application of human genome germline modification become technically feasible," Lawford Davies concludes, "it is highly likely that a similar process of review and consultation will unfold."⁵⁸

II) ANALYSIS

This is what we learned from the analysis of the selected national regulatory frameworks. However, each of those states, as any other state, has international legal obligations that frame and constraints their national legal frameworks, including a set of obligations deriving from two

⁵⁴ See in this book, Ch. 8, p. [INSERT]; and Ch. 10, p. [INSERT].

⁵⁵ Ibid, p. [INSERT] and [INSERT].

⁵⁶ See in this chapter, Sec. I.2, p. [INSERT].

⁵⁷ See in this book, Ch. 14, p. [INSERT].

⁵⁸ See in this book, Ch. 7, p. [INSERT].

specific branches of international law: international human rights law and international bioethics law. The international context in which we carry out our analysis should be clear to the readers by now.⁵⁹ However, it is worth reiterating here the key rights that inform our analysis: the ‘right to science’, also known as the right of everyone to benefit from scientific progress (benefit sharing), and the ‘rights of science’, of which the right to engage in scientific research (scientific freedom) is an essential component.

Both international human rights law and international bioethics law agree that freedom of research must be respected. Respecting freedom of research requires states to refrain from interfering directly or indirectly with it,⁶⁰ and avoiding taking measures that hinder or prevent the enjoyment of this right.⁶¹ Simply put: scientists must be allowed to engage in scientific inquiries freely. However, the ‘right to science’ and the ‘rights of science’ are not absolute rights. They can be limited. Restrictions on the enjoyment of these rights are allowed only if they are consistent with international human rights standards. Specifically, they require that three conditions are met: (1) any restriction must be prescribed by law (condition of legality); (2) any restriction must pursue a legitimate aim (condition of legitimacy); and (3) any restriction must be limited to what is necessary to fulfill that aim, and be the result of a careful balancing of interests (condition of proportionality).⁶² Governments bear the burden of showing that the restrictions they impose do not violate international human rights standards.⁶³ Until this burden is met, states must avoid imposing restrictive measures that interfere with the rights to scientific freedom and benefit sharing.

⁵⁹ See in this book, in general, Ch. 2.

⁶⁰ See UN Committee on Economic, Social and Cultural Rights (UNCESCR), General Comment No. 14 (2000) on the Right to the Highest Attainable Standard of Health (Article 12 of the International Covenant on Economic, Social and Cultural Rights), UN doc. E/C.12/2000/4, 11 August 2000, paras. 33; General Comment No. 17 (2005) on the Right of Everyone to Benefit from the Protection of the Moral and Material Interests Resulting from Any Scientific, Literary or Artistic Production of Which He or She is the Author (Article 15.1.c of the International Covenant on Economic, Social and Cultural Rights), UN doc., E/C.12/GC/17, 12 January 2006, paras. 28

⁶¹ Analogously, see UNCESCR, General Comment No. 13 (Twenty-first session, 1999) on the Right to Education (Article 13 of the International Covenant on Economic, Social and Cultural Rights), UN doc. E/C.12/1999/10, 8 December 1999, para. 47.

⁶² O de Schutter, *International Human Rights Law*, Cambridge University Press (2010), p. 288.

⁶³ Analogously, UN Commission on Human Rights, *Siracusa Principles on the Limitation and Derogation Provisions in the International Covenant on Civil and Political Rights*, UN doc. E/CN.4/1987/17, para. 12.

In the following subsections, we will discuss and critically examine the most important limits imposed on the effective enjoyment of the human rights to science in the area of human germline engineering. We will pay special attention to the question whether these limits are consistent with international human standards and states' obligations related to these rights.

1) Restrictions must be prescribed by law (condition of legality)

According to article 4 of the ICESCR, limitations to scientific freedom must be “determined by law” (condition of legality). In broad terms, this requirement entails that the “limitation should have a basis specifically in domestic law consistent with the Covenant; the law must be adequately accessible; the relevant domestic law must be formulated with sufficient precision”, and the law must not be arbitrary, unreasonable, discriminatory or incompatible with the principle of interdependence of all human rights”.⁶⁴ According to the requirement of clear and precise laws, captured by the principle of legal certainty, limitations are determined by law only when they are sufficiently clear to allow a reasonable person to regulate her conduct based on that law.⁶⁵ The empirical evidence presented in the national chapters shows that, in many countries, the laws regulating research on human germline genome modification are excessively vague. This raises the question whether laws in place actually provide a sufficient degree of legal certainty as required by human rights standards. Before analyzing this question, let us lay out the requirements of this principle within the international human rights framework.

The principle of legal certainty is a “general principle of law common to civilized nations”,⁶⁶ that is to say a legal principle that can be found in the legal system of several, if not all, ‘civilized nations.’⁶⁷ Indeed, it is a well-established legal concept, found both in the Civil Law and

⁶⁴ M Ssenyonjo, *Economic, Social and Cultural Rights in International Law*, Hart Publ. (2016), 2nd edition, p. 152, p. 152.

⁶⁵ *Siracusa Principles* (n 62), para. 17, according to which “legal rules limiting the exercise of human rights shall be clear and accessible to everyone”.

⁶⁶ *Charter of the United Nations and Statute of the International Court of Justice*, June 26, 1945, Art. 38.1.c. 59 Stat. 1031 [the Charter], 1055 [ICJ Statute], T.S. No. 993 [I.C.J. Statute at 25], 3 Bevens 1153 [I.C.J. Statute at 1179].

⁶⁷ For a comparative law discussion of the principle, see M Fenwick; M Siems; W Stefan (eds), *The Shifting Meaning of Legal Certainty in Comparative and Transnational Law*, Hart Publ. (2017). The authors show how widespread recognition of the principle is, while pointing out that pinning down what legal certainty means and when it is violated remains difficult.

in the Common Law legal traditions. In Europe, the concept of legal certainty has been recognized as one of the general principles of European Union law by the European Court of Justice since the 1960s. It is found in all European continental legal systems, those that follow the Romano-Germanic (Civil) legal tradition.⁶⁸ In the Common Law tradition, legal certainty is often explained in terms of citizens' ability to organize their affairs in such a way that does not break the law. In the United States, the principle of legal certainty is understood as 'fair warning' and the 'void for vagueness'.⁶⁹ In both legal traditions, legal certainty is regarded as grounding value for the legality of legislative and administrative measures taken by public authorities.⁷⁰ The principle is also given importance in the context of the UN work on the promotion of the rule of law at the national and international levels. Here the rule of law requires legal certainty, and both are an essential condition for the full realization of human rights.⁷¹

Invariably, human rights bodies resort to the principle of legal certainty to determine the legitimacy of restrictions on human rights. While there is no instrument that speaks directly to the limitations of scientific freedom, the UN Human Rights Committee has applied the principle of legal certainty to a cognate freedom: the freedom of expression. According to the Human Rights Committee's General Comment No. 34 on Article 19 of the International Covenant on Civil and Political Rights (Freedoms of Opinion and Expression), "a norm, to be characterized as a 'law', must be formulated with sufficient precision to enable an individual to regulate his or her conduct accordingly."⁷² Restrictions to freedom of expression "shall only be such as are provided by law and are necessary: (a) For respect of the rights or reputations of others; (b) For the protection of

⁶⁸ For instance, one can find it in the German legal system as 'Rechtssicherheit', in France as 'sécurité juridique', in Spain as 'seguridad jurídica', in Italy as 'certezza del diritto', in the Benelux countries as 'rechtszekerheid', in Sweden as 'rättssäkerhet', in Poland as 'pewność prawa', in Finland as 'oikeusvarmuus'. D Chalmers, *European Union Law: Text and Materials*, Cambridge University Press (2006), p. 454.

⁶⁹ E Claes, W Devroe, B Keirsblick, *Facing the Limits of the Law*, Springer (2009), pp. 93.

⁷⁰ *Ibid.*, pp. 92–93

⁷¹ E.g., Declaration of the High-Level Meeting of the General Assembly on the Rule of Law at the National and International Levels, UN doc. A/RES/67/1, 30 November 2012, para. 7. For a definition of the rule of law mentioning specifically legal certainty, see <<https://www.un.org/ruleoflaw/what-is-the-rule-of-law/>> accessed 23 January 2019.

⁷² UN Human Rights Committee, General Comment no. 34, Article 19, Freedoms of Opinion and Expression, 12 September 2011, CCPR/C/GC/34, para. 25.

national security or of public order (*ordre public*), or of public health or morals.”⁷³ The parallel with Article 4 of the Covenant on Economic, Social and Cultural Rights is striking. In both cases, restrictions on freedom, whether of expression or of research, must be provided by ‘law.’

Unclear laws are particularly problematic when they provide for criminal sanctions. At the international level, the European Court of Human Rights has asserted repeatedly the paramount importance of legal certainty in connection with criminal laws.⁷⁴ Because several countries surveyed in this book have chosen to regulate some, if not all, aspect of activities modifying the genome of human germline cells through criminal law, legal certainty is paramount. Australia, Canada, China, France, Germany, Israel, Italy, Mexico, the Netherlands, South Korea, Spain, Sweden, Switzerland, and the United Kingdom, criminalize certain activities connected with using human embryos and/or modifying the human genome. Yet, as we also have seen, some of these criminal prohibitions lack in clarity and precision. Granted, one could argue that what is not prohibited is permitted, and thus, unless research or clinical activity is expressly prohibited, it is lawful. Loopholes abound. Nonetheless, scientists are unlikely to take advantage of them and move ahead with innovative research when the risk is to be criminally prosecuted.

In many jurisdictions, the limitations to scientific freedom are contained in laws and regulations that are unnecessarily vague. For example, many regulatory frameworks do not address research on the human germline expressly, and therefore do not allow scientists to be sufficiently confident that their research can be done lawfully. Several fail to give scientists reasonable notice of exactly what is permitted and prohibited. Authors of the chapters on Canada, Italy, Mexico, The Netherlands, Singapore, Spain, and Sweden identify key aspects of the regulation of basic research

⁷³ International Covenant on Civil and Political Rights (adopted 16 December 1966, entered into force 23 March 1976) 999 UNTS 171 (ICCPR), Art. 19.3.

⁷⁴ C Grabenwarter, European Convention on Human Rights: A Commentary, Hart Publ. (2014), p. 68, pp. 178-181, p. 191, and p. 263. Several decisions of the European Court of Human Rights address the issue. E.g. see Kolevi v. Bulgaria, no. 1108/02, Judgment, 5 November 2009, page 29, § 174; Baranowski v. Poland, no. 28358/95, Judgment, 28 March 2000, page 12, § 52; Cantoni v. France, no. 17862/91, Judgment, 11 November 1996, page 14, § 29; C.R. v. the United Kingdom, no. 20190/92, Judgment, 22 November 1995, page 12, § 33; S.W. v. the United Kingdom, no. 20166/92, Judgment, 22 November 1995, page 13, § 35; Kokkinakis v. Greece, no. 14307/88, Judgment, 25 May 1993, pages 17-18, §; Streletz, Kessler and Krenz v. Germany, nos. 34044/96, 35532/97 and 44801/98, Judgment, 22 March 2001, page 26, § 50; Malone v. the United Kingdom, no. 8691/79, Judgment, 2 August 1984, pages 27-28, § 67; Valenzuela Contreras v. Spain, no. 58/1997/842/1048, Judgment, 30 July 1998, page 15, § 46.

as ‘unclear’. The authors of the chapters on China, France, Mexico, Spain, and Sweden talk about ‘uncertainties.’ They give us examples of instances where definitions and substantive provisions have not been updated, despite the advent of CRISPR, which has transformed our understanding of what constitutes ‘gene therapy’,⁷⁵ or of instances where new advancements are not expressly regulated, as in the case of *in vitro* gametogenesis.

Indecipherable laws and regulations have a chilling effect on scientific freedom. Faced with muddied regulatory frameworks, scientists likely refrain from doing something that is not expressly prohibited. Some authors explicitly acknowledge the chilling effect vague regulatory frameworks have on research. Song and Isasi conclude that, in China, “obscurity in the breadth and scope of normative instruments, paired with blurred jurisdictional boundaries between governmental actors, have created what it seems to be an unstable regulatory environment where accountability is uncertain, with chilling effects on research.”⁷⁶ De Miguel Beriain and Casabona note that, in Spain, “the prevailing view amongst scholars is that any intervention seeking to modify the human genome that is not for preventive, diagnostic, or therapeutic purposes is prohibited ... has chilling effect on Spanish researchers, who, currently, are not engaging in research in this direction.”⁷⁷ Timo Faltus point out that, in Germany, the ban on human germline genome modification “has chilling effects on the funding of borderline research (i.e. research on asexually produced embryos, triprounuclear embryos), too.”⁷⁸

Consider Article 15.2 of the International Covenant on Economic, Social and Cultural Rights, which recites: “The steps to be taken by the States Parties to the present Covenant to achieve the full realization of this right shall include those necessary for the conservation, the development, and the diffusion of science and culture.” We believe that that, whenever laws lack the necessary precision, thus inhibiting scientific freedom, governments have failed to take the steps “necessary for ... the development of science”. These steps “must be deliberate, concrete

⁷⁵ J Doudna and E Charpentier, “The New Frontier of Genome Engineering With CRISPR-Cas9” *Science*, Vol. 346, Issue 6213 (2014).

⁷⁶ See in this book, Ch. 17, p. [INSERT].

⁷⁷ See in this book, Ch. 13, p. [INSERT].

⁷⁸ See in this book, Ch. 18, p. [INSERT].

and targeted” towards the full realization of this right.⁷⁹ Incomplete and unclear statutes fail to comply with the principle of legal certainty and therefore cannot be considered to be truly ‘determined by law’. States must take steps to ensure that scientists are in a position to tell with reasonable precision whether their research is lawful. As we will discuss in the last section, the best way to meet international legal standards is for governments to enact legislation that regulates research on human genome germline modifications expressly and clearly.

2) Restriction must pursue a legitimate aim (condition of legitimacy).

Clarity is not sufficient. Restrictions must also be justified by the pursuit of a legitimate aim (condition of legitimacy). In this regard, article 4 of the ICESCR specifies that the rights the Covenant recognizes may be subject “only in so far as this may be compatible with the nature of these rights and solely for the purpose of promoting the general welfare in a democratic society”.⁸⁰ What this proviso means and consequently requires is somewhat unsettled. The notion of “general welfare” has been understood as “furthering the well-being of the people as a whole”.⁸¹ The expression “in a democratic society” should be construed as imposing a further restriction to the application of limitations by requiring the state to demonstrate that the limitations do not impair the democratic functioning of the society.⁸² According to the Committee on Economic, Social and Cultural Rights, at the very least it demands that a state ensures that limitations on economic, social and cultural rights are “necessary and proportionate and do not interfere with the core minimal content of the rights”.⁸³ The requirement that any limitation must be “necessary in a democratic

⁷⁹ See the following UNCESCR General Comments: No. 3: The Nature of States Parties’ Obligations (Art. 2, para. 1, of the Covenant), UN doc. E/1991/23, 14 December 1990, para. 2; General Comment 13 (n 60), para. 43; General Comment No. 14 (n 59), para. 30; General Comment No. 17 (n 59), para. 25.

⁸⁰ International Covenant on Economic, Social and Cultural Rights (adopted 16 December 1966, entered into force 3 January 1976) 993 UNTS 3 (ICESCR), art 4. At the time of writing, the UN Committee on Economic, Social and Cultural Rights has not yet adopted a General Comment concerning the interpretation of article 4.

⁸¹ Limburg Principles on the Implementation of the International Covenant on Economic, Social and Cultural Rights adopted in Maastricht on 2-6 June 1986, UN Commission on Human Rights, Note verbale dated 5 December 1986 from the Permanent Mission of the Netherlands to the United Nations Office at Geneva addressed to the Centre for Human Rights (“Limburg Principles”), 8 January 1987, E/CN.4/1987/17 para. 52.

⁸² *Ibid.*, paras. 53-54.

⁸³ UNCESCR, Concluding Observations, Vietnam, C/C.12/VNM/CO/2-4 (15 December 2014), para. 8. Also see A Müller, “Limitations to and Derogations from Economic, Social and Cultural Rights”, *Human Rights Law Review*, vol. 9, no. 4 (2009): 577-601, referring to the Principles on the Limitations and Derogation from Provisions in the ICCPR, E/CN.4/1985/4 (1985).

society” implies the existence of a “pressing social need” or a “high degree of justification” for the limitation in question.⁸⁴

Even if public safety, order, health, or morals are not mentioned explicitly as grounds that justify limitations of the Covenant rights, they are generally understood as providing valid grounds for limiting not only civil and political rights, but also economic, social and cultural rights.⁸⁵ However, although concerns with morals, safety, health or order may be aspects of the “general welfare of a democratic society”, to limit a right legitimately on these non-explicit grounds, it must be clear that the protection of these concerns is necessary for the promotion of welfare *in a democratic society*.

Thus, for example, a legislator that invokes safety or health concerns to justify restrictions has the burden of explaining how the balancing between the individual right to health and the right to health and safety of the many, has been achieved in conformity with the proportionality test. In meeting this test, it must be recalled that ‘public health’ may be invoked as a ground “to allow a state to take measures dealing with a serious threat to the health of the population or individual members of the population. These measures must be specifically aimed at preventing disease or injury or providing care for the sick and injured.”⁸⁶ Public safety “cannot be used for imposing vague or arbitrary limitations and may only be invoked when there exist adequate safeguards and effective remedies against abuse.”⁸⁷ . Likewise, a state may invoke public morality as a ground for restricting rights. However, even if enjoying a certain margin of appreciation, it “must demonstrate that the limitation in question is essential to the maintenance of respect for fundamental values of the community”,⁸⁸ and that these values have been identified and discussed through a democratic process that takes into account the voices and interests of particularly vulnerable groups and minorities.

⁸⁴ M Ssenyonjo, (n 63), p. 152.

⁸⁵ O De Schutter, (n 61), p. 291.

⁸⁶ Siracusa Principles (n 62), para. 25.

⁸⁷ Ibid., paras. 33-34.

⁸⁸ Ibid., para. 27.

The rules protecting the rights of research subjects, above all their right to free and informed consent, are a typical example of a legitimate restrictions, consistent with the need to protect the human rights of others, a legitimate goal. Another limitation accepted in democratic societies to promote the general welfare is that scientific research must be done responsibly. Scientists have an individual and collective duty to act responsibly. Just because you can do something, it does not mean that you will do it and damn the consequences, as Dr. He Jiankui did.⁸⁹ Scientists must adhere to the rules of good research conduct, and the scientific community has the duty of, but also the right to, self-regulation, that is, to regulate the scientific enterprise to ensure the integrity of the research process and the minimization of misconduct.

Restrictions must not be arbitrary, lest the condition of legitimacy would be violated. When limitations are arbitrary or unwarranted, the freedom indispensable for scientific research is not respected. For instance, while Italy bans the creation of embryos for research, Italian scientists are reported to import them from abroad to carry out their research.⁹⁰ It is hard to explain how the different protection afforded to ‘national embryos’ and ‘foreign embryos’ can be reconciled with the stated purpose of protecting the dignity of the embryo. Even if freedom of research may be restricted for reasons of public morality, as has been said, a state that invokes it “must demonstrate that the limitation in question is essential to the maintenance of respect for fundamental values of the community”.⁹¹ In the Italian case, it is unclear what that fundamental value would actually be, given the disparity of treatment between embryos created in the national territory and those coming from abroad.

3) Restrictions must be limited to what is necessary to fulfill legitimate aims, and be the result of a careful balancing of interests (condition of proportionality)

Restrictions must not only be the result of reasonably clear laws adopted democratically for legitimate goals. They must also be proportional, limited to what is necessary to fulfill those

⁸⁹ See in this book, Preface, p. [INSERT].

⁹⁰ See, generally, B Forest, “Three Courageous Italian Scientists – An Example for Louisiana”, World Congress for Freedom of Scientific Research, 19 Apr. 2010, <<https://www.freedomofresearch.org/three-courageous-italian-scientists-an-example-for-louisiana-by-barbara-forrest/>>, accessed 7 March 2017.

⁹¹ *Ibid.*, para. 27.

legitimate goals, and be the result of a careful balancing of interests (condition of proportionality). Total bans and so-called *ne plus ultra* prohibitions violate the condition of proportionality.

a) The prohibition of the creation of embryos

Of the 18 countries surveyed in this book, only seven permit the fertilization of an egg for research purposes (i.e. Belgium, China, Israel, Singapore, Sweden, the United Kingdom, and several jurisdictions in the United States). Of the other countries, ten prohibit scientists to create embryos for research (i.e. Canada, France, Germany, Italy, Japan Mexico, the Netherlands, South Korea, Spain, and Switzerland). One, Australia, has restrictions so extensive that amount to a *de facto* prohibition.⁹²

We believe allowing scientists to create research embryos is necessary for them to be able to enjoy their freedom of research. As deWert and colleagues noted, “only in countries where the creation of embryos for the exclusive purpose of research is allowed could [gene editing] be applied at earlier stages and with fresh oocytes and embryos.”⁹³ Research on supernumerary IVF embryos is only a second best, because of the limited number of embryos available and because a considerable percentage of those have not been implanted because they are either not viable or affected by various disorders. Modifying the genome of embryos is better than modifying the genome of gametes as the chances of off-target mutations and mosaicism are reduced.⁹⁴

We are not advocating unlimited freedom to create any embryos for research. The six jurisdictions that permit the creation of research embryos show that it is possible to strike a balance between the needs of science and ethical concerns. There, the creation of research embryos is limited by various rules, including the requirement to obtain consent from tissue donors, approval and oversight, and the ‘14-day’ rule. We believe these limitations are compatible with human rights standards as their rationale is to protect other human rights (the rights of the research subjects) and are enacted democratically. Ethical approvals and oversight ensure that the research

⁹² (n 8).

⁹³ G de Wert et al., “Responsible Innovation in Human Germline Gene Editing. Background Document to the Recommendations of ESHG and ESHRE”, *European Journal of Human Genetics*, Vol. 26, n. 4, 2018, p. 450-470.

⁹⁴ *Ibid.*, p. [INSERT].

is carried out responsibly, respecting the sensitivities of the societies where it is done. This regulatory approach, in our opinion, is the one that best balances freedom and the limits of this research because the limitations to scientific research are both appropriate and narrowly tailored.

b) Ne plus ultra prohibitions

Several countries allow the translational pipeline to advance only up to a certain point. They might allow basic research but prohibit clinical research. We believe these *ne plus ultra*, or blank, prohibitions are difficult to reconcile with everyone's right to "benefit from scientific and technological progress" and the principle of benefit sharing, even when lawful limitations to these rights are taken into account.⁹⁵ Noticeably, Article 15.2 of the Covenant requires governments to "take steps ... to achieve the full realization of this right shall include those necessary for ... the diffusion of science." If everyone is to truly enjoy the benefits of scientific progress, biomedical knowledge must be allowed to be translated into clinical applications, unless there are legitimate grounds for limiting the right. Claims to benefit sharing are particularly strong when knowledge might lead to developing new medical treatments that make it possible to cure or even prevent diseases that otherwise would be incurable.

In situations such as these, it is doubtful generic bans meet the legitimacy and proportionality tests. When discussing limitations on the right to health, the UN Committee on Economic, Social and Cultural Rights has noted that when several types of limitations are available, the least restrictive alternative must be adopted.⁹⁶ In this context, it also noted that the limitations should be of limited duration and be subject to review.⁹⁷ Even if some aspects of the bans may be justified, it seems important to consider whether they could at least be narrowed down.

⁹⁵ ICESCR, Articles 2.2 and 15.1.b.

⁹⁶ See, analogously, UNCESCR, General Comment No. 14 (n 59), para. 29.

⁹⁷ *Ibid.*

As we have seen earlier in this chapter, Canada, Japan, Singapore, South Korea, Switzerland, the United States,⁹⁸ and the European Union have adopted blank prohibitions of clinical research involving human genome germline modifications. In our judgment, blank prohibitions to translate basic research into clinical research, which, if safety and efficacy are proven, can lead to offering clinical applications to patients, conflict with the right to science contained in the Covenant.⁹⁹ The prohibition to test new cures, or methods to prevent deadly or severely impairing diseases that are otherwise incurable, can hardly be said to “promote the general welfare in a democratic society”. A more balanced approach that respects the proportionality test is needed. Israel is a good example. There, the law prohibits clinical research but leaves the door open to cases in which testing germline engineering may be warranted. The power to authorize clinical trials under exceptional circumstances is given to the Minister of Health, who can adopt a regulation greenlighting experimenting germline engineering on humans.¹⁰⁰ This approach is similar to the one recommended by influential ethical statements, such as those of the National Academies of Sciences, Engineering, and Medicine and the Nuffield Council on Bioethics.¹⁰¹ These statements reflect a shift in opinion from a blank prohibition to the permissibility of translational pathways to germline editing.

We do not advocate giving researchers *carte blanche*. They would have to adhere to widely accepted standards for clinical research and follow robust pre-clinical evidence supporting the clinical promise of modification of the human germline. The National Academies of Sciences, Engineering, and Medicine recommends, among others, that clinical trials using heritable genome editing be permitted only in “the absence of reasonable alternatives ... to prevent a serious disease or condition ... on genes that have been convincingly demonstrated to cause or to strongly

⁹⁸ In the United States, clinical research is not possible not because of a statutory ban, but rather because the legislative branch has barred the FDA from receiving any application for clinical research using germline genome modification. See in this book Ch. 4, p. [INSERT].

⁹⁹ Similar considerations are put forth by R Yotova, *The Regulation of Genome Editing and Human Reproduction under International Law, EU Law and Comparative Law*, Nuffield Council on Bioethics (2017). P. {INSERT}.

¹⁰⁰ See in this book Ch. 21, p. [INSERT].

¹⁰¹ Nuffield Council on Bioethics, *Genome Editing and Human Reproduction*, London: Nuffield Council on Bioethics (2018); National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance*, Washington, DC: The National Academies Press (2017).

predispose to that disease or condition ... and [with] reliable oversight mechanisms.”¹⁰² Admittedly, clinical experimentation for reproductive purposes seems to be premature at this point in history. However, while it would be untimely to do germline genome editing with the intent of bringing that possible future child to birth, blanket prohibitions of clinical research fall short of international human rights standards. They inhibit a conversation about what clinical research should and could look like, and whether it can be carried out promoting the “general welfare in a democratic society.” As Bryan Cwik persuasively argued prior to Dr. He Jiankui’s stunt, “it’s important to consider seriously what would be required for the conduct of ethically sound clinical trials of [gene editing]. Human germline gene editing raises a new set of ethical issues that are extremely difficult to resolve by current ethical guidelines and regulations.”¹⁰³

4) Obsolete regulatory frameworks violate the conditions of legality, legitimacy and proportionality

We believe obsolete regulatory frameworks fail to meet the conditions of legality, legitimacy and proportionality. Even if they may have met them in the past, restrictive measures on the right to science and the rights of science, such as any other Covenant right, must be reviewed on a regular basis in the light of changing circumstances, lest they would not be any longer ‘adopted by law’, ‘necessary’ or ‘proportionate’.

Human rights courts and other bodies “constantly stress that they interpret human rights in accordance with changing structures, values and priorities of societies”.¹⁰⁴ Article 4 requires states to adopt and upkeep laws that are appropriate, in the sense of being abreast with new scientific developments. States have an ongoing obligation to revise laws as science and technology advances and to ensure that, when progress is substantial and clear enough, a broad public dialogue takes place as to ensure existing regulations reflect current societal values.¹⁰⁵ If they do not, or do

¹⁰² Ibid., pp. 189-190.

¹⁰³ B Cwik, “Designing Ethical Trials of Germline Gene Editing”, *New England Journal of Medicine*, 377 (2017), p. 1911-1913.

¹⁰⁴ A Müller, “Limitations to and Derogations from Economic, Social and Cultural Rights”, *Human Rights Law Review*, vol. 9 no. 4 (2009): 557-601, at 560-561.

¹⁰⁵ See, A Chapman, ‘Towards an Understanding of the Right to Enjoy the Benefits of Scientific Progress and its Applications’ (2009) 8 *Journal of Human Rights* 17-18 (the author states her agreement with the findings the

not any longer, then these regulations cannot be considered anymore as promoting the welfare of the democratic society under present-day conditions: they have become obsolete and must be reformed.

Indeed, as all the other rights recognized in the Covenant, the obligations created by the right to science are not necessarily fulfilled once and for all by ‘one-time’ measures. Under Article 2.1 of the Covenant, states must take steps to discharge their obligations with a view to “achieving progressively the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures.” As repeatedly noted by the Committee on Economic, Social and Cultural Rights, the “progressive realization” of the rights recognized in the Covenant means that states parties have a “specific and continuing obligation to move as expeditiously and effectively as possible” towards the full realization of these rights, logically including the right to science and the rights of science.¹⁰⁶

In the case of the regulatory frameworks of heritable genome editing, only Japan has adopted a regulatory framework in recent times (in 2014). Only a handful of other countries (e.g. France, the Netherlands, South Korea, Sweden, and the United Kingdom) have undertaken formal policy discussions on germline engineering in the past five years. The others surveyed in this book have laws in that were drafted, debated, and enacted in the 1980s, 1990s, and 2000s, well before the advent of CRISPR.¹⁰⁷ To wit, Mexico adopted its key statute regulating basic research on germline engineering in 1982 and 2002,¹⁰⁸ Germany in 1991;¹⁰⁹ China adopted various instruments

National Bioethics Advisory Commission, pointing out that ‘limits on freedom of inquiry must be carefully set, must be justified and should be reevaluated on an ongoing basis’); National Bioethics Advisory Commission, Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission, Rockville, MD: NBAC (1997).

¹⁰⁶ See UNCESCR, General Comment No. 3 (n 78), para. 9; General Comment 13 (n 60), para. 44; General Comment No. 14 (n 59), para. 31; General Comment No. 17 (n 59), para. 26.

¹⁰⁷ CRISPR-Cas9 first appeared in the scientific literature in 2012. See, M Jinek and others, “A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity”, *Science*, Vol. 337 (2017), p. 816.

¹⁰⁸ The 1982 law was amended in 2011. See in this book Ch. 5, p. [INSERT].

¹⁰⁹ See in this book Ch. 8, p. [INSERT].

between 1993 and 2003;¹¹⁰ Switzerland in 1998 and 2003;¹¹¹ Australia and the Netherlands in 2002;¹¹² Canada,¹¹³ France;¹¹⁴ Italy,¹¹⁵ and South Korea in 2004;¹¹⁶ Spain in 2007.¹¹⁷

These prohibitions or restrictions have not yet been re-examined in light of the recent advancements in gene editing technology. The advent of CRISPR has fundamentally changed the cost-benefit analysis.¹¹⁸ While in the 1990s and 2000s the costs of human germline genome modification were clear while benefits were speculative, now the benefits are coming into focus. The regulatory frameworks adopted before the advent of CRISPR must be re-examined to be up-to-date with new scientific developments if the goal of achieving progressively the full realization of the human right to science, both scientific freedom and benefit sharing is to be reached. Where no public legislative debate took place in recent times, in spite of new important scientific developments, can it be argued that the purpose of those restrictions is still the protection of the “general welfare in a democratic society”?

Even the sacrosanct 14-day rule, the current prevailing universal standard, should be open to re-discussion should our understanding of what happens around that threshold change, or our values change.¹¹⁹ The 14-day rule was adopted about 30 years ago as an acceptable compromise between those who believe human life begins at fertilization, and those who believe the early stages of development do not yet constitute a human life. Since then, it is widely considered to be an acceptable balance between the moral imperatives of religious beliefs and the need to advance

¹¹⁰ The regulations of research with human subjects were adopted in 2016. See in this book Ch. 8, p. [INSERT].

¹¹¹ See in this book Ch. 15, p. [INSERT].

¹¹² See in this book Ch. 20, p. [INSERT], and Ch. 11, p. [INSERT].

¹¹³ See in this book Ch. 3, p. [INSERT].

¹¹⁴ In 2013, the French Parliament changed the default rule from a ban (on using human embryos for research excepting supernumerary embryos) to permissibility (of research with supernumerary embryos upon prior approval and under tight oversight). See in this book Ch. 14, p. [INSERT].

¹¹⁵ See in this book Ch. 12, p. [INSERT].

¹¹⁶ See in this book Ch. 18, p. [INSERT].

¹¹⁷ See in this book Ch. 13, p. [INSERT].

¹¹⁸ G Daley, R Lovell-Badge and J Steffann, “After the Storm — A Responsible Path for Genome Editing”, *New England Journal of Medicine*, 16 Jan 2019. [Epub ahead of print].

¹¹⁹ FS Collins and S Gottlieb, “The Next Phase of Human Gene-Therapy Oversight’ *New England Journal of Medicine*, Vol. 379 (2018), p. 1393, 1395; G Cavaliere, “A 14-day Limit for Bioethics: the Debate Over Human Embryo Research”, *BMC Medical Ethics*, Vol. 18 (2017), p.38; I Hyun, A Wilkerson & J Johnston, “Embryology Policy: Revisit the 14-day Rule”, *Nature*, 4 May 2016, p. 169.

science.¹²⁰ The 14-day rule is a “legal and regulatory line in the sand that has for decades limited in vitro human-embryo research to the period before the ‘primitive streak’ appears.”¹²¹ That being said, the 14-day rule “was never intended to be a bright line denoting the onset of moral status in human embryos.”¹²² Instead it has been a “theoretical [line respected] until now because scientists have been technologically incapable of moving past the 14-day threshold.”¹²³ However, recent developments have raised the question of further extending the possibility of researching on embryos beyond 14 days. Until 2016, culturing human embryos in-vitro had never gone beyond nine-days.¹²⁴ In 2016, human embryos were sustained in-vitro for 12-13 days.¹²⁵

Obsolescence of regulatory frameworks is certainly not a new problem in science and technology law and policy, or a problem only of science and technology law and policy. As often happens with disruptive scientific and technological breakthroughs, lawmakers are struggling to adjust the regulatory frameworks with these developments. Elen Stokes refers to this problem as one of ‘inherited rules.’ “New technologies”, she points out, “do not always elicit new regulatory responses. More often than not, policymakers deal with new technologies by deferring to existing regulatory regimes”.¹²⁶ However, the fact that this problem occurs “more often than not” does not make it acceptable. Indeed, it directs attention to the fact that the Sisyphean task of meeting human rights obligations is a never-ending enterprise that requires legislative bodies to be well-informed about new developments with a view to revise and update laws accordingly.

CRISPR is a significant scientific and technological advancement that has accelerated the timeline of clinical applications based on germline engineering becoming available to patients. It

¹²⁰ J Harris, “It’s Time to Extend the 14-Day Limit for Embryo Research”, The Guardian, 6 May 2016.

¹²¹ I Hyun, A Wilkerson & J Johnston, “Embryology Policy: Revisit the 14-day Rule”, Nature, 4 May 2016, p. [INSERT]. The appearance of the “primitive streak” (i.e. a transient structure whose formation marks the start of the process in which the inner cell mass is converted into the three germ layers: ectoderm, mesoderm and endoderm) signals that the individuality of an embryo is assured.

¹²² Ibid. p. [INSERT].

¹²³ M Kaplan, “Call to Re-Examine “14 Day Rule” Limiting In-Vitro Human Embryo Research”, Case Western Reserve University of Medicine, Press Release 4 May 2016, <https://casemed.case.edu/newscenter/news-release/newsrelease.cfm?news_id=302> accessed 15 March 2017.

¹²⁴ Ibid.

¹²⁵ Revisit the 14-day rule (n 120), p. [INSERT].

¹²⁶ E Stokes, “Nanotechnology and the Products of Inherited Regulation”, Journal of Law and Society, Vol. 39 (2012), p. 93.

is a game changer, one that puts in question how governments have regulated human genome germline modifications in the past, and that calls “for a broad public dialogue about these technologies and their applications”.¹²⁷ Obsolete legislation may not reflect how the public values the benefits and risks of heritable genome editing. Governments must engage legislatures, ministerial bodies, national science councils and other venues for public engagement to ensure that regulatory frameworks adopted years before the advent of CRISPR are adjusted to how to best promote the welfare in a democratic society considering the opportunities offered by new technology and scientific progress here and now, not a decade ago.¹²⁸

III) RECOMMENDATIONS

To conclude, as a recommendation, we would like to sketch what we believe a regulatory framework for human genome germline modifications that is informed by international human rights law and, more specifically, the right to science and the rights of science should look like.

To begin, we believe the primary responsibility for regulating heritable gene editing falls on (legitimately elected) governments rather than international organizations or civil society bodies. International law creates obligations that national governments must discharge to ensure progressively the full realization of human rights in the area of scientific and technological progress, not least the human right to science. International organizations or civil society bodies can play an important governance role in supporting the implementation of these obligations. However, they cannot substitute the role national governments are expected to play.

As with the rest of the rights recognized in the Covenant, the right to science and the rights of science imply different sets and levels of obligations. The key obligations governments have in this regard are to “respect, protect, and fulfill” everyone’s rights to contribute scientific progress (scientific freedom) and to enjoy such progress (benefit sharing).¹²⁹ As discussed in the previous

¹²⁷ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance*, The National Academies Press (2017), p. 163.

¹²⁸ *Ibid.*

¹²⁹ See the following general comments by the UNCESCR, General Comment 13 (n 60), para. 46; General Comment No. 14 (n 59), para. 33; General Comment No. 17 (n 59), para. 28. According to these, the obligation to protect

section, the ‘obligation to respect’ requires that governments do not interfere in the enjoyment of the right to science unless they have a legitimate reason for doing so, one that is based on science and actual risks, as opposed to political opportunity and speculation. However, just as important to our analysis is the ‘obligation to fulfill’. This obligation translates into the creation of a legal framework and a regulatory environment that is conducive to the effective enjoyment of the right to science, both scientific freedom and benefit sharing.¹³⁰ The same obligation requires states to “adopt appropriate legislative, administrative, budgetary, judicial, promotional and other measures” towards the full realization of the rights to science.¹³¹ At a minimum, governments are expected to adopt legislative measures that allow a person to exercise or enjoy scientific freedom and benefit sharing effectively. As we discussed in the previous section, this requires, *inter alia*, that the legal framework is sufficiently certain and up-to-date.¹³² In taking legislative measures, governments are expected to engage legislatures, ministerial bodies, national science councils and other venues for public engagement to ensure that regulatory frameworks reflect current values in their respective societies.

From a policy perspective, legislative measures in the biomedical field must guarantee, as a default rule, the freedom to engage in basic and clinical research and to make safe and effective treatment, therapies and other applications available to patients in a clinical setting.¹³³ In regulating heritable gene editing, legislative measures must guarantee, again as the default rule, scientists’ freedom to use CRISPR, and any other gene editing tools that might be invented in the future, to create and modify human gametes and embryos, and identify reasonable opportunities for translational pathways of therapies to cure heritable genetic disorders.

requires states also to prevent third parties from interfering in the enjoyment of the right to science. This issue will not be discussed in this chapter.

¹³⁰ Analogously, UNCESCR, General Comment No. 13 (n 60), para. 46.

¹³¹ Analogously, UNCESCR, General Comment No. 14 (n 59), para. 33; and General Comment No. 17 (n 59), para. 28. Also see UNCESCR, General Comment No. 3 (n 78), para. 9.

¹³² Article 2.1 of the ICESCR limits state duties to ‘taking steps, individually and through international assistance and co-operation, especially economic and technical, to the maximum of its available resources, with a view to achieving progressively the full realization of the rights recognized in the present Covenant by all appropriate means, including particularly the adoption of legislative measures.’

¹³³ The rules governing access to clinical applications are better analyzed within the framework of the right to health, which exceeds the scope of our analysis. On the international human rights to health, see, in general, J Tobin, *The Right to Health in International Law*, Oxford University Press, 2012.

We recognize that this is a controversial area of science and that not all societies are willing, at least for now, to move forward with heritable gene editing, even if the goal is strictly therapeutic. Human rights law accommodates this diversity of viewpoints by establishing that the human right to science, which incorporates scientific freedom and benefit sharing, is not absolute. As it has already been mentioned several times before, according to Article 4 of the Covenant, rights can be restricted by law for the purpose of promoting the general welfare in a democratic society. Governments may, and in certain cases must, restrict scientific freedom and benefit. They can certainly ban applications of gene editing techniques to enhance humans or for cosmetic reasons, if they democratically and lawfully decide to do so.

We believe blank prohibitions, such as those banning all research on human embryos and all clinical research, to be in violation of international law. Limitations based on safety health considerations are easier to defend since preclinical research has so far failed to show that germline engineering is sufficiently safe to be experimented on humans, due to the risk of off-target mutations and mosaicism. However, states must discharge the burden of proving an actual risk to health and safety and explain how and why the health of the many trumps the right of those who are sick to be cured. In addition, the only lawful prohibitions are those determined by law, and law must be sufficiently clear. Given the transformative nature of CRISPR, prohibitions that date back a decade or two, cannot be considered to have been truly democratically accepted. These issues need to be debated again and, only if a broad agreement is reached in favor of prohibiting this kind of research applied to humans, as it happened in the case of the 14-day rule, limitations will be acceptable.

We want to stress that we do not argue against the need for restrictions on freedom of research and benefit sharing, when necessary to ensure respect for the fundamental values of the community. Such restrictions might allow national governments to accommodate considerations of ethical or religious diversity, and give some margin for societies to choose the appropriate speed at which they wish to participate in innovation. The international human rights framework allows countries to choose, in consideration of their available resources, as long as they use their resources to the maximum, to be at the forefront of innovation to develop a regulatory framework favorable

for making advances in the area of gene editing. This is another reason to entrust national, rather than international, lawmakers to find the right balance between the right to science and the rights of science and their limitations. The goal is to promote science and technological development while being mindful and respectful of international human rights standards as well as the different sensitivities with which citizens from different parts of the world approach this complex problem. That being said, national policies must fulfil article 2 of the Covenant, which requires the *progressive* realization of the rights.

They must also be in accordance with Article 15.3, which requires governments to encourage and develop “international contacts and co-operation in the scientific and cultural fields”. International cooperation is particularly important in germline genome engineering. The scientific and technical complexities of this field demand scientific efforts that transcend national boundaries and often involve scientists from multiple countries. These efforts may take the form of collaborations among researchers across borders, pooling and sharing resources and expertise, and validation of results with scientists traveling to other countries to attend meetings, to visit labs, to lecture, or to access resources and expertise. National policies must enable international cooperation, especially since only a few countries have chosen to be at the forefront of innovation in this field. When clinical applications become reality, international cooperation will foster exchanges that ensure the sharing of benefits to patients of countries that have chosen a more conservative approach. International bodies have a role to play as facilitators of regulatory harmonization, custodians of knowledge of best practices and current regulations, and as promoters of a global conversation on how innovation can be balanced against other considerations.

The framework we propose must also ensure that other human rights are protected. The rights of research participants are particularly important in this area. Any research must be carried out in accordance with international standards of research involving human subjects, of which the right to free and informed consent is the first. In addition, research preapproval and oversight, which are commonplace in biomedical research, are necessary to ensure a responsible exercise of scientific freedom. To the extent possible, legal frameworks must be narrowly tailored, and be

limited to setting out basic guarantees, leaving space to the scientific community for self-regulation. Here, we see an important role for scientific societies, expert bodies, and ministerial bodies to design “soft law” instruments, such as guidelines and ethical standards, in accordance with international human rights standards. These instruments might then be embraced by funding agencies or professional bodies, thus empowering either government agencies or the scientific community to monitor best practices. The ideal framework must also incorporate considerations of solidarity. In the context of heritable gene editing, solidarity translates into rules guaranteeing, at minimum, fairness in access, nationally and transnationally, to the clinical applications of germline engineering, outlawing any form of genetic discrimination, and ensuring intergenerational equity.¹³⁴ These are important goals, which cannot be fully articulated within the limits of these conclusions. It suffices to say that, if proper legal mechanisms are in place to ensure that these policy goals are achieved, some of the objections to heritable gene editing would be defeated and the public would likely be more willing to support its legalization. Considerations of solidarity can inform policies with regard to cost of treatments (if treatments are expensive and thus unaffordable to some), to reproductive tourism (if treatments are only available in certain countries and thus only available to those who can afford to travel to foreign countries), and genetic enhancement (if everybody can ‘enhance’ their offspring, at least fairness is no longer an issue).

Finally, as to the elephant in the room, the governance framework must be respectful of human dignity. That is required by all existing international regulatory standards. However, what respecting human dignity entails is a question that we do not intend to settle here. The concept has always been and remains undefined, and probably humanity will never agree on a clear definition of it. That being said, we believe it is essential to distinguish between different concepts of dignity. The concept of human dignity in the sense of autonomy, rank or status of human beings, should not be confused with other uses of dignity. When Christian theology stresses the absolute worth and sacredness of human life from the time of conception, it stretches the concept beyond what is accepted in international human rights. International human rights law’s understanding of dignity

¹³⁴ ICESCR, Article 2.2; UNCESCR, General Comment No. 20: Non-Discrimination in Economic, Social and Cultural Rights (art. 2, para. 2) U.N. Doc. E/C.12/GC/20 (2009). More in-depth analysis of the intersection between equity, right to health, and right to science would be necessary, but it exceeds the scope of this book.

is limited to the protection of the autonomy, rank and status of human beings and to the furtherance of the highest attainable level of health. Although international law upholds the rights to science and to health, and in this sense is inclined to promote scientific progress and applications that strengthen the protection of these rights, it does not settle the question of the status of embryos as such, or whether it is contrary to dignity to interfere with gametes or embryos. From an international human rights perspective, once a person is born, genetically modified or not, she has the same rights and freedoms as all others. If her genes have been modified, she is no less of a person with dignity than someone whose genes have not been modified.

The question whether the current regulatory framework for human germline genome engineering should be eased is giving rise to ethical and moral disagreements in pluralistic societies. On one extreme, there are believers and religious authorities that demand full respect for the absolute worth and sacredness of human life from time of conception. Indeed, these demands often translate into claims not just about the need to ban human genome germline modification, but also stem cell research and other experiments involving the use of human embryos, and beyond, to abortion and end-of-life issues. At the other extreme, there are those who defend the need for scientific progress to cure serious diseases and human suffering, even if it requires modification of the germline of embryos. For them the duty to make use of novel scientific tools to assist people to attain the highest attainable standard of health made possible by new scientific developments overshadows any other consideration.

In a democratic society, which is a society characterized by pluralism, tolerance and broad-mindedness, no particular view is acceptable a priori. No one has the right to impose their view on the rest through laws and regulations or *fait accompli*. Moral and ethical disagreement and the state of evolving technology demand some form of debates, possibly open, inclusive and transparent. International human rights law, including the right to science and the rights of science, should frame and inform these debates. The rights in focus in this volume point to some fundamental interests of humans that may have not been considered fully, such as the universal right to enjoy the benefits of scientific research and all its applications, as well as the right to scientific freedom within the limits established by international human rights law. The same rights also point to the

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need for democratic debates concerning how to meet the international obligations that flow from these rights. Let the debate begin.