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Human Gene Editing

Traversing Normative Systems

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34.1 INTRODUCTION

Gene editing technologies consist of a set of engineering tools, such as CRISPR/Cas9, that seek to deliberately target and modify specific DNA sequences of living cells.[1] They can enable both *ex vivo* and *in vivo* deletions and additions to DNA sequences at both somatic and germline cell levels. While technical and safety challenges prevail, particularly regarding germline applications, these technologies are touted as transformational for the promotion and improvement of health and well-being. Furthermore, their enhanced simplicity, efficiency, precision, and affordability had spurred their development. This in turn, has brought to the fore scientific and socio-political debates concerning their wide range of actual and potential applications together with their inexorable ethical implications.

The term 'inevitable' refers to the certainty or the unavoidability of an occurrence. Such was the worldwide response after the 2018 announcement – and later confirmation[2]– of the live birth of twin girls whose genomes were edited during *in vitro* fertilisation procedures. While foreseeable, shock followed and ignited intense national and international debates. China was placed at the epicentre of controversy, as the ubiquitous example of inadequate governance and moral failure. Yet, as the facts of the case unfolded, it became clear that the global community shared a critical level of responsibility.[3] Crisis can provoke substantial changes in governance and fundamentally alter the direction of a given policy system. While the impact of the shock is still being felt, the subsequent phase of readjustment has yet to take place. A 'window of opportunity' is thereby present for collective assessment of its impact, for ascertaining accountability, and for enacting resulting responses. Reactionary approaches can be predicted, as demonstrated by the wave of policies in the 1990s and 2000s following the derivation of the first human embryonic stem cell line or the birth of 'Dolly' the cloned mammal. Indeed, the 'embryo-centric' approach that characterised these past debates is still present.[4] Additionally, the globalisation phenomenon has permeated the genomics field, reshuffling the domain of debate and action from the

[1] K. E. Ormond et al., 'Human Germline Genome Editing', (2017) *The American Journal of Human Genetics*, 101(2), 167–176.

[2] D. Normile, 'Government Report Blasts Creator of CRISPR Twins', (2019) *Science*, 363(6425), 328.

[3] J. Qiu, 'American Scientist Played More Active Role in "CRISPR Babies" Project than Previously Known', (Stat News, 31 January 2019), www.statnews.com/2019/01/31/crispr-babies-michael-deem-rice-he-jiankui/.

[4] B. M. Knoppers et al., 'Genetics and Stem Cell Research: Models of International Policy-Making' in J. M. Elliot et al. (eds), *Bioethics in Singapore: The Ethical Microcosm* (Singapore: World Scientific Publishing, 2010), pp. 133–163.

national to the international. A case in point are the past International Gene Editing Summits aimed at fostering global dialogue.[5]

So far, human gene editing (HGE) has stimulated a new wave of policy by an extensive range of national and international actors (e.g. governments, professional organisations, funding agencies, etc.). This chapter outlines some of the socio-ethical issues raised by HGE technologies, with focus on human germline interventions (HGI), and addresses a variety of policy frameworks. It further analyses commonalities as well as divergences in approaches traversing a continuum of normative models.

34.2 NAVIGATING NORMATIVE SYSTEMS FOR HGE

Across jurisdictions, the regulation of genomics research has generally followed a linear path combining 'soft' and 'hard' approaches that widely consider governance as a 'domestic matter'.[6] Driven by scientific advances and changes in societal attitudes that resulted in greater technological uptake, genomics has increasingly become streamlined. This is reflected in the departure from the exceptionalist regulation of somatic gene therapy, now ruled by the general biomedical research framework, or in the increasing acceptance of reproductive technologies, where preimplantation genetic diagnosis is no longer considered as an experimental treatment.

Normative systems cluster a broad range of rules or principles governing and evaluating human behaviour, thereby establishing boundaries between what should be considered acceptable or indefensible actions. They are influenced by local historical, socio-cultural, political and economic factors. Yet, international factors are not without effect. These systems are enacted by a recognised legitimate authority and unified by their purpose, such as the protection of a common good. Often, they encompass set criteria for imposing punitive consequences in the form of civil and criminal sanctions, or by moral ones, in the form of social condemnation for deviations. The boundaries normative systems impose are sometimes set arbitrarily, while in others, these divisions are systematically designed. Thus, they either create invisible or discernible ethical thresholds by making explicit the principles and values underpinning them.

At the same time, normative systems are often classified by their coercive or binding nature, as exemplified in the binary distinction between 'soft' and 'hard' law. While this categorisation is somewhat useful, it is important to note that 'hard' and 'soft' laws are not necessarily binary; rather, they often act as mutually reinforcing or complementary instruments. The term 'soft law' refers to policies that are not legally binding or are of voluntary compliance, such as those emanating from self-regulatory bodies (e.g. professional guidelines, codes of conduct) or by international agencies (e.g. declarations) without formal empowered mechanisms to enforce compliance, including sanctions. In turn, 'hard law' denotes policies that encompass legally enforceable obligations, such regulations. They are of binding nature to the parties involved and can be coercively enforced by an appropriate authority (e.g. courts).

In the context of HGI, normative systems have opted for either a public ordering model consisting of state-led, top-down legislative approaches, or a private ordering one, which adopts a bottom-up, self-regulatory approach. In between them, there is also a mix of complex public–private models. Normative systems are present in a continuum from permissive, to intermediate,

[5] Human Genome Editing Initiative, 'New International Commission on Clinical Use of Heritable Human Genome Editing', (National Academies of Science Engineering Medicine, 2019), www.nationalacademies.org/gene-editing/index.htm.

[6] R. Isasi et al., 'Genetic Technology Regulation: Editing Policy to Fit the Genome?', (2016) *Science*, 351(6271), 337–339.

and to restrictive, reflecting attitudes towards scientific innovation, risk tolerance and considerations for proportional protections to cherished societal values (e.g. dignity, identity, integrity, equality and other fundamental freedoms). The application of HGE technologies in general, and HGI in particular, are regulated in over forty countries by a complex set of legislation, professional guidelines, international declarations, funding policies and other instruments.[7] Given their diverse nature, these norms vary in their binding capacity (e.g. legislation vs self-regulation), their breadth and their scope (e.g. biomedical research vs clinical applications vs medical innovation). Notwithstanding all the previously stated heterogeneity in normative models, harmonised core elements are still present between them.

Resistance towards applying HGE in the early stages of development commonly rest on beliefs regarding the moral – and fortiori legal – status of the embryo, social justice and welfare concerns. Their inheritable capacity, in turn, brings to the fora issues such as intergenerational responsibility and the best interests of the future child, together with concerns regarding their population (e.g. genetic diversity), societal (e.g. discrimination, disability) and political impacts (e.g. public engagement, democracy).[8] Remaining safety and efficacy challenges are also of chief importance and often cited to invoke the application of the 'precautionary principle'. Lastly, fears over 'slippery slopes' leading to problematic (e.g. non-medical or enhancements) uses and eugenic applications are at the centre of calls for restrictive normative responses.[9] However, across these systems the foundational principles underpinning a given norm and reflecting a society's or an institution's common vision and moral values are not always sufficiently substantiated, if at all articulated. As such, calls for caution to protect life, dignity and integrity, or against eugenic scenarios, appear as mere blanket or rhetorically arguments used for political expediency. As a consequence, the thresholds separating what is deemed as an acceptable or indefensible practice remain obscure and leave an ambiguous pathway to resolve the grey areas, mostly present in the transition towards clinical applications.

An unprecedented level of policy activity followed the rapid development of HGE. National and international scientific organisations, funding and regulatory agencies, as well advocacy groups have responded to these advances by enacting 'soft laws' appealing for caution, while others have opted for assessing the effectiveness of extant 'hard' and 'soft' policies.

34.2.1 *National Policy Frameworks*

Normative systems are often conceptualised using a hierarchy that differentiates between restrictive, intermediate and permissive approaches. Under this model, restrictive policies set up ethical and political boundaries by employing upstream limits – blank bans or moratoria – to interventions irrespective of their purpose. Pertaining to the application of HGI, restrictive approaches essentially outlaw or tightly regulate most embryo and gamete research. Supported by concerns over degrading dignity and fostering commodification of potential life, these approaches are based on attributing a moral – personhood or special – status to embryos, and thus advocating for robust governmental controls. Stipulations forbidding 'genetic engineering

[7] Isasi et al. 'Genetic Technology Regulation'.
[8] Ormond et al., 'Human Germline Genome Editing'.
[9] D. Baltimore et al., 'Biotechnology: A Prudent Path Forward for Genomic Engineering and Germline Gene Modification', (2015) *Science*, 348(6230), 36–38.

on human germ cells, human zygotes or human embryos"[10] or stating that no 'gene therapy shall be applied to an embryo, ovum or fetus"[11] exemplify this model.

While apparently wide-ranging, restrictive policies contain several potential loopholes. Among their major shortcomings are their reliance on research exceptions for therapeutic interventions that are deemed beneficial or life preserving to the embryo, or which are necessary in order to achieve a pregnancy. Terminological imprecisions will render as inapplicable a norm once a particular intervention could be considered as medical innovation or standard medical practice. Similar gaps are present in norms referencing specific technologies and in legal definitions of what constitute a embryo or a gamete, as all of these could later be outpaced by scientific advances, such as those brought by developments in the understanding of embryogenesis, organoids, and pluripotent stem cells. Indeed, the growth of HGE technologies has brought back to centre stage reflections over what is a reproductive cell. Evocative of the debates that took place during the peak of the stem cell era, the scientific, legal, and moral status of these entities continue to be tested, while at the same time remaining as the most prevalent policy benchmark. Whether silent or overtly present in distinct conceptualisations (e.g. developmental capacity or precise time period), criteria defining these early stages of human development are at the core of policies directing the permissibility of certain interventions.

The most favoured policy position is, however, an intermediate one, in which restrictions are applied downstream by banning research with reproductive purposes. Yet, this position considers permissible the practices that are directed at fundamental scientific research activities, such as investigating basic biology or aspects of the methodology itself. Policies adopted in countries such the Netherlands,[12] reflect this moderate perspective by outlawing any intervention directed at initiating – including attempts to initiate – a pregnancy with an embryo – or a reproductive cell – that has been subject to research or whose germline has been intentionally altered. Balancing social and scientific concerns, this approach calls for modest governance structures, yet close oversight. Nevertheless, it is at the risk of internal inconsistencies and ambiguities, given that norms are often the result of political compromises, which seem necessary in order to achieve policy adoption. A case in point are those research policies that confer moral and legal status to the human embryo while – at the same time – mandating their destruction after a certain period of time, or in ambiguous norms regarding the permissibility of clinical translation.

Largely misinterpreted, liberal models do not necessarily postulate a laissez-faire or a blanket unregulated approach. Rather, they provide significant scientific freedom predicated on the strength of their governance frameworks. They seek to promote scientific advances as a tool for social progress. In the context of HGI, liberal policies[13] allow for basic and reproductive research while banning clinical implementation. Given that these approaches depend on the effectiveness of their governance structures (e.g. licensing, oversight) with decisions often on a case-by-case or a de-facto basis, they are at the risk of arbitrary applications and system failure. Moreover, when the model rests on self-regulatory approaches devoid of effective enforcement mechanisms, they risk being – or being perceived to be – self-serving and following a market consumer model.

[10] Biosafety Law, Law No. 11, 2005 (Brazil).
[11] Bioethics and Safety Act 2013 (South Korea).
[12] Act Containing Rules Relating to the Use of Gametes and Embryos [The Embryos Act] 2002 (The Netherlands).
[13] Isasi et al. 'Genetic Technology Regulation'; S. Lingqiao and R. Isasi, *The Regulation of Human Germline Genome Modification in China. Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (Cambridge: Cambridge University Press; 2019).

Throughout policy models, the progression from research to clinical purposes is at times blurred in the peculiarities of such approaches. In fact, uncertainty regarding the scope of requirements is particularly present when there are permissible exceptions to norms forbidding HGE in reproductive cells. This is the case of Israel, which outlaws 'using reproductive cells that have undergone a permanent intentional genetic modification (germline gene therapy) in order to cause the creation of a person',[14] yet permits to apply to a research licence 'for certain types of genetic intervention' provided that 'human dignity will not be prejudiced'.[15] Similarly in France where 'eugenic practice aimed at organizing the selection of persons' and alteration(s) 'made to genetic characteristics in order to modify the offspring of a person' are banned,[16] yet at the same time the law exempts interventions aiming 'for the prevention and treatment of genetic diseases'[17] without providing further guidance.

Notwithstanding heterogeneous normative approaches, these models share a common objective: fostering scientific innovation and freedoms while protecting their vision of a common good, mostly expressed in safeguarding human dignity. In order to do so, sanctions and other coercive mechanisms are often adopted as deterrents. Indeed, the global HGE policy landscape is frequently accompanied by some form of sanctions, ranging from criminal to pecuniary and other social penalties. In particular, when such systems are based on legislative models, criminal penalties – substantial imprisonment and fines – are the standard. Upholding criminal law in biomedical research is an exceptional approach, and societies around the world use this tool to send the strongest condemnatory message. Here, as in other fields, criminal law serves as a tool for moral education and for achieving retribution, denunciation, and/or deterrence. But other type of penalties, such as moral sanctions, could be equally powerful. A radical example of the latter is China's 'social credit system'[18] where research misconduct is sanctioned by a wide umbrella of actors, which can impose an equally wide set of penalties and can even reach far beyond the traditional academic setting – from employment to funding, insurance, and banking eligibility. However, employing criminal law can be problematic because it often requires intentionality (mens rea). In the context of HGI, criminal law could create loopholes for downstream interventions when restrictions are limited to certain applications. For instance, German law bans the 'artificial' alteration of 'the genetic information of a human germ line cell'[19] and the use of such cell for fertilisation. Yet, such prohibition would not be applicable 'if any use of it for fertilisation has not been ruled out.'[20] While under Canadian legislation, it is an offense to 'knowingly' 'alter the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants.'[21]

Comparably, an issue of shared concern across normative systems are references to the eugenic potential of HGI. Fears over the ability to alter the germline infringing dignity and integrity have been widely articulated in policies. These concerns are best illustrated in France, where a new crime against the integrity of the human species has been typified and which

[14] Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law 1999 last renewed, 2009 (Israel).
[15] Prohibition of Genetic Intervention.
[16] Bioethics Law/Loi No. 2004-800 du aout 6 2004 relative à la bioethique and Code Civil (1804) 2004 last amendment 2015 (France).
[17] Bioethics Law.
[18] D. Cyranoski, 'China Introduces 'Social' Punishments for Scientific Misconduct', (*Nature*, 14 December 2018).
[19] Embryo Protection Act. 1990 (Germany).
[20] Embryo Protection Act.
[21] An Act respecting human assisted reproduction and related research (Assisted Human Reproduction Act) 2004 (Canada).

forbids 'carrying out a eugenic practice aimed at organizing the selection of persons.'[22] Similarly, Indian guidelines restrict 'eugenic genetic engineering for selection against personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics.'[23] In the same vein, Belgium outlaws carrying out 'research or treatments of eugenic nature that is to say, focused on the selection or amplification of non-pathological genetic characteristics of the human species.'[24] However, these policies provide little guidance for interpretation: when should interventions seeking to repair deleterious gene mutations or confer disease immunity – at the individual or population level – be considered eugenic interventions? Or a non-medical or enhancement practice? Selecting or de-selecting traits, while not an ethically neutral intervention, is not *per se* eugenics. Therefore, contextualising thresholds and defining the paraments for scientific and ethical acceptability of such interventions are required not only to provide much needed legal clarity, but also to avoid being perceived as simply rhetorical calls for political expediency.

34.2.2 *International Policy Frameworks*

Significant policy activity followed the refinement of HGE. A wide range of professional organisations, funding and regulatory agencies, quickly reacted to these developments with statements reflecting an equally varied range of positions.[25]A common theme among them is a circumspect attitude with appeals for the protection of dignity and integrity. While these positions endorse different normative approaches, they all pay particular attention to intergenerational responsibilities in their calls for principled restrictions to reproductive HGI.

Among the earliest international instruments addressing HGI are several non-binding Declarations adopted under the United Nations' framework. First, are the UNESCO's Universal Declaration on the Human Genome and Human Rights and the ensuing report on HGE by their International Bioethics Committee, which conceptualise the genome as the 'heritage of humanity' and in that vein, they plea for a moratorium on HGI that is based on prevailing 'concerns about the safety of the procedure and its ethical implications.'[26] Succeeding UNESCO's efforts, and after a failed attempt to adopt legally binding policy, the United Nations passed the UN Declaration on Human Cloning, calling on states 'to adopt the measures necessary to prohibit the application of genetic engineering techniques that may become contrary to human dignity.'[27] The pleas raised by these UN bodies remain a contemporary mandate, appealing for concrete measures to implement moral commitments into national legislation with the necessary enforcement measures.

Following the human rights approach enshrined in the abovementioned instruments, two important regional policies were enacted: the Council of Europe's Oviedo Convention[28] and

[22] Bioethics Law.

[23] Indian Council of Medical Research, 'Ethical Guidelines for Biomedical Research on Human Participants', (Indian Council of Medical Research, 2000 last amendment 2006).

[24] Act on Research on Embryos In Vitro – Loi relative à la recherché sur les embryons in vitro 2003 (Belgium).

[25] National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance*, (The National Academies Press, 2017); HUGO Ethics Committee, 'Statement on Gene Therapy Research', (Human Genome Organisation, 2001).

[26] UNESCO Constitution, 'Universal Declaration on the Human Genome and Human Rights', (United Nations Educational, Scientific, and Cultural Organization, 1997)

[27] United Nations, 'United Nations Declaration on Human Cloning', (United Nations, 2005).

[28] Council of Europe, 'Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine', (Council of Europe, 1997).

the European Union Clinical Trials Regulation.[29] These remain to date as the only international legally binding instruments governing HGI. The Oviedo Convention – as a general rule – explicitly forbids research and clinical interventions seeking to modify the genome. Yet, it exempts interventions that are 'undertaken for preventive, diagnostic or therapeutic purposes' when the aim is 'not to introduce any modification in the genome of any descendants'.[30] In turn, the cited EU Regulation focuses on gene therapy, banning clinical trials resulting 'in modifications to the subject's germ line genetic identity'.[31] Yet, no guidance has been provided to define or interpret the notion of 'genetic identity' in order to fully grasp the scope and breadth of such provisions.

Actors from different fields and parts of the world[32] have been quite prolific in articulating their positions with regards to HGE and in conveying how they envisage – or not – a path forward to reproductive HGE.[33] Even in China after the birth of the HGE twins, funding and professional organisations have swiftly publicised their positions,[34] aligning to mainstream ones. Indeed, all of these statements share several common threads. First, they all endorse a guarded approach to HGI, calling for temporary halts or moratoria, rather than advocating for permanent bans. The scope and breadth of such restrictions vary, from positions that seek to prevent clinical applications but allow reproductive research, to those that condemn any use. Second, a prospective approach also characterises them. While recent developments might render prevention a futile goal, precautionary measures fostering scientific integrity are still relevant. Third, they are by far based on scientific concerns, given the current inability to fully assess HGE's safety and efficacy. Notably, societal considerations focusing on protecting human rights are also prevalent. Lastly, appeals for public engagement are widespread, including calls for participatory, inclusive and transparent dialogue in order to empower stakeholders, inform policy-making efforts, and foster trustworthiness.[35]

34.3 THE ROAD TO HARMONISATION

Reactionary responses often follow the advent of scientific developments deemed to be disruptive to notions of integrity and dignity, such as with HGI. A concomitant result of the debates over genetic engineering techniques that started decades ago, is an overall fraught policy landscape that generally seeks to condemn such interventions but is void of global governance. However, they steered a level of policy convergence.

[29] European Union Clinical Trials Regulation 536/2014, OJ No. L 158/1, 2014.

[30] Council of Europe, 'Convention for the Protection of Human Rights'.

[31] European Union Clinical Trials Regulation.

[32] Ormond et al., 'Human Germline Genome Editing'; National Academies, 'Human Genome Editing'; Genetic Alliance Germline Gene Editing, 'A Call for Moratorium on Germline Gene Editing, Commentary by Genetic Alliance', (Genetic Alliance, 2019), www.geneticalliance.org/advocacy/policyissues/germline_gene_editing; National Academies of Sciences, Engineering, and Medicine, *International Summit on Human Gene Editing: A Global Discussion*, (The National Academies Press, 2015); National Academies of Sciences, Engineering, and Medicine, *Second International Summit on Human Genome Editing: Continuing the Global Discussion Proceedings of a Workshop—in Brief*, (The National Academies Press, 2019); International Society for Stem Cell Research, 'The ISSCR Statement on Human Germline Genome Modification', (ISSCR: International Society for Stem Cell Research, 2015).

[33] C. Brokowski, 'Do CRISPR Germline Ethics Statements Cut It?', (2018) *The CRISPR Journal*, 1(2), 115–125.

[34] Enforcement of Scientific Ethics Committee, Academic Division of the Chinese Academy of Sciences (CASAD), 'Statement About CCR5 Gene-edited Babies', (CASAD, 2018) www.english.casad.cas.cn/bb/201811/t20181130_201704.html; Chinese Society for Stem Cell Research & Genetics Society of China, 'Condemning the Reproductive Application of Gene Editing on Human Germline', (Chinese Society for Cell Biology, 2018), www.cscb.org.cn/news/20181127/2988.html.

[35] M. Allyse et al., 'What Do We Do Now?: Responding to Claims of Germline Gene Editing in Humans', (2019) *Genetics in Medicine*, 21(10), 2181–2183.

The plethora of social debates and policies emanating in the context of HGE demonstrate that across the globe, policy harmonisation remains a laudable objective. These efforts seek convergence in fundamental ethical safeguards for research participants – and future patients – coupled with criteria for regulating the application of these technologies. Throughout the world, and with diverse levels of success, governance mechanisms have been established empowering authorities with granting licences, conducting ethical oversight and enforcing compliance. However, for these requirements to be effective, consistent implementation is needed in a manner that respects scientific integrity and freedoms.

Harmonisation is therefore apparent in convergent criteria that bar or condemn HGI. Yet, in some cases, these positions are only transitory by virtue of established moratoria or other precautionary temporary measures. Thus, they remain effective only while extant safety and other technical concerns remain. In fact, some responses seemed to be solely based on our current state of knowledge, as exemplified below:

> Although our report identifies circumstances in which genome interventions of this sort should not be permitted, we do not believe that there are absolute ethical objections that would rule them out in all circumstances, for all time. If this is the case, there are moral reasons to continue with the present lines of research and to secure the conditions under which heritable genome editing interventions would be permissible.[36]

Additional examples of the latter are found in Singapore policy forbidding HGI due to 'insufficient knowledge of potential long-term consequences'[37] and pending 'scientific evidence that techniques to prevent or eliminate serious genetic disorders have been proven effective'.[38] The same rationale underpins Indian policy restricting 'gene therapy for enhancement of genetic characteristics (so called designer babies)' based on 'insufficient information at present to understand the effects of attempts to alter/enhance the genetic machinery of humans'.[39]

Despite diverse normative systems and societal contexts, the world seems to be disposed towards harmonisation.[40] Which factors help explain this phenomenon? Policy transfer and emulation[41] might be factors supporting policy growth and the emergence of global convergence. However, such consensus is still quite precarious as best exemplified by the level of international involvement and the strength of the response to recent developments.[42] Scepticism over the stability of an emerging or actual consensus is based on the fact that policy responses thus far are grounded in distinct rationale. While they all call for 'action' and 'caution', they legitimately differ in their significance and understanding of such terms. As we have seen, in some instances a cautious approach has been translated in voluntary moratoria. This is the

[36] Nuffield Council on Bioethics. 'Genome Editing and Human Reproduction: Social and Ethical Issues', (Nuffield Council on Bioethics, 2018), 154.

[37] Bioethics Advisory Committee Singapore, 'Ethics Guidelines for Human Biomedical Research', (Bioethics Advisory Committee Singapore, 2015), 50.

[38] Ibid.

[39] Indian Council of Medical Research, 'Ethical Guidelines for Biomedical Research'.

[40] Nuffield Council on Bioethics, 'Genome Editing and Human Reproduction'; The Hinxton Group, 'Statement on Genome Editing Technologies and Human Germline Genetic Modification', (The Hinxton Group: An International Consortium on Stem Cells, Ethics, & Law, 2015).

[41] European Academies' Science Advisory Council, 'Genome Editing: Scientific Opportunities, Public Interests and Policy Options in the European Union', (EASAC: European Academies' Science Advisory Council, 2017).

[42] R. Isasi, 'Human Genome Editing: Reflections on Policy Convergence and Global Governance' in ZfMER (eds), *Genomeditierung – Ethische, rechtliche und kommunikations – wissenschaftliche Aspekte im Bereich der molekularen Medizin un Nutzplanzenzüchtung, Zeitschrift für Medizin-Ethik-Recht*, (Nomos, 2017), pp. 287–298.

temporarily halting of certain types of clinical interventions or in promoting public engagement[43] so as to allow for policy to reflect changes in scientific knowledge or societal values. In other instances, precautionary responses – under vigilant oversight – purposely do not deter or outlaw research given the need for evidence in quantifying risks and benefits. Finally, in other circumstances, caution has signified enacting blank legal prohibitions.[44]

Conceptual misunderstandings between the notion of harmonisation[45]and standardisation are often present.[46] As such, appeals for standardisation frequently do not realise that they entail the creation of uniform legal and ethical standards, which are not only highly unachievable, but also undesirable particularly with respect to HGE. In the latter, sovereignty and moral diversity must be respected. Harmonisation[47] processes do not seek uniformity as the end result, they rather entail substantial correspondence between fundamental ethical principles present across the continuum of normative responses. They aim to foster cross-jurisdictional collaboration and thus governance. Still, harmonisation is not without challenges, particularly in regards to criteria for evaluating policy convergence and assessing variations in the regulation of fundamental ethical requirements, where thresholds for determining the significance of a given policy can vary. The latter is of great importance as variations could potentially undermine the integrity of ethical safeguards or societal values.

34.4 CONCLUSION

For the sceptics, attempts to meaningfully engage a global community of stakeholders to adopt binding policy and governance will inevitably end in 'pyrrhic' victories[48] – as in the past. History seems to be full of examples to support this position.[49] Indeed, thus far the inability to form a representative community to reconcile conflicting interests – economic and otherwise – and to prevent egregious actions, has taught us that sole condemnation of a particular intervention is futile for preventing abuses absent morally binding obligations and 'actionable' regulatory frameworks. For the optimists, the level of societal engagement, emergent policy convergence and swift condemnatory responses following the most contemporaneous and appalling gross violations of human rights and scientific standards[50] are grounds to believe that a level of policy harmonisation remain a realistic endeavour. Crisis provides the opportunity to significant alter the direction and strength of a given policy system, including reshaping governance mechanisms and reconfiguring the power of stakeholders. It therefore has the ability to transform more than policy; it can stir real change in collective behaviour. In the aftermath of this crisis, the central lesson must be that without defining and achieving societal consensus and governance at both the local and global level, no policy system would ever be completely effective.

[43] E. S. Lander et al., 'Adopt a Moratorium on Heritable Genome Editing', (2019) *Nature*, 567(7747), 165–168; Allyse et al., 'What Do We Do Now?'.

[44] Allyse et al. 'What Do We Do Now?'.

[45] M. Boodman, 'The Myth of Harmonization of Laws', (1991) *The American Journal of Comperative Law*, 39(4), 699–724.

[46] R. Isasi, 'Policy Interoperability in Stem Cell Research: Demystifying Harmonization', (2009) *Stem Cell Reviews and Reports*, 5(2), 108–115.

[47] Oxford English Dictionary, 'Harmonization', (2019) *Lexico*, https://en.oxforddictionaries.com/definition/harmonization.

[48] R. Isasi and G. J. Annas, 'To Clone Alone: The United Nations Human Cloning Declaration', (2006) *Revista de Derecho y Genoma Humano*, 49(24), 13–26.

[49] United Nations, 'United Nations Declaration on Human Cloning'; D. Lodi et al., 'Stem Cells in Clinical Practice: Applications and Warnings', (2011) *Journal of Experimental & Clinical Cancer Research*, 30(1), 9.

[50] Normile, 'Government Report', 328.