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Article (Published Version)

Bu, Qingxiu (2019) Reassess the law and ethics of heritable genome editing interventions: lessons for China and the world. *Issues in Law & Medicine*, 34 (2). pp. 115-144. ISSN 8756-8160

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Reassess the Law and Ethics of Heritable Genome Editing Interventions: Lessons for China and the World

Qingxiu Bu, LL.M., LL.M, Ph.D.*

ABSTRACT: The current ethical and legal standards for human subjects research do not adequately address human gene editing technologies, because scientific advancements in this field have outpaced regulatory policy. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technique allows the rewriting of life's code, but is fraught with scientific and ethical quandaries. In particular, the genetic alteration of human embryos in vitro in China has caused worldwide repercussions. It is hard to predict the long-term effects of proposed edits, which raises an inquiry about whether it is appropriate for humans to purposely alter any aspect of their genetic future. Genome editing is moving too quickly for processes of critical reflection, such as law and regulation, to keep pace. The ethical, legal and social implications of the use of these technologies in humans remain uncertain.

* LLM (Soochow); LL.M (Groningen); Ph.D. (Birmingham); PGCHET (Queen's). Dr. Qingxiu has published widely in a variety of areas of law, many of which are themed around law and ethics, with a particular focus on the development of legal infrastructures in China. He joined Sussex Law School in 2013 as Associate Professor, having previously been a lecturer in law at Cardiff Law School, Cardiff University (2007-08) and School of Law, Queen's University Belfast (2008-13), during which he taught Transnational Business Law at Centre of Transactional Legal Studies (CTLS), Georgetown University as Adjunct Professor. Qingxiu was appointed as Li Kashing Professor of Practice at Faculty of Law, McGill University in 2019. He has held visiting posts at various institutions, including Lund University, Sweden, University College Dublin, Ireland, Tel Aviv University, Israel and the Max Planck Institute for Comparative and International Private Law in Germany. He worked also as Docent at the Institute of Global Law and Policy (IGLP), Harvard Law School in January 2013 and 2014. Qingxiu has completed four projects funded respectively by the British Academy, Department for Business, Energy & Industrial Strategy (BEIS), Newton Fund, and British Council (PMI) during the past years.

The resultant tension within the existing framework calls into question the underlying values on which moral and legal norms repose. This article explores the implications for law, ethics, regulation and health policy. Balancing potential benefits against the risk of unintended harms will shape perspectives on whether and how to use these technologies. Responsible engagement with decision makers and stakeholders, among other things, will promote transparency, confer legitimacy, and improve policy making.

Introduction

The crossover between ethics and adequate governance in science seems particularly acute in the case of genome editing. The emerging technology has revolutionised genetics and marked a new generation in biomedical sciences. China has launched ground-breaking human clinical trials making use of the CRISPR gene editing tool. A Chinese scientist, Jiankui He, claimed to have used the technology to alter the DNA of two new babies in China. The practice exacerbates uncertainties that exist in applying governance systems and existing norms. The use of CRISPR puts pressure on the normative judgements enshrined in moral and legal codes. He's claims highlight the immediate need to develop strong global consensus and legal frameworks on the ethical use of human genome editing. Given the unprecedented growth of technology and the current inadequacy of scientific governance, an inquiry arises as to whether societal values will be reflected in how genome editing is eventually applied in practice.

In response to this rapidly shifting global concern, this study proceeds in five parts to address challenges arising from questions about the ethical, legal and social implications (ELSI) of genome editing.¹ Part I looks at CRISPR's pros and cons and ascertains theoretically whether He's conduct represents a game changer or opens a Pandora's Box. Part II explores ethical and social implications of using CRISPR, considers the theory of social licence underlying the relevant governance, and looks at the ethical and regulatory concerns that CRISPR has raised. This section also examines how ethical reflection and governance systems can engage effectively with the technology, and whether equitable access to technology is both warranted and available. Part III provides a critical analysis of the current legal framework on this topic in the Chinese context. China's lax regulation and enforcement results inevitably in ethical arbitrage. A variety of contributing factors will be discussed as well. Part IV refers to international norms in respect to the global challenge. Notably, enforcement makes a significant difference apart from the need for reaching international consensus. Part V considers how the implementation of germline procedures will interact with current and future societal discourse, institutions,

¹ Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review Section 3-Moral Perspectives' (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 115.

and law. Some regulatory models are examined herein, which can address the ensuing scientific, socio-ethical and legal challenges. This section then moves to analyse the different levels and scope of regulation and the challenges of a global situation in which varying approaches to legislation express diverse ethical values. A model that might suit China's situation will be explored.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR): Pros and Cons

A lab in the Massachusetts Institute of Technology (MIT) has managed to genetically alter human embryos.² A new tool of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) acts like molecular scissors, enables targeted genomic editing and more precise and efficient genetic modifications.³ It is considered as “the hallmark of a bacterial defence system,” serving as the immune system in bacteria.⁴ As a commentator asserted, the revolutionary technology has vast potential for improving human life, as “the biggest biotech discovery of the century.”⁵ An international consensus says that it is ethical to improve gene editing, but that it should not be used to establish a pregnancy.⁶ It is essential to evaluate whether the anticipated benefits are reasonable with respect to the risk of adverse effects.

Pros and Cons

Genome editing holds conceptually transformative medical potential.⁷ There are implications arising from the scope and scale of the techniques. Rewriting genes is fraught with scientific and ethical quandaries.⁸ The safety of gene editing on human beings has not been confirmed, and the treatment cannot be withdrawn if adverse effects are identified. Its mistakes would be amplified by their extension to innumerable future generations. It is the magnification of genetic harm that distinguishes germline editing from other types of intervention. While CRISPR has shown significant promise for treating disease, little is known about its long-term risks.⁹ The most obvious safety concerns are called ‘off-target’ mutations, representing unintended changes to the ge-

² Steve Connor, ‘First Human Embryos Edited in U.S., Using CRISPR’ *MIT Technology Review* (29 December 2017).

³ Guy Riddihough, ‘CRISPR-Cas9 Molecular Scissors’ (2016) 351 *Science* 867.

⁴ Samuel H. Sternberg, Hagen Richter, et al., ‘Adaptation in CRISPR-Cas Systems’ (2016) 61 *Molecular Cell Review* 797, 808.

⁵ Carl Zimmer, ‘Breakthrough DNA Editing Born of Bacteria’ *Quanta Magazine* (6 February 2015).

⁶ Jeanne Snelling and Mike King, ‘Rogue Scientist: The Human CRISPR Experiment’ (Blog: *Journal of Medical Ethics*, 29 November 2018). <<https://blogs.bmj.com/medical-ethics/2018/11/29/rogue-scientist-the-human-crispr-experiment/>>.

⁷ John Loike, ‘Don’t Ban the Use of CRISPR in Embryos’ *TheScientist* (29 November 2018).

⁸ Preetika Rana, Amy Dockser Marcus and Wenxin Fan, ‘China, Unhampered by Rules, Races Ahead in Gene-Editing Trials’ *The Wall Street Journal* (21 January 2018).

⁹ Matthew Campbell, ‘China Shrinks from the Gattaca Age’ *Bloomberg* (5 December 2018).

nome.¹⁰ Irresponsible practice might bring about unforeseen disastrous outcomes in the long run. Unwanted genetic conditions might be permanently removed, any unintended consequences from altering the germ-line will be passed on though.¹¹ Adverse effects might even be multiplied by reverberation across generations,¹² which could be irreversible.

Potential precise medication. Genome editing is an exciting technology to improve human health, given its nature in transformation. CRISPR can be used to treat genetic diseases and prevent extremely severe conditions being passed on to their descendants. Using it to selectively insert, delete or replace DNA is conducive to far greater precision. The ability to make precise changes to the genes of humans offers new ways to tackle global challenges in health. It is an attempt at an ultimate cure, since it treats disease at its very root.¹³ It might eliminate the root causes of hereditary human diseases, and even correct genetic errors or reduce the risk of disease.¹⁴ With the potential to permanently eradicate certain genetic disorders, some assert CRISPR could bring about an end to some of humanity's worst diseases. Instead of temporarily fixing defective cells through the introduction of corrected or functional genes, CRISPR promises to correct the defect in the reproductive cells, producing progenies that are free of the defective gene.¹⁵ Furthermore, genetic modification could open up possibilities to carry out preventative procedures before the body has even begun to exhibit symptoms of a given disease.¹⁶ However, explicit scientific standards have not been established to quantify off-target genome alterations.¹⁷

¹⁰ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 122; Christopher Gyngell, Thomas Douglas and Julian Savulescu, 'The Ethics of Germline Gene Editing' (2017) 34 (4) *Journal of Applied Philosophy* 498, 513; Pinar Akcakaya, Maggie L. Bobbin, et al., 'In vivo CRISPR Editing with no Detectable Genome-wide off-Target Mutations' (2018) 561 *Nature* 416, 419.

¹¹ Kelly E. Ormond, Douglas P. Mortlock, et al., 'Human Germline Genome Editing' (2017) 101 (2) *American Journal of Human Genetics* 167, 176.

¹² National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 122.

¹³ Marcel Doerflinger, W. Leonard Forsyth, et al., 'CRISPR/Cas9-The Ultimate Weapon to Battle Infectious Diseases?' (2017) 19 (2) *Cellular Microbiology* e12693.

¹⁴ 'Explainer: CRISPR Technology Brings Precise Genetic Editing-And Raises Ethical Questions' Conversation (26 March 2015).

¹⁵ 'Explainer: CRISPR Technology Brings Precise Genetic Editing-And Raises Ethical Questions' Conversation (26 March 2015).

¹⁶ Karin Christiansen, 'Genome Editing: Are We Opening a Back Door to Eugenics?' *ScienceNodic* (14 November 2017).

¹⁷ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 17-29.

Furthermore, a theoretical issue remains unaddressed in the ambit of consequentialism.¹⁸ An action to be selected should be the one that produces the best consequences, with all factors taken into account.¹⁹ A major concern arises from uncertain consequences that germline changes could have on future generations. As some commentators observed:

Philosophically or ethically justifiable applications for this technology, should any ever exist, are moot until it becomes possible to demonstrate safe outcomes and obtain reproducible data over multiple generations.²⁰

It always takes years for a new discovery to be tested regarding its harms and benefits. The risks and benefits of technological interventions of such a kind should not be resolved as abstract moral issues by philosophers. In this regard, CRISPR might one day be useful for permanently eliminating genetic traits in the human species, but not without enormous risks.²¹

Safety. Safety is paramount among the arguments against modifying the human germ line, which concern has not been adequately addressed. It is unrealistic to preclude some off-target effects, neither possible to avoid inflicting more harm than good on future humans.²² Changes in one gene that has been “knocked out” and replaced with another could have unforeseen and harmful effects elsewhere in the genome.²³ In this vein, the genome editing may cause more damage to DNA, and its editing process may disrupt healthy genes. Likewise, the prospect of enhancements for future generations may be viewed as problematic, because it could change the properties of healthy embryos.²⁴ Adding genes instead of repairing them might interfere with the normal expression of other genes. It is necessary to demonstrate that the editing procedures will not lead to any significant increase in unintended variants.²⁵ Governing the rapidly emerging technology through adequate assessment will reduce its associated risks. Higher safety

¹⁸ Sarah Chan and John Harris, ‘Consequentialism without Consequences: Ethics and Embryo Research.’ (2010) 19 (1) *Cambridge Quarterly of Healthcare Ethics* 61, 74.

¹⁹ Philip Gardiner ‘A Virtue Ethics Approach to Moral Dilemmas in Medicine’ (2003) 29 (5) *Journal of Medical Ethics* 297, 302.

²⁰ Edward Lanphier, Fyodor Urnov, et al., ‘Don’t Edit the Human Germ Line’ (2015) 519 (7544) *Nature* 410, 411.

²¹ Laurie Garrett, ‘CRISPR: Transformative and Troubling’ (Council on Foreign Relations, 13 April 2016) <<https://www.cfr.org/expert-brief/crispr-transformative-and-troubling>>.

²² ‘Genome Editing: Are We Opening a Back Door to Eugenics?’ *ScienceNordic* (14 November 2017).

²³ Noah Feldman, ‘Outrage Over Human Gene Editing Will Fade Fast’ *Bloomberg* (27 November 2018).

²⁴ Edward Lanphier, Fyodor Urnov, et al., ‘Don’t Edit the Human Germ Line’ (2015) 519 (7544) *Nature* 410, 411.

²⁵ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 111.

standards need to be applied to gene editing research.²⁶ However, for safety to be assessed requires years if not decades of studying how genes play out in a lifespan.

Germline interventions make changes that are heritable.²⁷ Accordingly, it has sparked serious debate about the ethical implications of the heritable changes to human genetic code. Affecting all cells in an organism, the method allows precise editing of genes for targeted traits, which can be passed down to future generations.²⁸ It is going to deeply affect the future generations, and even affect the make-up of species of the human being. The issue is that the standard of scientific governance varies across jurisdictions. Heritable genome editing interventions should only be permitted provided that legitimate and effective mechanisms are in place to redress those effects.²⁹ The technology is so new that the potential risks to human subjects cannot possibly justify the hypothetical benefits. Scientists do not fully understand the scope of the unintended damage CRISPR may do to DNA elsewhere in the genome or how deactivating C-C chemokine receptor type 5 (CCR 5) might leave people vulnerable to other diseases.³⁰ Disproportionate risks of editing the germline may outweigh the potential benefits. The benefits are at best hypothetical whereas the risks are high, which is partly unknowable.³¹ It is essential to weigh up the potential benefits, risks and harms, and evaluate off-target events and other potential side effects.³² A recent Chinese scandal has escalated the concerns.

The China Case

China was first out of the block testing CRISPR on humans.³³ A Chinese researcher, Jiankui He, recently claimed that he had created the first genetically engineered human babies in November 2018.³⁴ He's conduct would potentially alter the genetic makeup

²⁶ David Baltimore, Paul Berg, et al., 'Biotechnology. A Prudent Path Forward for Genomic Engineering and Germline Gene Modification' (2015) 348 *Science* 36, 38.

²⁷ Ainsley Newson and Anthony Wrigley, 'Being Human: The Ethics, Law, and Scientific Progress of Genome Editing' (2016) 87 (1) *The Australian Quarterly* 3, 8.

²⁸ Mary Todd Bergman, 'Perspectives on Gene Editing' *The Harvard Gazette* (9 January 2019).

²⁹ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 137.

³⁰ 'The Era of Human Gene-Editing May Have Begun. Why That Is Worrying' *The Economist* (1 December 2018).

³¹ J. Benjamin Hurlbut, Sheila Jasanoff and Krishanu Saha, 'The Chinese Gene-Editing Experiment Was an Outrage. The scientific Community Shares Blame' *The Washington Post* (29 November 2018).

³² Shixiong Zhang, Xiangtao Li, et al., 'Synergizing CRISPR/Cas9 Off-Target Predictions for Ensemble Insights and Practical Applications' (2019) 35 (7) *Bioinformatics* 1108, 1115.

³³ Preetika Rana, Amy Dockser Marcus and Wenxin Fan, 'China, Unhampered by Rules, Races Ahead in Gene-Editing Trials' *The Wall Street Journal* (21 January 2018).

³⁴ Gina Kolata, Sui-Lee Wee and Pam Belluck, 'Chinese Scientist Claims to Use CRISPR to Make First Genetically Edited Babies' *The New York Times* (26 November 2018).

of the human race.³⁵ He's development of the technique and the capability will result in that capability becoming widely available across borders. Germline mistakes made in China and inherited indefinitely will, in all probability, filter into the worldwide human genome affecting future generations. As such, it should be of concern to the whole world since people will be even more genetically interconnected in the future. Given a largely-unresolved dimension of science ethics, the use of CRISPR to modify human embryos has prompted a debate on the ethics of human genetic technologies.³⁶

Responsible use of the CRISPR: More inquiries than answers. Responsible research will actualise CRISPR's potential to cure those most devastating genetic diseases.³⁷ However, a question of unethical use has been perceived from the outset of the technology. He flouted conventions of safety and research ethics.³⁸ Due to the absence of thorough oversight, his act constitutes a departure from a variety of ethical and legal norms that prevent use of this technology in human reproduction.³⁹ Risks in the case have not been properly assessed. Many safety issues may have unintended irreversible effects that may not be known for years,⁴⁰ and could even spark a dangerous immune reaction. He ignored the complex ethical problems related to creating and destroying human embryos. As Collins said:

the concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed.⁴¹

Similarly, a statement by an International Summit⁴² convened by the Science and Medicine Academies of the United States, the United Kingdom and China provides that:

It would be irresponsible to proceed with any clinical use of germline editing unless and until

³⁵ Stefan Kunzelmann and Klaus Förstemann, 'Reversible Perturbations of Gene Regulation after Genome Editing in *Drosophila* Cells' (2017) 12 (6) *PLoS ONE* (28 June 2017).

³⁶ Alice Park, 'Experts Are Calling for a Ban on Gene Editing of Human Embryos. Here's Why They're Worried' *Time* (13 March 2019).

³⁷ John Loike, 'Opinion: Don't Ban the Use of CRISPR in Embryos' *The Scientist* (29 November 2018)

³⁸ 'Germline Gene-Editing Research Needs Rules' *Nature* (13 March 2019).

³⁹ Jeanne Snelling and Mike King, 'Rogue Scientist: The Human CRISPR Experiment' (Blog: *Journal of Medical Ethics*, 29 November 2018).

⁴⁰ Preetika Rana, Amy Dockser Marcus and Wenxin Fan, 'China, Unhampered by Rules, Races Ahead in Gene-Editing Trials' *The Wall Street Journal* (21 January 2018).

⁴¹ Francis Collins, *Statement of NIH Funding of Research Using Gene-Editing Technologies in Human Embryos* (Maryland, National Institutes of Health, 28 April 2015) <<https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>>.

⁴² The National Academies of Sciences, Engineering, and Medicine (NASEM), 'International Summit on Human Gene Editing' (2015) <<http://nationalacademies.org/gene-editing/Gene-Edit-Summit/>>; Travis Germline, 'Editing Dominated DNA Summit' (2015) (350) *Science* 1299, 1300.

- (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives; and
- (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight.⁴³

The above approaches demonstrate that there is a considerable need to address the social and ethical implications of inherited genetic modifications. To establish safety and ethical consensus is the first imperative. It is sensible to demand strong evidence of safety and reasonable risk/benefit ratios before new technologies are made available clinically.⁴⁴ He's case heightened the global awareness about the uncertain risks and the need to regulate powerful new human biotechnologies. Of the utmost importance is to make responsible use of human germline modifications, in order to treat or cure human diseases.

A Game Changer vis-à-vis A Pandora's Box. The concern is mainly focused upon the core of the ethical prohibition on modification of the human germline. The safety and efficacy have not been demonstrated sufficiently through research in human embryos.⁴⁵ Regalado observed that:

The genetic editing of a speck-size human embryo carries significant risks, including the risks of introducing unwanted mutations or yielding a baby whose body is composed of some edited and some unedited cells.⁴⁶

Once it becomes scientifically safe to proceed with human gene editing, the legitimate ethical concern is likely to be outweighed by the ethical imperative to avoid disease.⁴⁷ Given grave concerns regarding the ethical and safety implications, the clinical application in human embryos could have unpredictable effects on future generations, which is dangerous and ethically unacceptable. Problematically, there is no adequate pre-clinical data to justify a first-in-humans trial.⁴⁸ The Chinese case raises questions

⁴³ National Academies of Sciences, Engineering, and Medicine (NASEM), *Communicating Science Effectively: A Research Agenda* (Washington, DC: The National Academies Press, 2016) 9.

⁴⁴ 'Why Treat Gene Editing Differently in Two Types of Human Cells?' *The Conversation* (7 December 2015).

⁴⁵ Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review Section 3-Moral Perspectives' (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 115.

⁴⁶ Antonio Regalado, 'Chinese scientists are creating CRISPR babies' *MIT Technology Review* (25 November 2018).

⁴⁷ Noah Feldman, 'Outrage over Human Gene Editing Will Fade Fast' *Bloomberg* (27 November 2018).

⁴⁸ Jeanne Snelling and Mike King, 'Rogue Scientist: The Human CRISPR Experiment' (Blog: *Journal of Medical Ethics*, 29 November 2018). <<https://blogs.bmj.com/medical-ethics/2018/11/29/rogue-scientist-the-human-crispr-experiment/>>.

about humanity, human identity, integrity and dignity.⁴⁹ A new boundary in unethical behaviour has been crossed. The risks extend not only to the health and safety of the children, but also to the integrity of the social relationships.⁵⁰ As discussed above, the potential harms may outweigh the benefits of altering the genome of an embryo. Germline editing changes reproductive cells, meaning that any alterations will remain in the gene pool and be passed to each subsequent generation. The changes are riskier because early mistakes could have lasting consequences on future generations, altering the inheritance permanently.⁵¹ It is implied that ethics are clearly not keeping pace with the development of the gene editing technologies in China. There is potential for marginalisation of persons, and the ways in which social inequalities could be reinforced by limited access to them.⁵² The Chinese trial practice should not proceed until a more equitable approach to setting the terms of debate is achieved. They should come up with guidelines at the international level, and avoid any possible large-scale negative implications for future generations.⁵³ It is worth exploring how to address the issue from moral and ethical perspectives.

Moral and Ethical Responses to Genome Editing

The process of human germline modification has been the subject of ethical debates long before the technology existed. There has been little research of the critical ethical issues involved with the unknown risks in resulting future generations. An ethical approach to risk calls for revaluations of the possible consequences.⁵⁴ In addition, societal-level concerns are particularly acute with respect to genome-editing interventions aimed at enhancing human capabilities.⁵⁵ Wider issues of social justice remain unaddressed in terms of the equity in distributing its benefits.⁵⁶ It is vital to give special consideration to possible negative effects that could cause discrimination, injustice or disadvantage in society.

⁴⁹ J. Benjamin Hurlbut, Sheila Jasanoff and Krishanu Saha, 'The Chinese Gene-Editing Experiment Was an Outrage. The scientific Community Shares Blame' *The Washington Post* (29 November 2018).

⁵⁰ Anna Zaret, *Editing Embryos: Considering Restrictions on Genetically Engineering Humans* (2016) 67 *Hastings Law Journal* 1805, 1839.

⁵¹ National Scientific Council on the Developing Child, 'Early Experiences Can Alter Gene Expression and Affect Long-Term Development' (Working Paper No. 10, Centre on the Developing Child, Harvard University, 2010) <<http://www.developingchild.net>>.

⁵² Christine DiPasquale, 'Gene Editing and Human Identity: Promising Advances and Ethical Challenges' (15 April 2018). <<https://www.aaas.org/news/gene-editing-and-human-identity-promising-advances-and-ethical-challenges>>.

⁵³ Reenita Das, 'Gene Editing With CRISPR-Cas9: The Next Step In Human Evolution Will Be Worth \$25 Billion By 2030' *Forbes* (14 December 2017).

⁵⁴ Greg Licholai, 'Is CRISPR Worth the Risk?' *Yale Insights* (21 August 2018).

⁵⁵ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 24.

⁵⁶ Ainsley Newson and Anthony Wrigley, 'Being Human: The Ethics, Law, and Scientific Progress of Genome Editing' (2016) 87 (1) *The Australian Quarterly* 3, 8.

Social Licence Theory

Any innovation has an implicit responsibility towards society.⁵⁷ The Universal Ethical Code for Scientists recognises the responsibility corresponding to the ‘social licence to practise’ as one of its three cardinal principles.⁵⁸ There is theoretic hazard in genome editing though. The concept of inherent dignity proposes to supply an objective ground for making distinctions between acceptable and unacceptable uses of technology.⁵⁹ The use of these technologies must be regulated through ethical oversight. As a leading ethics watchdog,⁶⁰ the Nuffield Council on Bioethics reiterates the value from a perspective of human rights as well. The effect of asserting human rights is essentially to mark out and defend limits of tolerable behaviour.⁶¹ People whose genomes that have been edited should be entitled to the full enjoyment of human rights.⁶² In this sense, the processes of ethical oversight should ideally reflect society’s shared values and norms, not merely as they pertain to informed consent, but as they pertain to our sensibilities about the right ways to care for next generations.⁶³

Equitable Concerns: Exacerbating Social Inequities and Injustice

Benefits from CRISPR innovation raise concerns and controversies about fairness and distributive justice across all layers of society.⁶⁴ Such interventions could be used not just for treatment, but also for enhancement, of which the latter is accessible only

⁵⁷ Walter D. Valdivia and David H. Guston, ‘Responsible Innovation: A Primer for Policymakers’ (Centre for Technology Innovation at Brookings, May 2015) <https://www.brookings.edu/wp-content/uploads/2016/06/Valdivia-Guston_Responsible-Innovation_v9.pdf>.

⁵⁸ Department for Business, Energy & Industrial Strategy (BEIS), ‘Rigour, Respect, Responsibility: A Universal Ethical Code for Scientists’ (London, 12 September 2007) <<https://www.gov.uk/government/publications/universal-ethical-code-for-scientists>>.

⁵⁹ Nuffield Council on Bioethics, ‘Genome Editing: An Ethical Review Section 3-Moral Perspectives’ (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 28.

⁶⁰ ‘Ethics Backing for Tailored Drugs’ *BBC* (23 September 2003); The Nuffield Council on Bioethics was established in 1991, and funded jointly by the Nuffield Foundation, the Medical Research Council (MRC) and The Wellcome Trust. It examines and reports on the ethical questions raised by advances in biological and medical research.

⁶¹ Nuffield Council on Bioethics, ‘Genome Editing: An Ethical Review Section 3-Moral Perspectives’ (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 28.

⁶² Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 145.

⁶³ ‘CRISPR Babies Raise an Uncomfortable Reality-Abiding by Scientific Standards Doesn’t Guarantee Ethical Research’ *The Conversation* (3 December 2018).

⁶⁴ Carolyn Brokowski and Mazhar Adli, ‘CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool’ (2019) 431 (1) *Journal of Molecular Biology* 88, 101.

to a few rather than to everyone.⁶⁵ The ability to modify people's genes could lead to disparities between genetic haves and have-nots⁶⁶ and further result in systematic disadvantage. This could make the CRISPR product available to only the world's elites,⁶⁷ which, in substance, not only exacerbates existing social inequalities, but also creates new ones. There is an impact on social, intergenerational or even global justice, that is, fair distribution of advantages or opportunities among different groups in a society.⁶⁸ It remains uncertain how to ensure that the most vulnerable or marginalised sections of the population are not to be disadvantaged.

Aside from using gene-editing to tackle medical issues, He's research raises the spectre of gene-editing enhancements. An enhancement would be a modification to a normative non-disease trait to make an improvement to it.⁶⁹ The distinction between treatment and enhancements and between normal functioning and disease remains vague.⁷⁰ The lines between what are considered prevention and enhancement are not easily discernible in some cases.⁷¹ There is no clear line between disease treatment and enhancement.⁷² There is no ethical consensus as to how to define the blurry boundaries, particularly, in the case of nontherapeutic enhancement.⁷³ Permitting the practice could result in the creation of super humans who have an unfair genetic advantage over those unenhanced ones. Savulescu defends by referring to the principle of Procreative Beneficence, arguing that there are significant moral reasons to select the finest child.⁷⁴ Nevertheless, there is a range of moral arguments against selective technologies.⁷⁵ The pursuit of the 'perfection' of human traits cannot be ethically justified, either. The ben-

⁶⁵ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 127; Lisa Sowle Cahill, 'Germline Genetics, Human Nature, and Social Ethics' in Ronald Cole-Turner (ed.) *Design and Destiny: Jewish and Christian Perspectives on Human Germline Modification* (Cambridge, MA: MIT Press, 2008) 145-166.

⁶⁶ George Church and Marcy Darnovsky, 'Should Heritable Gene Editing Be Used on Humans?' *The Wall Street Journal* (10 April 2016).

⁶⁷ Carolyn Brokowski and Mazhar Adli, 'CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool' (2019) 431 (1) *Journal of Molecular Biology* 88, 101.

⁶⁸ John Rawls, *A Theory of Justice* (Cambridge, MA: Belknap Press, 1971) 3-10.

⁶⁹ Congressional Research Service (CRS) Report 'Advanced Gene Editing: CRISPR-Cas9' (7 December 2018 <<https://fas.org/sgp/crs/misc/R44824.pdf>>19).

⁷⁰ Joseph Roberts, 'Treating the Enhancement Debate: Irrelevant Distinctions in the Enhancement Medicine Debate' (2014) (28) (1) *Journal of Philosophy* 1, 12.

⁷¹ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 181, 194.

⁷² Mary Todd Bergman, 'Perspectives on Gene Editing' *The Harvard Gazette* (9 January 2019).

⁷³ Saskia Nagel, 'Enhancement for Well-being is Still Ethically Challenging' (2014) 8 *Frontiers in Systems Neuroscience* 72.

⁷⁴ Julian Savulescu, 'Procreative Beneficence: Why We Should Select the Best Children' (2001) 15 (5) *Bioethics* 413, 426.

⁷⁵ Julian Savulescu and Guy Kahane, 'The Moral Obligation to Create Children with the Best Chance of the Best Life' (2009) 23 (5) *Bioethics* 274, 290.

efits and harms of genome editing are not necessarily distributed equitably between all people.⁷⁶ A variety of underlying factors, such as wealth may disproportionately affect certain group of people. It raises questions of social virtues, equity and justice, given that it would benefit the rich far more than the poor.⁷⁷ Inevitably, commercialisation may extend many potential inequalities if patents through genome editing techniques take hold.⁷⁸ As such, this technology could not be accessible to the vulnerable, which would increase existing undesired disparities. It could lead to new lines of discrimination between the genetically “perfected” and those left behind.⁷⁹ This is against public policy that is justified to forestall negative personal and social consequences, such as exacerbating existing inequalities.⁸⁰

It is essential to ensure that the interests of those potentially marginalised receive adequate protection in accordance with principles of social justice. At the current stage, it is more appropriate to use CRISPR to change a disease-causing genetic in the reasonable short term. Otherwise, efforts will lack legitimacy.⁸¹ The impact of social and health inequality needs to be considered to prevent uses which reinforce prejudice and worsen inequalities within societies.⁸² In certain circumstances, the ethical considerations need be settled by legal and regulatory authorities.

The Lax Regulation and Enforcement in China

There is a “regulatory asymmetry” between the West and China, of which the latter has inadequate regulation and serious oversight. Under the existing framework, China’s regulations governing research ethics are not as stringent as they are in other parts of the world. In principle, clinical trials of somatic gene modifications are legally permissible within the terms and conditions set out in regulations.⁸³ The lax ethical environment has

⁷⁶ Clara C. Hildebrandt and Jonathan M. Marron, ‘Justice in CRISPR/Cas9 Research and Clinical Applications’ (2018) 20 (9) *AMA Journal of Ethics* 826, 833.

⁷⁷ Noah Smith, ‘Gene Editing Needs to Be Available to Everyone’ *Bloomberg* (25 January 2018).

⁷⁸ Ainsley Newson and Anthony Wrigley, ‘Being Human: The Ethics, Law, and Scientific Progress of Genome Editing’ (2016) 87 (1) *The Australian Quarterly* 3, 8.

⁷⁹ J. Benjamin Hurlbut, Sheila Jasanoff and Krishanu Saha, ‘The Chinese Gene-Editing Experiment Was an Outrage. The scientific Community Shares Blame’ *The Washington Post* (29 November 2018).

⁸⁰ Nuffield Council on Bioethics, ‘Genome Editing: An Ethical Review Section 3-Moral Perspectives’ (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 30.

⁸¹ Eric Lander, Françoise Baylis, et al., ‘Adopt a Moratorium on Heritable Genome Editing’ *Nature* (13 March 2019).

⁸² Eric Lander, Françoise Baylis, et al., ‘Adopt a Moratorium on Heritable Genome Editing’ *Nature* (13 March 2019).

⁸³ Achim Rosemann, Li Jiang, and Xinqing Zhang, ‘The Regulatory and Legal Situation of Human Embryo, Gamete and Germ Line Gene Editing Research and Clinical Applications in the People’s Republic of China’ (Nuffield Council on Bioethics, May 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Background-paper-GEHR.pdf>> 16-17.

led many to consider China the “Wild East” in biomedical research.⁸⁴ It is important to heed the warnings of the scientific community to develop legal and ethical parameters before the technology is developed. At such, China is supposed to regulate CRISPR in a manner that accounts for both the safety concerns and the ethical dilemmas.⁸⁵

Legal and Regulatory Frameworks

While gene editing technologies have been developed, the laws related to their use are outdated. There is a legitimate concern in terms of He’s clinical trial. In China, there are no clear laws but guidelines in place to prevent these actions. Regulations clearly stipulate that gene manipulation on the human gamete, zygote and embryo for the purpose of reproduction is banned in China. It is the weak enforcement that complicates the implementation of the regulations.

Regulatory Guidelines

The *Technical Norms of Human Assisted Reproductive Technologies* provides that “gene manipulation on human gametes and embryos is banned for the purpose of reproduction.”⁸⁶ In 2003, China’s Ministry of Science and Technology (MoST) together with the Ministry of Health (MoH) issued the *Ethical Guidelines for Human Embryonic Stem Cell Research*.⁸⁷ Similar to the UK’s Human Fertilisation and Embryology Act (HFEA 1990), it prohibits the conduct of research on embryos after a period of 14 days beginning with the day on which the process of creating the embryo began.⁸⁸ The *Guideline* to in-vitro clinics bars clinical experiments which violate ethical or moral principles. In 2007, the MoH promulgated *Measures for the Ethical Review of Biomedical Research Involving the Human Body (for Trial Implementation)*.⁸⁹ The National Commission of Health and Family Planning (NCHFP) issued the *Ethical Review of Biomedical Research Involving Humans*.⁹⁰ Notably, beneficence is to be addressed to promote patients’ welfare and consider the risk/benefit balance. It highlights that the risk should be controllable, and the patient’s benefits should be prioritised compared with the scientific research.⁹¹

⁸⁴ Yangyang Cheng, ‘China Will Always Be Bad at Bioethics’ *Foreign Policy* (13 April 2018).

⁸⁵ Tracey Tomlinson, ‘A CRISPR Future for Gene-Editing Regulation: A Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing’ (2018) 87 (1) *Fordham Law Review* 437, 483.

⁸⁶ *Technical Norms of Human Assisted Reproductive Technologies* (2003) Articles 3.

⁸⁷ Ministry of Science and Technology and Ministry of Health of the PRC, *Ethical Guidelines for Human Embryonic Stem Cell Research* (MoST, 2003). It came into effect on 14 January 2004. <http://www.most.gov.cn/fggw/zfwj/zfwj2003/200512/t20051214_54948.htm>.

⁸⁸ *Ethical Guiding Principles for the Research of Human Embryonic Stem Cell* (2003) Articles 6.1 & 6.2.

⁸⁹ Ministry of Health of the PRC. *Measures for the Ethical Review of Biomedical Research Involving the Human Body (for Trial Implementation)* <http://www.nhfpc.gov.cn/mohbgt/pw10702/200804/18816.shtml> (MoH, 2007).

⁹⁰ *Measures for the Ethical Review of Biomedical Research Involving Humans* came into effect on 1 December 2016.

⁹¹ *Measures for the Ethical Review of Biomedical Research Involving Humans* 2016 Article 18.2.

Recently, the NCHFP issued the *Measures for the Administration of the Clinical Application of Medical Technologies* (2018).⁹² Medical technologies shall be prohibited from being applied clinically, if they have major ethical concerns.⁹³

One of the regulatory issues is informed consent arising from the uncertain consequences that germline changes could have on future generations.⁹⁴ Signed informed consent is considered a standard requirement ensuring that patients are fully informed of the benefits and adverse effects.⁹⁵ The consent conditions are more complex, given the consent of the parents is not sufficient to exhaust the putative moral duty towards the future person.⁹⁶ Any genetic manipulation of an embryo has to proceed with the understanding that the person who is affected cannot consent to the initiative.⁹⁷ It is arguable that gene editing is unethical as the future generations that will inherit the altered DNA did not consent to the procedure nor its potential adverse effects.⁹⁸ At present, the heritable gene editing may not involve fully-developed notions of informed consent. There may be little involvement of ethics review boards compared to practices within developed countries.⁹⁹

Concerns Still Remain Unaddressed

Even though the Ministry of Health (MoH) has issued ethical rules, the legal responsibility is unclear and the penalties are lenient. While MoH's *Guidelines* provides that ethical reviews are based upon the principles of ethics accepted by the international community, the implementation of China's legal and regulatory system has proved ineffective in practice.¹⁰⁰ The Chinese *Guidance* is ambiguous, although it prohibits clinical research that breaches ethical or moral principles. It lacks enforcement mechanisms and

⁹² Measures for the Administration of the Clinical Application of Medical Technologies came into effect on 11 November 2018.

⁹³ Measures for the Administration of the Clinical Application of Medical Technologies (2018) Article 9.2.

⁹⁴ Jon Heggie, 'Should We Edit the Human Germline?' *National Geographic* (17 December 2018).

⁹⁵ Neil Lunt, Richard Smith, et al., 'Medical Tourism: Treatments, Markets and Health System Implications: A Scoping Review' (Paris: OECD, 2011) <<https://www.oecd.org/els/health-systems/48723982.pdf>> 43.

⁹⁶ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 123.

⁹⁷ John Mulvihill, Benjamin Capps, et al., 'Ethical Issues of CRISPR Technology and Gene Editing through the Lens of Solidarity' (2017) 122 (1) *British Medical Bulletin* 17, 29.

⁹⁸ Ekaterina Perets, 'Why Does Europe Lag Behind the US and China in the Gene Editing Race?' (31 January 2018) <<https://labiotech.eu/features/gmo-gene-editing-europe/>>.

⁹⁹ Norra MacReady, 'The Murky Ethics of Stem-Cell Tourism' (2009) 10 *The Lancet Oncology* 317, 318.

¹⁰⁰ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 111.

provides few instructions for investigators.¹⁰¹ Apparently, He's work flouted the 2003 *Regulations* governing in vitro fertilisation, which bans the use of gene-manipulated embryos for reproduction. The approaches are silent on gene editing in adult humans where changes will not affect future generations.¹⁰² As a result, the ethics review process is often reduced to a formality, which is always considered as "a rubber stamp." Furthermore, *Nulla poena sine lege* is a fundamental principle of criminal law, which is closely related to a basic understanding of criminal justice in China.¹⁰³ Only the law can define a crime and prescribe a penalty. Accordingly, the offences and corresponding penalties should be clearly defined by law, that is, no punishment without law. There is no legal regime to prohibit the implantation into a human a genetically modified egg or sperm or human embryo. There might be some international regulations, being soft law in nature, which is not legally-binding in terms of enforcement. Given China does not recognise judge-made law, the *nulla poena sine lege* as principle is adopted in China's judicial practice. There is no law in China that covers gene editing on human embryos, and none of the Chinese laws detail the consequences of violating them. Despite the above Guidelines, there are no adequate laws to be applicable in He's case. Unsurprisingly, the NCHFP reported that He's conduct had been in serious violation of relevant national regulations and creates a pernicious influence at home and abroad.¹⁰⁴ China seems to rely primarily upon regulation, that is, the detailed administrative rules adopted pursuant to legislative direction and authority, which appears to be more responsive.¹⁰⁵ However, technology develops faster than regulatory codes and legal instruments, which renders it difficult to keep up with the ethical and social implications. Although the above-mentioned regulations allude to ethical review committees and respect for human dignity, they do not refer to modification of the human germline or provide for coercive enforceability, active monitoring or sanctions. In this regard, it is hardly justified if He were to be prosecuted for criminal liability.

Contributing Variables to Inadequate Governance

China does not have efficient review and approval procedures in place. Its relatively lax legal frameworks could be exploited by rogue researchers. There are many deeply-rooted factors that contribute to the inadequate governance and control. Among

¹⁰¹ Yangyang Cheng, 'China Will Always Be Bad at Bioethics' *Foreign Policy* (13 April 2018).

¹⁰² 'Despite Gene-editing Flap, Chinese Scientists Still Aiming for Supremacy in Experimental CRIS-PR Tech' *Bloomberg* (13 December 2018).

¹⁰³ Li Li, 'Nulla Poena Sine Lege in China: Rigidity or Flexibility?' (2010) 43 (3) *Suffolk University Law Review* 655, 667.

¹⁰⁴ Owen Dyer, 'Creator of First Gene Edited Babies Faces "Stern" Punishment' *The BMJ* 364 (22 January 2019).

¹⁰⁵ Alta Charo, 'The Legal and Regulatory Context for Human Gene Editing' (2016) 32 (3) *Issues in Science and Technology* 39, 44.

other things, the lack of transparency and public engagement contribute to the inefficient governance of China's development in gene editing.¹⁰⁶

Transparency and Public Engagement

The changes brought about by gene-editing should not increase “disadvantage, discrimination or division in society” and such changes should not harm the welfare of the future person.¹⁰⁷ It is essential to facilitate public engagement before any field testing.¹⁰⁸ The ethical issues should be subject to a broad and inclusive societal debate on the framing, evaluation and prioritisation of societal challenges.¹⁰⁹ Anyone subject to the jurisdiction has a legitimate interest in the debate, through which it can bring shared and competing values to the surface.¹¹⁰ Unlike the West where public debate tends to be more coherently orientated towards regulatory or parliamentary activities among a variety of stakeholders, there is little public engagement in China.¹¹¹ On 26 February 2019, National Commission of Health and Family Planning (NCHFP) sought for public opinions about Regulations on Biomedical Experiments,¹¹² which represents a meaningful beginning for public engagement in this controversial issue. Furthermore, the lax regulatory environment stems in part from lack of adequate awareness. More significantly, a top-down approach is well-proved efficient strategy to address the challenge. It is advised that China commit to transparency and public engagement in this scenario, which is indispensable for raising public awareness and fostering a coherent environment therein. It is viable to address a gap for policymakers in China who need to be well-informed about the ethical concerns and potential hazards of this technology.

¹⁰⁶ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 163-180.

¹⁰⁷ Nuffield Council on Bioethics, ‘Genome Editing and Human Reproduction: Social and Ethical Issues’ (London, July 2018) <<http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf>>.

¹⁰⁸ Congressional Research Service (CRS) Report ‘Advanced Gene Editing: CRISPR-Cas9’ (7 December 2018 <<https://fas.org/sgp/crs/misc/R44824.pdf>> 31.

¹⁰⁹ Nuffield Council on Bioethics, ‘Genome Editing and Human Reproduction: Social and Ethical Issues’ (London: Nuffield Council on Bioethics, 2018) <<http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf>>135.

¹¹⁰ Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 141.

¹¹¹ Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 112.

¹¹² NCHFP, *Regulations on Gene Editing and Other Potentially Risky Biomedical Technologies* (26 February 2019).

Plausible Perception

There are substantial implications over the potential competition in this cutting-edge area. He's clinical trial is partly driven by international technological competition as well as China's nationally-prioritised strategy. The trials align with China's industrial policy.¹¹³ As part of its drive to place China on the global stage in a multitude of industries, China highlighted gene editing in a 2016 Five-Year-Plan.¹¹⁴ Such a systematic breach stems from a common perception that enforcement of stringent regulatory norms compromises research innovation.¹¹⁵ There is a regulatory asymmetry between the West and China, and the resulting legal playing field is uneven, ranging from essentially unrestricted to a complete ban.¹¹⁶ Another factor normally neglected is that economic costs have not been well weighed against the medical and social costs incurred by CRISPR's mistakes. Even so, competitive advantage may come into being due to the uneven playing field in regulating genome editing. The economic advantages of genome editing may readily lead to a rapid expansion of application of the technique. China could beat its counterparts to apply CRISPR pioneered in the West.¹¹⁷ There would be substantial economic implications of health economics arising from heritable genome editing interventions for health services.¹¹⁸ Unsurprisingly, some Chinese scientists pursue a "calculative balance of observing and subverting institutional constraints" to circumvent those toothless regulatory initiatives.¹¹⁹ Thus, laws and regulations may not provide substantial deterrence in the control and monitoring of research. This may also undermine efforts to control immoral research based on the CRISPR technology. The research is sometimes faced with a catch-22 scenario where advancement is not likely without facing enormous moral and ethical challenges.¹²⁰ In response, the West will have to commit to developing a regulatory regime that is flexible enough to allow

¹¹³ Preetika Rana, Amy Dockser Marcus and Wenxin Fan, 'China, Unhampered by Rules, Races Ahead in Gene-Editing Trials' *The Wall Street Journal* (21 January 2018).

¹¹⁴ National Development and Reform Commission (NDRC), *China's 13th Five Year Plan (2016-2020)* <<http://en.ndrc.gov.cn/newsrelease/201612/P020161207645765233498.pdf>>.

¹¹⁵ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 112.

¹¹⁶ Motoko Araki and Tetsuya Ishii, 'International Regulatory Landscape and Integration of Corrective Genome Editing into in Vitro Fertilization' (2014) 12 (1) *Reproductive Biology and Endocrinology* 108.

¹¹⁷ Preetika Rana, Amy Dockser Marcus and Wenxin Fan, 'China, Unhampered by Rules, Races Ahead in Gene-Editing Trials' *The Wall Street Journal* (21 January 2018).

¹¹⁸ Oviedo Convention Article 15.

¹¹⁹ Joy Yueyue Zhang, 'The 'Credibility Paradox' in China's Science Communication: Views from Scientific Practitioners' (2015) 24 (8) *Public Understanding of Science* 913, 927.

¹²⁰ Hannah Brown, 'Human Embryo CRISPR Advances Science but Let's Focus on Ethics, Not World Firsts' *The Conversation* (1 August 2017).

them to build competitiveness, while strict enough to prevent unintended societal and ethical consequences.¹²¹

Institutional Void in Oversight

The Chinese governance framework includes administrative measures, ethical guidelines, principles and technical norms and standards. Oversight is specified at three levels in China, that is, by laws, regulations and ministerial guidelines. The ministerial guidelines are most closely related to the issue under discussion, although they are enforceable only if mentioned in a law, regulation or administrative measure.¹²² The relevant governance is centralised under the National Commission of Health and Family Planning (NCHFP), which is responsible for laws, regulations and policies related to the gene ethics. China does not have adequate abilities to regulate CRISPR. The breach may even be considered as an unsuccessful product of China's regulatory and legal landscape. It is the lax regulatory environment that may have contributed to He's gene-editing experiments.¹²³ The dispersal of the regulatory oversight of gene editing lacks integration among a large number of government agencies.¹²⁴ Inevitably, the regulatory frameworks do not function properly at a lower level, such as the implementation by provincial departments. Furthermore, genome editing should be licensed for clinical use only once risks of adverse outcomes have been assessed by a national authority.¹²⁵ However, the ethical governance has long been the Achilles' heel of China's scientific endeavour.¹²⁶ In He's clinical trial, the research even does not need national regulators' approval. As Larson observed:

He took advantage of the loosely worded and irregularly enforced regulations and generous funding available today in China, in some cases skirting even local protocols and possibly laws.¹²⁷

¹²¹ Carlene Dooley, 'Regulatory Silos: Assessing the United States' Regulation of Biotechnology in the Age of Gene Drives' (2018) 30 (3) *Georgetown Environmental Law Review* 547, 568.

¹²² Tetsuya Ishii, 'Germline Genome-Editing Research and Its Socioethical Implications' (2015) 21 (8) *Trends in Molecular Medicine* 473, 481.

¹²³ Rob Schmitz, 'Gene-Editing Scientist's 'Actions Are A Product Of Modern China' NPR (5 February 2019).

¹²⁴ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 111.

¹²⁵ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 138.

¹²⁶ 'The Affair of the Gene-Edited Babies Rumbles On' *Economist* (13 December 2018).

¹²⁷ Christina Larson, 'Gene-editing Chinese Scientist Kept Much of His Work Secret' *Medical Express* (27 November 2018).

China's inability to adhere to international ethical norms in the knowledge system ends up harming itself.¹²⁸

Ethical Arbitrage

Laws in China around this kind of research are more lax than in the West. There is a substantial gap between the practice in China and that under an international standard. Similar to the forum shopping, this unlevelled playing field makes it possible for ethically controversial practices to migrate to more accommodating regulatory environments, which is abused by some opportunists.¹²⁹ They may take advantage of China's toothless regulations and their ambiguity to undertake those heavily-restricted clinical trials in their home countries.¹³⁰ As practices move between jurisdictions across ethical thresholds, one likely consequence is a form of 'ethical arbitrage' that may have the effect of eroding these differences.¹³¹ The ethical gap is likely to be exploited due to a technological advantage. It would be possible if a technologically-advantaged party could cooperate with a Chinese researcher for the gene editing trial of such a kind. A Western scientist could even gain financial support in China when he cannot secure grants or approval for this most controversial project.¹³² Therefore, some factors must be taken into account while forging an established framework for healthcare ethics of heritable gene editing, such as autonomy, nonmaleficence and beneficence.¹³³ A benefit/harm balance needs to be maintained proportionate given all the gene editing involves some kind of harm inevitably. A scientist must avoid doing harm and endeavour to reduce risk reasonably. Patients' welfare should be promoted with the risk-benefit ratio considered properly.¹³⁴

International Norms in Response to the Challenges

There is no international treaty that directly regulates the human genome or the possibilities for its modification. Given gene editing is not contained by borders, an

¹²⁸ Caroline Wagner, 'CRISPR Babies and Other Ethical Missteps in Science Threaten China's Global Standing' *The Conversation* (4 December 2018).

¹²⁹ Carolyn Brokowski and Mazhar Adli, 'CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool' (2019) 43 (1) *Journal of Molecular Biology* 88, 101.

¹³⁰ Achim Rosemann and Jiang Li, 'Human Embryo Gene Editing in China: The Uncertain Legal Status of the Embryo' (2019) 14 (1) *BioSocieties* 46, 66.

¹³¹ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 113.

¹³² Christina Larson, 'Gene-editing Chinese Scientist Kept Much of His Work Secret' *Medical Express* (27 November 2018).

¹³³ Tom Beauchamp and James Childress, *Principles of Biomedical Ethics* (7th ed. Oxford: Oxford University Press, 2013) Chapters 5-7.

¹³⁴ Adam Cribbs and Sumeth Perera, 'Science and Bioethics of CRISPR-Cas9 Gene Editing: An Analysis Towards Separating Facts and Fiction' (2017) 90 (4) *Yale Journal of Biology and Medicine* 625, 634.

ethical debate is vital to the future viability of gene editing, particularly in an international regulatory environment struggling to keep up.¹³⁵ Effective regulatory oversight mechanisms have sufficient legal authority and enforcement capability.¹³⁶ It remains a challenge to identify what principles or frameworks can provide effective oversight for gene editing, and further to assess the prospect of international harmonisation of policies. China may learn from those best practices to govern the controversial research. It is worth looking at the existing system of regulatory oversight and ethical norms around the world.

Soft Law Without Teeth

The introduction of intergenerational genome editing needs to consider a much broader range of norms and consequences. Global agreements are required as to exactly how gene editing is to be managed, so as to avoid the putatively undesirable moral and social consequences.¹³⁷ Currently, there is a considerable need for international community to work out a framework with viable spill-over effect on enhancing the national legal and regulatory approaches. It is reasonable for the global community to consider instantiating national and supranational regulations for the sake of future enforcement.¹³⁸

International Initiatives

There are a variety of universally accepted international documents including the Nuremberg Code,¹³⁹ Helsinki Declaration,¹⁴⁰ and CIOMS/WHO International Ethical Guidelines.¹⁴¹ The International Ethical Guidelines for Health-related Research Involving Humans reiterates that scientific value and respect for the rights of participants underpins the ethical conduct of research.¹⁴² The International Society for Stem Cell Research (ISS-

¹³⁵ Tom Bangay, 'Gene Editing: Can the Law Keep Up?' (22 March 2017) <<https://www.ibanet.org/Article/NewDetail.aspx?ArticleUid=fc0bd200-63e1-472f-a6b9-c86440859b83>>.

¹³⁶ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 106.

¹³⁷ Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review Section 3-Moral Perspectives' (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 27.

¹³⁸ Carolyn Brokowski and Mazhar Adli, 'CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool' (2019) 431 (1) *Journal of Molecular Biology* 88, 101.

¹³⁹ The Nuremberg Code is a set of research ethics principles for human experimentation created as a result of the Nuremberg trials in 1947.

¹⁴⁰ The Declaration of Helsinki (DoH) is the World Medical Association's (WMA) best-known policy statement. The first version was adopted in 1964 and most recently at the General Assembly in October 2013.

¹⁴¹ Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO), 'International Ethical Guidelines for Health-related Research Involving Humans' (Geneva, 2016) <<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>>.

¹⁴² International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. (Geneva, Council for International Organizations of Medical Sciences (CIOMS), 2016) <<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>>.

CR) provides that: “Until further clarity emerges on both scientific and ethical fronts, the ISSCR holds that any attempt to modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should be prohibited at this time.”¹⁴³

These international guidelines play an active role in ethical debate and establishment of international norms.¹⁴⁴ As discussed above, the Oviedo Convention focuses on the integrity of the inheritance of genetic endowment, whereas the United Nations Educational Scientific and Cultural Organization (UNESCO) focuses on the integrity of the ‘human genome’.¹⁴⁵ The latter imposes an international ban on any gene-editing research in human embryos. The Universal Declaration on the Human Genome and Human Rights (UDHGHR) refers to the principles of dignity, diversity and equality, and supports the concept of the human genome as a symbol of humanity’s heritage.¹⁴⁶ UDHGHR mandates that practices contrary to human dignity should be forbidden. It suggests that practices like germ line interventions could be contrary to human dignity and should not be permitted.¹⁴⁷ It is also worthy to put risk assessment and management into place adequately. Important mechanisms for securing that the freedom of scientific research does not violate the rights of others include requirements for favourable risk or impact assessments, linked to the requirement for due diligence.¹⁴⁸ A principle of intergenerational equity is well elaborated in international law, which calls on states to take into account the rights of future generations when undertaking activities that may affect them.¹⁴⁹ For instance, the Declaration on the Responsibilities of the Present Generations towards Future Generations contains a reference to the protection of the human genome linked with the preservation of the human species.¹⁵⁰ The principle

¹⁴³ The International Society for Stem Cell Research (ISSCR), ‘Guidelines for Stem Cell Research and Clinical Translation’ (2016) <<http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinicaltranslation.pdf?sfvrsn=2>> 8.

¹⁴⁴ Organisation for Economic Cooperation and Development (OECD), ‘Gene Editing for Advanced Therapies: Governance, Policy and Society’ (2018) <https://www.oecd-ilibrary.org/industry-and-services/geneediting-for-advanced-therapies_8d39d84e-en> UNESCO International Bioethics Committee (2018) <<http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/international-bioethics-committee/>>; UNESCO International Bioethics Committee Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights (2015) <<http://unesdoc.unesco.org/images/0023/002332/233258E.pdf>>.

¹⁴⁵ Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 116.

¹⁴⁶ United Nations Educational, Scientific and Cultural Organization (UNESCO 1997) Article 1.

¹⁴⁷ The Universal Declaration on the Human Genome and Human Rights Article 11.

¹⁴⁸ The Universal Declaration on Bioethics and Human Rights Article 20.

¹⁴⁹ Itziar de Lecuona and María Casado, et.al., ‘Gene Editing in Humans: Towards a Global and Inclusive Debate for Responsible Research’ (2017) 90 (4) *The Yale Journal of Biology and Medicine* 673, 681.

¹⁵⁰ UNESCO Declaration on the Responsibilities of the Present towards Future Generations 1997 Art. 1: “[t]he present generations have the responsibility of ensuring that the needs and interests of present

requires that states should take into account the need to preserve the human species in its diversity for future generations. International consensus is needed to reflect and affect the 'moral fabric of society' that should partly be reflected in norms of law and governance.¹⁵¹

Lack of International Standard

Heritability of germline changes is a novel form of risk not adequately accounted for in current regulatory frameworks.¹⁵² Currently, it is the jurisdiction of individual countries that decides what to allow when it comes to gene editing. Given the lack of an internationally agreed-upon regulatory framework, there is a need for regulations on a cross-border level. The Chinese case has prompted calls for international regulation of CRISPR research, which can serve to orientate moral action.¹⁵³ As Nuffield Council on Bioethics observed, what counts as normal is therefore a legitimate question but often one that is highly contested with regard to the extent to which norms are related to medical intervention and enhancement.¹⁵⁴ The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonise regulations, in order to discourage unacceptable activities while advancing human health and welfare.¹⁵⁵ As such, a shared global standard for this purpose should be put in place as soon as possible.

International Framework vis-à-vis National Enforcement

It is significant to develop principles for editing reproductive cells, because the ethical and social issues posed by human genome editing transcend national boundaries.¹⁵⁶ In principle, the use of CRISPR should live up to the existing norms and standards for normal functioning in a scientifically enlightened society.¹⁵⁷ There are neither actual international rules covering specifically gene editing, nor international regulatory agencies

and future generations are fully safeguarded"; UNESCO Declaration on Science and the Use of Scientific Knowledge 1999 §39.

¹⁵¹ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 147-156.

¹⁵² Owen Schaefer, 'Why Treat Gene Editing Differently in Two Types of Human Cells?' *SciTech Connect* (18 December 2015).

¹⁵³ Laurie Garrett, 'CRISPR: Transformative and Troubling' (Council on Foreign Relations, 13 April 2016) <<https://www.cfr.org/expert-brief/crispr-transformative-and-troubling>>.

¹⁵⁴ Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review Section 3-Moral Perspectives' (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 28.

¹⁵⁵ The National Academies of Sciences, Engineering, and Medicine (NASEM), 'International Summit on Human Gene Editing' (2015) <<http://nationalacademies.org/gene-editing/Gene-Edit-Summit/>>.

¹⁵⁶ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 19.

¹⁵⁷ Giulia Cavaliere, Katrien Devolder and Alberto Giubilini, 'Regulating Genome Editing: For an Enlightened Democratic Governance' (2019) 28 (1) *Cambridge Quarterly of Healthcare Ethics* 76, 88.

with the capacity to enforce legal and ethical use of genetic technologies.¹⁵⁸ Although the legislative and regulatory frameworks have great normative value, no country has yet adopted CRISPR-specific regulations.¹⁵⁹

Forum Shopping in Scenarios of Medical Tourism: The Regulatory Heaven

A regulatory haven could emerge that would tempt providers or consumers to travel to jurisdictions with more lenient or non-existent regulations to access the restricted procedures.¹⁶⁰ The phenomenon of medical tourism has thus come into being, which encompasses the search for faster and cheaper therapeutic options, as well as newer or less regulated interventions.¹⁶¹ Given this legal and regulatory asymmetry, it will be unlikely to control efficiently if the technical capabilities exist in more permissive jurisdictions.¹⁶² It is not viable to seek to address a transnational problem with national legislation, but it would be meaningful to reach international consensus on the use of this technology. Harmonisation across national borders is crucial to seek a prudent path forward for genomic engineering and germline gene modification.¹⁶³ An optimum global governance purports to offer a procedurally legitimate solution to controversial inquiries in morally plural societies.¹⁶⁴ This highlights significance of more proactive engagement with other countries and international institutions in the development of international norms.¹⁶⁵ International dialogue along with governance should be promoted with particular regard to heritable genome editing research and innovation.¹⁶⁶

¹⁵⁸ James Kozubek, 'CRISPR-Cas9 Is Impossible to Stop' (2017) 18 (2) *Georgetown Journal of International Affairs* 112, 119.

¹⁵⁹ Laurie Garrett, 'CRISPR: Transformative and Troubling' (Council on Foreign Relations, 13 April 2016) <<https://www.cfr.org/expert-brief/crispr-transformative-and-troubling>>.

¹⁶⁰ Alta Charo, 'On the Road (to a Cure?): Stem-cell Tourism and Lessons for Gene Editing' (2016) 374 (10) *New England Journal of Medicine* 901, 903.

¹⁶¹ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 136.

¹⁶² National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 181, 194.

¹⁶³ David Baltimore, Paul Berg, et al., 'A Prudent Path Forward for Genomic Engineering and Germline Gene Modification' (2015) 348 (6230) *Science* 36, 38.

¹⁶⁴ Michael Parker, 'Deliberative Bioethics' in Richard Ashcroft, Angus Dawson, et al., *Principles of Health Care Ethics* (Eds. Chichester: John Wiley & Sons) 185-191.

¹⁶⁵ Michael Mazarr, Timothy Heath and Astrid Stuth Cevallos, 'China and the International Order' (RAND Corporation, 2018) <https://www.rand.org/content/dam/rand/pubs/research_reports/RR2400/RR2423/RAND_RR2423.pdf>.

¹⁶⁶ Nuffield Council on Bioethics, 'Genome Editing and Human Reproduction: Social and Ethical Issues' (London, July 2018) <<http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf>>150.

At Stake is Enforcement

Global efforts should be aimed at developing and integrating legal strategies for the prevention and penalisation of unacceptable research.¹⁶⁷ It makes sense that an international platform can call for consensus regarding how to regulate the use of CRISPR. A purely regulatory approach will not suffice. The lack of functional enforcement system at international levels will inevitably slide into an institutional void. Such a regulatory framework relies largely upon whether the most effective enforcement will occur at a national or regional level ultimately. Otherwise, an international ban would only play a symbolic role, whereas a national one can regulate it through its direct control and levers.¹⁶⁸ To a greater extent, it is up to national regulatory agencies to set up appropriate frameworks to govern the use of CRISPR. However, many countries lack the resources to enforce those well-established international regulations.¹⁶⁹ Thus, the crucial question is not what rules were broken, but whose judgments about what is right and appropriate should rule the future.¹⁷⁰ He's case underscores the importance of Guidelines, rather than reactive prohibitions.¹⁷¹ A systematic overview of the embryo research performed on each national territory should be put in place, at least, at the current stage. During the implementation of the governance tools, ethical and regulatory considerations should distinguish clearly between clinical and research applications, and appreciate the particular set of ethical challenges surrounding research involving human embryos.¹⁷²

Legal and Regulatory Frameworks: A Comparative Perspective

Gene editing technology is moving ahead of society's ability to assimilate its implications to normative frameworks.¹⁷³ The legal and regulatory response to advances in CRISPR continues apace, with different jurisdictions having different levels of flexibility to accommodate the latest development.¹⁷⁴ There are enormous implications over the potential competition in this scenario. It is imperative that China learn from best practices of other countries in both statutory and institutional approaches.

¹⁶⁷ 'Germline Gene-Editing Research Needs Rules' *Nature* (13 March 2019).

¹⁶⁸ James Kozubek, 'CRISPR-Cas9 Is Impossible to Stop' (2017) 18 (2) *Georgetown Journal of International Affairs* 112, 119.

¹⁶⁹ Tracey Tomlinson, 'A CRISPR Future for Gene-Editing Regulation: A Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing' (2018) 87 (1) *Fordham Law Review* 437, 483.

¹⁷⁰ 'CRISPR Babies Raise an Uncomfortable Reality-Abiding by Scientific Standards Doesn't Guarantee Ethical Research' *The Conversation* (3 December 2018).

¹⁷¹ Bob Grant, 'Genome Editing on Board' *TheScientist* (1 January 2019).

¹⁷² Gholson Lyon and Jeremy Segal, 'Practical, Ethical and Regulatory Considerations for the Evolving Medical and Research Genomics Landscape' (2013) 2 (1) *Applied & Translational Genomics* 34, 40.

¹⁷³ Nuffield Council on Bioethics, 'Genome Editing: An Ethical Review Section 3-Moral Perspectives' (London, September 2016) <<http://nuffieldbioethics.org/wp-content/uploads/Section-3-Moral-perspectives.pdf>> 31.

¹⁷⁴ Tom Bangay, 'Gene editing: Can the law keep up?' *IBA Global Insight* (22 March 2017).

Criminal Offences

Germline human genome editing is a criminal offence in some countries which have specific statutes to robustly regulate the conduct. Australia has one of the strictest regulatory environments for gene editing research in the world.¹⁷⁵ The Prohibition of Human Cloning Act (PHCA 2002) makes it illegal to alter the genomes of embryonic cells. The law permits certain types of embryo research subject to licence. Under the Regulation of Human Embryo Research Amendment Act 2006 (RHERAA, 2006) and PHCA 2002, germline modification is punishable by imprisonment for up to 15 years.¹⁷⁶ Similarly, research and clinical trials on gene editing are illegal in Canada. The conduct is forbidden even if germ cells will not actually be used to create a new life. *The Assisted Human Reproduction Act* (AHRA 2004) forbids a wide range of research and in vitro and in vivo germ line alterations,¹⁷⁷ including the creation of embryos¹⁷⁸ or chimeras.¹⁷⁹ It is a criminal offense for using gene-editing tools on cells that could lead to heritable genetic change in humans.¹⁸⁰ The AHRA 2004 states that: “No person shall 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.”¹⁸¹

Penalties by law may lead to heavy fines and potentially incarceration, which plays a more deterrent role.¹⁸² For instance, sanctions range from a fine up to \$500,000 to imprisonment up to 10 years.¹⁸³ The severe penalties chill the research environment, which inevitably compromise the countries’ global competitiveness in the arena of gene editing, let alone its potential commercialisation.

United States: Framework and Institutions

The United State has rather a cautious approach when it comes to the use of biotechnology in the context of human clinical trials.¹⁸⁴ It does not have specific laws directly forbidding germline editing, but the country does have a robust regulatory machinery.

¹⁷⁵ Christopher Gyngell and Julian Savulescu, ‘UK Gene Editing Breakthrough Could Land an Aussie in Jail for 15 Years: Here’s Why Our Laws Need to Catch up’ *The Conversation* (25 September 2017).

¹⁷⁶ PHCA 2002 Article 15.

¹⁷⁷ AHRA 2004 s. 5(1) (f).

¹⁷⁸ AHRA 2004 s. 5(1) (b).

¹⁷⁹ AHRA 2004 s. 5(1) (i).

¹⁸⁰ Guido de Wert, Björn Heindryckx, et al., ‘Responsible Innovation in Human Germline Gene Editing Background Document to the Recommendations of ESHG and ESHRE’ (2018) 1 *Human Reproduction Open* 1, 18.

¹⁸¹ AHRA 2004 s.5(1) (f).

¹⁸² Carolyn Brokowski and Mazhar Adli, ‘CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool’ (2019) 431 (1) *Journal of Molecular Biology* 88, 101.

¹⁸³ AHRA 2004 s.60.

¹⁸⁴ Heidi C. Howard, Carla G. van El, et al., ‘One Small Edit for Humans, One Giant Edit for Humankind? Points and Questions to Consider for a Responsible Way forward for Gene Editing in Humans’ (2018) 26 (1) *European Journal of Human Genetics* 1, 11.

A complicated regulatory scheme makes it difficult to perform germline modification.¹⁸⁵ The Food and Drug Administration (FDA) and the Recombinant DNA Advisory Committee (RAC) at the National Institute of Health (NIH) are two main authorities that regulate gene transfer technology. The FDA has regulatory jurisdiction to deal with the controversial issue.¹⁸⁶ First, the FDA regulations concerning the editing of somatic cells are implemented by the Recombinant DNA Advisory Committee (RAC).¹⁸⁷ The NIH forbids federal funding of human germline editing, while the RAC only regulates organisations that receive NIH funding.¹⁸⁸ Second, there are funding restrictions on embryo research that might have a strong effect on the underlying basic science.¹⁸⁹ Under the FDA's comprehensive regulation and multiple laws, genome editing for embryos is not allowed for clinical use.¹⁹⁰ The FDA does not accept applications for research in which human embryos are made to have heritable DNA changes. A Congressional Budget Bill 2015 stated: "None of the funds made available by this Act may be used...in research in which a human embryo is intentionally created or modified to include a heritable genetic modification."¹⁹¹

Furthermore, the Consolidated Appropriations Act of 2016 prohibits federal funding for such kind of research.¹⁹² The National Academies of Sciences, Engineering, and Medicine (NASEM) set down a position on heritable genome editing, filling out the spectrum of positions seeking a pathway to eventual translation into the clinic, which finally led to a consensus report in February 2017.¹⁹³ As such, heritable genome editing is subject to a complex framework of laws and regulations at both state and federal levels. In addition, appropriate consideration of social concerns is also resolved within the context of civil rights jurisprudence and legal decisions.¹⁹⁴ The strong regulatory

¹⁸⁵ Alta Charo, 'The Legal and Regulatory Context for Human Gene Editing' (2016) 32 (3) *Issues in Science and Technology* 39, 44.

¹⁸⁶ US Food and Drug Administration (2018) 'Therapeutic Cloning and Genome Modification' <<https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm2007205.htm>>.

¹⁸⁷ Alta Charo, 'The Legal and Regulatory Context for Human Gene Editing' (2016) 32 (3) *Issues in Science and Technology* 39, 44.

¹⁸⁸ Sarah Ashley Barnett, 'Regulating Human Germline Editing in Light of CRISPR' (2017) 51 *University of Richmond Law Review* 553, 559.

¹⁸⁹ Brendan P. Foht, 'CRISPR and the Ethics of Human Embryo Research: What U.S. Government Policy Should Be' *Foreign Affairs* (14 August 2017).

¹⁹⁰ Katherine Drabiak, 'Untangling the Promises of Human Genome Editing' (2018) 46 (4) *The Journal of Law, Medicine & Ethics* 991, 1009.

¹⁹¹ Consolidated Appropriations Act of 2016, HR 2029, 114 Cong., 1st Sess. (6 January 2015) <<https://www.congress.gov/114/bills/hr2029/BILLS-114hr2029enr.pdf>>.

¹⁹² Consolidated Appropriations Act of 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2283 (2015).

¹⁹³ National Academies of Sciences, Engineering, and Medicine (2017) *Human Genome Editing: Science, Ethics, and Governance* <<https://doi.org/10.17226/24623>>.

¹⁹⁴ National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington DC, National Academies Press, 2017) 119.

framework effectively prohibits modification to heritable code, although the US does not have a legal ban.

The EU's Approaches

Gene editing methods can have off-target events with still unknown consequences, so the European Union (EU) has put in place stricter safety regulations. In 1997, thirty-five countries signed and ratified the Convention on Human Rights and Biomedicine (Oviedo Convention), to limit alterations to the human genome.¹⁹⁵ It provides that predictive genetic tests should be used only for medical purposes. Ambiguously, there is no consensus about whether genome modification should be permitted for the avoidance of serious disease.¹⁹⁶ The Oviedo Convention does call for a prohibition below on the use of genetic engineering of the germline or changing the makeup of later generations: “an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”¹⁹⁷

The Convention does not take a stand on the acceptability of research on in vitro embryos.¹⁹⁸ It appears that Article 13 prohibits heritable genome editing interventions. In practice, there is no prohibition, although there are limits on the use of genome editing involving human embryos for research purposes.¹⁹⁹ More specifically, it does not allow interventions that lead to the birth of children with a modified genome. However, Article 18 (1) provides that if national law allows such research, it shall ensure adequate protection of the embryo. As such, the editing and transplantation procedure would be governed by national quality and safety legislation implementing the EU Tissues and Cells Directive, which also concerns the traceability of cells used for human application.²⁰⁰

The EU Clinical Trials Regulation also provides: “No gene therapy clinical trials may be carried out which result in modifications to the subject’s germ line genetic identity.”²⁰¹ In May 2016, the EU revised its Clinical Trials Regulation (EU No 536/2014) and

¹⁹⁵ Peter Sykora and Arthur Caplan, ‘The Council of Europe Should Not Reaffirm the Ban on Germline Genome Editing in Humans’ (2017) 18 (11) *EMBO Reports* 1871, 1872.

¹⁹⁶ Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 117.

¹⁹⁷ Oviedo Convention 1997 Article 13.

¹⁹⁸ Guido de Wert, Björn Heindryckx, et al., ‘Responsible Innovation in Human Germline Gene Editing Background Document to the Recommendations of ESHG and ESHRE’ (2018) 1 *Human Reproduction Open* 1, 18.

¹⁹⁹ Nuffield Council on Bioethics, ‘Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments’ (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 116.

²⁰⁰ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004.

²⁰¹ Regulation 536/2014/EU on Clinical Trials on Medicinal Products for Human Use.

maintained the view that gene therapy trials that result in alterations to an individual's germline should continue to be prohibited. There is no room for the gene editing to be compatible in the clinical trials regime in a reproductive context.²⁰² In this vein, genome editing might well fall within the definition of a 'clinical study'.²⁰³ There should be no move to implement heritable genome editing interventions. In addition, the EU Biotechnology Directive states: "there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against ordre public and morality."²⁰⁴

Apart from the above official positions, there are some civil campaigns for a more responsible use of this technology. A group of European scientists founded the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) to examine and provide guidance about the ethical use of genome editing.²⁰⁵ In addition, the Hinxton Group published a consensus statement in September 2015 calling, among other things, for a roadmap for research to establish the safety of genome editing for use in humans.²⁰⁶

The UK's Permissive But Tightly-Controlled Safeguarding Regime

The UK is often at the forefront of ethical reflection internationally,²⁰⁷ which regime is regulated but permissive. UK law does not currently permit any editing of heritable DNA-genetic information contained in an embryo, egg or sperm. Any gene-editing that would affect the germline would be unlawful.²⁰⁸ It is illegal to use genome editing on human cells and embryos that are intended for fertility treatments to result in pregnancy. All reproductive applications of gene editing are banned under the UK's regulatory regime. However, it is allowed for strictly controlled research purposes.²⁰⁹ The laws make a distinction between the research and reproductive applications of gene editing.²¹⁰ This

²⁰² Joyce Harper, Kristiina Aittomäki, et al., 'Recent Developments in Genetics and Medically Assisted Reproduction: from Research to Clinical Applications' (2018) 26(1) *European Journal of Human Genetics* 12, 33.

²⁰³ Clinical Trials Regulation Article 2 §2 (1).

²⁰⁴ EU Biotechnology Directive Recitals §16; Directive 98/44/EC on the Legal Protection of Biotechnological Inventions <<https://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:31998L0044&from=EN>>.

²⁰⁵ Martin Enserink, 'Interested in Responsible Genome Editing? Join the (New) Club' *Science* (27 March 2018) <<https://doi.org/10.1126/science.aat7183>>.

²⁰⁶ Statement on Genome Editing Technologies and Human Germline Genetic Modification (2015) <http://www.hinxtongroup.org/Hinxton2015_Statement.pdf>.

²⁰⁷ Nuffield Council on Bioethics, 'Genome Editing and Human Reproduction: Social and Ethical Issues' (London: Nuffield Council on Bioethics, 2018) <http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL_website.pdf>101.

²⁰⁸ Kelly E. Ormond, Douglas P. Mortlock, et al., 'Human Germline Genome Editing' (2017) 101 (2) *American Journal of Human Genetics* 167, 176.

²⁰⁹ Alex Matthews-King, 'Designer babies: Picking Traits for Non-Medical Reasons Could be 'Morally Permissible', Says UK Ethics Group' *The Independent* (16 July 2018).

²¹⁰ Sarah Chan, 'Regulating Human Genome Editing: Negotiating Ethical Concerns Through Science and Policy' in Krishnarao Appasani (ed.) *Genome Editing and Engineering: From TALENs, ZFNs and CRISPRs*

is a similar approach to Australian laws that distinguish between the use of cloning for reproductive purposes and cloning for research. It bans such modifications for reproductive purposes, but regulates research purposes via a licensing process overseen by the Human Fertilisation and Embryology Authority (HFEA 1990).²¹¹ Institutionally, the UK has a regulatory system established by legislation. The governance and oversight of human embryo research lies in the hands of authorities that are legally regulated.²¹² The use of genome editing in human embryos for research has been approved by the HFEA 1990.²¹³ In principle, it is only permitted in practice if licensed by the HFEA.²¹⁴ Activities that cannot be licensed include using an embryo in treatment that is not a 'permitted' embryo as defined in the Act.²¹⁵ Genome editing can be used in humans where the genetic change cannot be inherited, or in embryos that are used in research with no intention of implantation.²¹⁶ Scientists are "only allowed to genetically edit human embryos for 14 days for research purposes, after which they must be destroyed, and it is illegal to implant them into a womb."²¹⁷ This enables clearly beneficial research to proceed while preventing controversial applications.²¹⁸ These mandatory requirements are enshrined in the HFEA 1990, which, when combined with the HFEA Code of Practice, sets out a framework for new technologies that is both flexible and unambiguous.²¹⁹

In sum, the UK has adopted a more permissive approach to germline modifications. Unlike Australia and Canada's stringent laws, the UK takes a more regulatory approach to gene editing research. The framework offers guidance for establishing similar norms

to *Molecular Surgery* (Cambridge, Cambridge University Press, 2018) 453-464.

²¹¹ Ewen Callaway, 'UK Scientists Gain Licence to Edit Genes in Human Embryos' *Nature* (1 February 2016).

²¹² Françoise Baylis, 'Genome Editing of Human Embryos Broadens Ethics Discussions' *The Conversation* (1 October 2017).

²¹³ Achim Rosemann, Li Jiang, and Xinqing Zhang, 'The Regulatory and Legal Situation of Human Embryo, Gamete and Germ Line Gene Editing Research and Clinical Applications in the People's Republic of China' (Nuffield Council on Bioethics, May 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Background-paper-GEHR.pdf>> 13.

²¹⁴ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 138.

²¹⁵ Human Fertilisation and Embryology Act (HFEA 1990) s3 (2).

²¹⁶ Sarion Bowers, 'Genome Editing in Humans' (Wellcome Sanger Institute) <<https://www.sanger.ac.uk/about/who-we-are/influencing-policy/genome-editing>>.

²¹⁷ Human Fertilisation and Embryology Act (HFEA 1990) s3.

²¹⁸ Ana Nordberg, Timo Minssen, et al., 'Cutting Edges and Weaving Threads in the Gene Editing (R) evolution: Reconciling scientific progress with Legal, Ethical, & Social Concerns' (2018) 5 (1) *Journal of Law and the Biosciences* 35, 83.

²¹⁹ Tom Bangay, 'Gene Editing: Can the Law Keep Up?' (22 March 2017) <<https://www.ibanet.org/Article/NewDetail.aspx?ArticleUid=fc0bd200-63e1-472f-a6b9-c86440859b83>>.

and oversight mechanisms for genome editing of somatic cells.²²⁰ It takes a position that encourages prudence and transparency.²²¹ The UK's model provides an external structure and orientation. With regard to the Oviedo Convention 1997, the UK may have already gone beyond the prohibition in Article 13 by legalising and licensing mitochondrial donation.²²² Notably, the UK has not signed the Oviedo Convention, which is the most relevant to heritable genome editing interventions. It is not a State Party to the Oviedo Convention and thus not bound by it. After all, it allows testing on embryos in the lab, but does not extend to allowing pregnancies to be induced via gene-editing.

Which Model Suits China's Situation?

As discussed above, laws governing gene editing vary, with some countries banning it outright and others, including China, having no or less clear policies.²²³ Civil law may offer less flexibility than that in common law jurisdictions, which, may alternatively leave much work to be addressed through Guidelines and judicial interpretations.²²⁴ The gene editing has, de facto, been conducted as an open secret in China. A range of gene editing activities still goes on despite the existing governance frameworks. There is no clear law to regulate such attempts. In response to China's case, legal and ethical checks on this erratic progression of science will be necessary now more than ever.²²⁵ To achieve adequate deterrence, a criminal liability scheme is indispensable, which is similar to those in the governance regimes of Australia and Canada. The imposition of criminal liability would not harm China's competitive position in the world of biotechnology, but create a strong deterrent.²²⁶ He's case also highlights the immediate need to develop strong international agreements on the ethical use of human genome editing, and the

²²⁰ National Academies of Sciences, Engineering, and Medicine (NASEM), *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017) 5.

²²¹ David Baltimore, Paul Berg, et al., 'A Prudent Path forward for Genomic Engineering and Germline Gene Modification' (2015) 348 (6230) *Science* 36, 38.

²²² Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 116.

²²³ Tina Hesman Saey, 'First Genetically Engineered Humans' (27 November 2018) <<https://www.cryonics.org/news/first-genetically-engineered-humans>>.

²²⁴ Nuffield Council on Bioethics, 'Human Embryo Culture, Discussions Concerning the Statutory Time Limit for Maintaining Human Embryo in Culture in the Light of Some Recent Scientific Developments' (London, August 2017) <<http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf>> 108.

²²⁵ Sireesh Ramesh, 'Using CRISPR to Create Genetically Engineered 'Superbabies' Is An Ethical Nightmare' *The Daily Pennsylvanian* (12 December 2018).

²²⁶ Ana Nordberg, Timo Minssen, et al., 'Cutting Edges and Weaving Threads in the Gene Editing () evolution: Reconciling scientific progress with Legal, Ethical, & Social Concerns' (2018) 5 (1) *Journal of Law and the Biosciences* 35, 83.

necessity of strong legal frameworks surrounding what modifications are permitted.²²⁷ At least, China should adopt and apply rigidly the 14-day rule, which draws a “legal and regulatory line in the sand” after which continued research on human embryos is forbidden.²²⁸ A new regulatory regime should be introduced to incorporate a licensing programme for human embryo research.²²⁹ Institutionally, China may take after the UK’s institutional innovation by creating a Chinese version of the HFEA, which works as an independent regulator of research involving human embryos and gametes.²³⁰

Conclusion

Genome editing has the potential to give rise to transformative technologies in the field of human reproduction. Ethical considerations with respect to the use of CRISPR arise predominantly. Heritable genome editing interventions may be inherited by future generations, which should be subject to strict regulation and oversight. There is a considerable need for more proactive rules governing such a transformative technology. Given the lack of an internationally agreed-upon regulatory framework, He’s case highlights the importance of instituting formal regulation of gene editing in China. Furthermore, a well-established system is highly demanded to define a global ethical code of conduct. It is similarly important to affirm and codify international principles for protecting human dignity. More significantly, regulatory oversight will need to include legal authority and enforcement capacity. It is essential to address the principles underlying governance, international governance perspectives and potential applications for germline editing. Notably, it is unrealistic to design a ‘one-size-to-fit-all’ mechanism though. In the direction toward global governance and shared responsibility, it would be prudent to allow heritable genome editing interventions to be initially licensed on a case-by-case basis, complemented with a criminal liability regime.

²²⁷ Alta Charo, ‘The Legal and Regulatory Context for Human Gene Editing’ (2016) 32 (3) *Issues in Science and Technology* 39, 44.

²²⁸ Insoo Hyun, Amy Wilkerson & Josephine Johnston, ‘Embryology Policy: Revisit the 14-Day Rule’ *Nature* (4 May 2016).

²²⁹ Tracey Tomlinson, ‘A CRISPR Future for Gene-Editing Regulation: A Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing’ (2018) 87 (1) *Fordham Law Review* 437, 483.

²³⁰ ‘Germline Gene-Editing Research Needs Rules’ (2019) 567 *Nature* 145.

