Title: Analysing Ireland's Proposed Regulation of Mitochondrial Replacement Techniques

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Analysing Ireland's Proposed Regulation of Mitochondrial Replacement Techniques

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In late 2017, the Irish Government proposed legislation that would completely prohibit mitochondrial replacement techniques ('MRTs'), whether in the context of in-vitro research or in clinical practice. However, there are two flaws in the proposed legislation that may lead to significant problems in the future. First, it is not clear whether the legislation intends to treat MRTs and 'germline genetic editing' as conceptually distinct. This ambiguity potentially undermines the prohibition as it may allow MRTs to be deliberately reframed in a more publicly acceptable way. Second, the justification for the prohibition given in the accompanying Explanatory Note is not sufficiently explained. Both flaws amount to poor legislative practice, especially in an area where the ethical concerns are significant. This paper explores these two issues in the context of the global debate on MRTs and makes some suggestions as to how the Irish government might address them.

Introduction

On 6 April 2016, a boy was born in Mexico.[2] His parents were of Jordanian origin and the delivery team came from New York. The boy's parents had already lost two children to Leigh Syndrome: a severe neurological disorder which leads to a progressive loss of mental and physical abilities. Affected children typically die within three years.[3] The condition is sometimes associated with inherited mutated mitochondria. Hoping for a healthy child who shared their genes, the couple decided to pursue mitochondrial replacement techniques. Mitochondrial replacement techniques ('MRTs') involve taking gametes from intending parents[4] and replacing the intending mother's deleteriously mutated mitochondria with

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[2] Jessica Hamzelou, 'Exclusive: World's first baby born with new "3 parent" technique' (*New Scientist*, last updated 27 September 2016), <https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique> accessed 15 April 2019.

[3] National Institutes of Health, 'Leigh Syndrome' (NIH US National Library of Medicine: Genetics Home Reference) <https://ghr.nlm.nih.gov/condition/leigh-syndrome> accessed 15 April 2019.

[4] 'Intending parents' will be used throughout this paper to refer to a woman and man who use MRTs in an attempt to avoid passing on a mitochondrial mutation while having a genetically related child. 'Intending mother' will be used to refer to the woman who is attempting to use MRTs to

donated mitochondria. The techniques are relatively new, and many objections have been made to its use. Nevertheless, the use of this techniques is spreading.[5]

In 2015, the UK became the first jurisdiction to introduce legislation to permit the use of MRTs. The US and Australia have also engaged in formal public assessment of the techniques, but have not, to date, drafted legislation. In late 2017, the Irish government published the General Scheme of the Assisted Human Reproduction Bill (the 'General Scheme').[6] This draft legislation appears to completely prohibit MRTs.[7] This paper intends to remain neutral on the question of whether MRTs should be permitted in Irish clinical practice. However, it will argue that there are two flaws in the proposed legislation and legislative process. First, it is not clear whether 'germline genetic editing' and 'mitochondrial donation' are characterised as distinct technologies under the General Scheme. Supporters of MRTs in other jurisdictions have distanced MRTs from germline genetic editing. The ambiguity in the Irish General Scheme leaves the text open to deliberate reframing and may undermine the prohibition. Second, the justification for the prohibition given in the accompanying Explanatory Note is not sufficiently explained. This is poor legislative practice, especially in an area where the ethical concerns are significant. It risks harming the public perception of the government's technological assessment process and sets a poor precedent for future legislative treatment of controversial technologies.

In Part I, this paper provides a brief explanation of mitochondrial disease and mitochondrial replacement techniques. In Part II, this paper provides an overview of the process that led to the regulation of MRTs in the UK, as well as the recent public debate in the US and Australia, to provide background and context to the critique of the Irish proposals.[8] Part III explores the

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produce a child that carries her nuclear DNA but not her mutated mtDNA. 'Intending father' will refer to the man whose nuclear DNA is used. This simplified, heteronormative example presumes that the 'intending father' is also the biological father and that the oocyte of the intending mother will be fertilised with the sperm of the man who will raise the child and be recognized as the child's social father. There are, of course, many reasons why this might not be the case. The intending father may have fertility issues or other health problems that necessitate a sperm donor. A sperm donor might also be used if the intending mother is not in a relationship or is homosexual. It may also be the case that the intending mother is unable to carry the child or otherwise wishes to use a surrogate. The mechanisms of MRTs will be explained here using this simplified example, but the reader may wish to keep other possibilities in mind.

[5] Andy Coughlan, 'First baby born using 3-parent technique to treat infertility' (*New Scientist*, 18 January 2017) <https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/> accessed 15 January 2019.

[6] Department of Health, General Scheme of the Assisted Human Reproduction Bill 2017, available at <https://health.gov.ie/wp-content/uploads/2017/10/AHR-general-scheme-with-cover.pdf> (hereinafter referred to as: 'The General Scheme'). See also, Department of Health, 'Government approves the drafting of the Assisted Human Reproduction Bill' The Department of Health: Press Release, (3 October 2017) <https://health.gov.ie/blog/press-release/government-approves-the-drafting-of-the-assisted-human-reproduction-bill/>.

[7] The General Scheme (n 6), Head 61.

[8] Singapore's Bioethics Advisory Committee conducted a public consultation on MRTs from April - June 2018, but no report on that consultation had been published at the time of writing. Bioethics

provisions of the Irish General Scheme as they relate to MRTs and outline some concerns. Finally, Part IV examines how these concerns might be addressed.

Part I: Mitochondrial Disease

Mitochondria are structures within cells whose primary function is to produce energy.[9] Whilst most DNA is nuclear, the genes in mitochondria carry approximately 0.1% of the cell's DNA.[10] Like nuclear DNA, this 'mtDNA' is subject to a risk of spontaneous mutation. Mutations may also be inherited.[11] Some mutations are minor or harmless and do not affect cellular processes. Others can cause significant cellular dysfunctions, often known as 'mitochondrial diseases.'[12] The most significant effects are seen in the parts of the body that require the most energy: the heart, nervous system, muscles, and lungs.[13] At present, there are no cures for those born with a deleterious mtDNA mutation and, many of these

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Advisory Committee, 'Public Consultation on Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology' (Bioethics Singapore: BAC News/Press Releases, 19 April 2018) <http://www.bioethics-singapore.org/images/uploadfile/BAC%20MGRT%20Press%20Release.pdf> accessed 7 April 2019.

[9] Although many commentators have pointed to evidence that mitochondria are involved in other processes, and that their functions are more closely connected to the functions of other parts of the cell than previously thought. See, for example, Eli Y Adashi and I Glenn Cohen 'Going Germline: Mitochondrial Replacement as a Guide to Genome Editing' (2016) 164 Cell 832; Tetsuya Ishii, 'Potential impact of human mitochondrial replacement on global policy regarding germline gene modification' (2014) 29 Reproductive Biomedicine Online 150; Neill Gemmell and Jonci N Wolff, 'Mitochondrial Replacement Therapy: Cautiously replace the master manipulator' (2015) 37(6) Bioessays 584.

[10] Bruce Alberts et al, *Molecular Biology of the Cell* (4th edn, New York, Garland Science, 2002); Jonathon Montgomery et al, Nuffield Council on Bioethics, *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: an Ethical Review* (2012) 18.

[11] Nuffield Council on Bioethics, *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: an Ethical Review* (2012) (hereinafter the '2012 Nuffield Report').

[12] There are mitochondrial diseases which are not the result of genetic mutations. See Erica Haimes and Ken Taylor, 'Sharpening the cutting edge: additional considerations for the UK debates on embryonic interventions for mitochondrial diseases' (2017) 13 Life Science: Society and Policy 1; Katherine Drabiak, 'Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes' (2018) 20(1) DePaul Journal of Health Care Law.

[13] The 2012 Nuffield Report (n 11), 21. See also, Margaret Klehm, Mark Korson, 'Mito Action, A clinician's guide to the management of mitochondrial disease' (Mito Action) <http://www.mitoaction.org/guide/table-contents> accessed 15 January 2019. The variation in the symptomology of mitochondrial diseases make it difficult to put an exact figure on the number of people affected, but some estimates suggest that there are 152 births per year in the UK and 778 per year in the USA that involve women who risk transmitting a mtDNA defect. Gráinne S Gorman et al, 'Mitochondrial Donation—How Many Women Could Benefit?' (2015) 372 New England Journal of Medicine 885.

mitochondrial diseases are fatal. According to the Mitochondrial Disease Foundation, the goal of treatment is simply 'to alleviate symptoms' and to slow the progression of the disease.[14]

Human mtDNA is not inherited in the same way as nuclear DNA. An embryo receives nuclear DNA from both its mother and father, but all its mtDNA comes from the mother.[15] Therefore, efforts to prevent the disease have focused on the inheritance of mitochondria from the female gamete. A number of different approaches have been developed.[16] The techniques (collectively known as 'mitochondrial replacement techniques') use donated mitochondria and in-vitro fertilisation (IVF) to create an embryo that carries all the intending mother's nuclear DNA but none of her mitochondrial DNA. The common goal of all MRTs is to combine the intending mother's nucleus, the intending father's gamete and the donor's healthy mitochondria into the same cell. The resulting embryo[17] contains the nuclear DNA of both intending parents with the (healthy) mitochondria and mitochondrial DNA of the donor. After fertilisation, the embryo is screened for mtDNA mutations and viability[18] before being implanted into the intending mother's uterus.[19]

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[14] United Mitochondrial Disease Foundation, 'Treatment and Therapies', (United Mitochondrial Disease Foundation) <http://www.umdf.org/what-is-mitochondrial-disease/treatments-therapies/> accessed 14 January 2019.

[15] DT Brown et al, 'Transmission of mitochondrial DNA disorders: possibilities for the future' (2006) 368 The Lancet 87. Although there is some debate about this: see, eg ED Ladoukakis, A Eyre-Walker, 'Evolutionary Genetics: Direct Evidence of Recombination in Human Mitochondrial DNA (2004) 93 Nature: Heredity 321; Friderun Ankel-Simons and Jim M Cummins, 'Misconceptions about mitochondria and mammalian fertilization: Implications for theories on human evolution' (1996) 93(24) Proceedings of the National Academy of Sciences of the United States of America 13859, available at http://www.pnas.org/content/93/24/13859.full (accessed 15 January 2019) and Marianne Schwartz and John Vissing, 'Paternal Inheritance of Mitochondrial DNA', (2002) 347 New England Journal of Medicine 576.

[16] The UK regulatory process focussed on two techniques known as maternal spindle transfer and pronuclear transfer. See the 2012 Nuffield Report (n 11), 32-36. A third technique, polar body transfer, was also reviewed. See Andy Greenfield et al, Human Fertilisation and Embryology Authority, *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease, Addendum to 'Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update'* (October 2014). A proposed fourth technique was discussed in The Senate of Australia, Community Affairs References Committee, 'Science of mitochondrial donation and related matters', (27 June 2018) <https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report> accessed 12 January 2019, 38 (para 3.31).

[17] Or more accurately, at that early stage of development, a zygote.

[18] At this stage, fertilised zygotes may also be screened for sex. The US National Academies of Sciences, Engineering and Medicine recommended that initially, only male embryos created through MRTs be brought to term. They argue that this is an appropriate risk mitigation strategy. Because mtDNA is only passed through the maternal line, any deleterious effects cause by MRTs would not enter the broader gene pool. National Academies of Sciences, Engineering and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations* (The National Academies Press, 2016).

[19] Bearing in mind that a surrogate may be used to carry the child to term.

Part II: MRTs in the UK, the US, and Australia

MRTs are a relatively new technology and only a handful of jurisdictions have specifically considered them to date. The UK became the first country to specifically legislate for their use in 2015, while the US and Australia have engaged in public reviews. Before considering the draft Irish legislation, this paper will give a brief description of those three processes, to provide context and comparison for the critique of the Irish proposals.

The Regulation of MRTs in the UK

Since the establishment in 1978 of the Committee of Inquiry into Human Fertilisation and Embryology, more commonly known as the Warnock Committee,[20] the UK have been at the vanguard of the assessment and regulation of reproductive medicine.[21] Initially, the implantation of genetically modified human embryos was totally prohibited.[22] This effectively prohibited any steps towards MRTs. However, attitudes shifted[23] and in 2005 the Newcastle Centre for Mitochondrial Research was granted a licence to investigate the feasibility of using IVF-based techniques to prevent the transfer of mitochondrial disease.[24] As the research continued, the UK government commissioned reports from experts in three different fields.

First, the Nuffield Council on Bioethics was commissioned to report on the ethical implications of MRTs. That report was published in 2012 and concluded that it would be ethical to use MRTs, provided they were proven to be safe and effective, and the users were given appropriate information and support.[25] Second, the Human Fertilisation and Embryology Authority convened an expert panel to produce a report on the 'safety and effectiveness of mitochondrial transfer'. That report was published in 2014.[26] The expert panel

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[20] After Mary Warnock (later, Dame Warnock), philosopher and Chair of the committee.

[21] The Committee produced the 'Warnock Report', which became the basis for most of the UK's approach to the regulation of reproductive medicine. See Committee of Inquiry into Human Fertilisation and Embryology, *Report of the Committee of Inquiry into Human Fertilisation and Embryology* (1984).

[22] Section 3, Human Fertilisation and Embryology Act 1990, Chapter 37 (as amended). See also, Human Fertilisation and Embryology Act (as amended), 2008, Chapter 22, *Explanatory Notes: Commentary on Sections: Part 1, 'Section 3: Prohibitions in connection with embryos'*, 28-30, available at <http://www.legislation.gov.uk/ukpga/2008/22/notes/division/6/1> accessed 15 January 2019.

[23] Due to advancements in research on animal models and the publication a report of the Chief Medical Officer, which noted the potential for mitochondrial transfer to prevent mitochondrial disease. See Department of Health, Chief Medical Officer's Expert Group, *Stem Cell Research: Medical Progress with Responsibility* (June 2000), available at <http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4065085.pdf> accessed 15 January 2019.

[24] The 2012 Nuffield Report (n 11) vii.

[25] The 2012 Nuffield Report (n 11) xvi.

[26] Andy Greenfield et al, The Human Embryology and Fertilisation Authority, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update, 2014* (June

concluded that MRTs would be effective in preventing the transmission of mitochondrial disorders and that there was no evidence to suggest that they were unsafe for clinical use.[27] Third, an 'Impact Assessment' was undertaken by the UK's Department of Health.[28] Published in 2015, it attempts to quantify the effects of legalising MRTs in monetary terms. It estimated a significant net economic gain, based on healthcare savings and on QALYs[29] gained by those who would have otherwise suffered from a mitochondrial disease.

The British government also launched a wide-ranging public dialogue initiative in 2012.[30] They found general public support for MRTs. The public largely held that the ethical concerns were largely outweighed by the potential benefits. On the basis of the scientific, ethical, financial and public approvals, the UK government drafted legislation to permit MRTs. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations were signed into law in March 2015.[31] The regime currently allows individuals to apply to closely-monitored clinical trials.[32]

2014), *available at* <https://www.hfea.gov.uk/media/2614/third_mitochondrial_replacement_scientific_review.pdf> accessed 15 January 2019. A comprehensive overview report was published in 2016, after the law had been changed. Andy Greenfield et al, Report to the Human Fertilisation and Embryology Authority, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 updated* (November 2016), *available at* <https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf> accessed 15 January 2019.

[27] Explanatory Memorandum to the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations, SI 2015/572, 7.4, <http://www.legislation.gov.uk/uksi/2015/572/pdfs/uksiem_20150572_en.pdf> accessed 15 January 2019.

[28] Department of Health, *Impact Assessment: The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations, 2015* (12 September 2014), <http://www.legislation.gov.uk/ukia/2015/138/pdfs/ukia_20150138_en.pdf> accessed 15 January 2019.

[29] Quality Adjusted Life Years: a commonly used measure of the benefits of a medical intervention. The benefits, in additional years of life, are weighted to take account of the quality of that life. See National Institute for Health and Care Excellence, 'Glossary: Quality Adjusted Life Years', (*NICE: Glossary*) <https://www.nice.org.uk/glossary?letter=q> accessed 15 January 2019.

[30] Richard Watermeyer and Gene Rowe, Cardiff University, Gene Row Evaluations, *Evaluation of the Project: 'Mitochondria Replacement Consultation'* July 2013, <http://webarchive.nationalarchives.gov.uk/20170110134326/http://www.sciencewise-erc.org.uk/cms/assets/Uploads/Mitochondria-evaluation-FINAL-2013.pdf> accessed 15 January 2019.

[31] The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, SI 2015/572.

[32] Newcastle University: Press Office, 'Newcastle awarded world's first mitochondrial licence' (*Newcastle University*, 16 March 2017) <https://www.ncl.ac.uk/press/articles/archive/2017/03/mitochondrialicence> accessed 15 January 2019.

Public Discussion of MRTs in the US

Perhaps the most significant contrast between the UK and US regulatory landscapes is that the UK has a centralised governing body for reproductive technologies[33] and the US does not.[34] As a result, the treatment of MRTs by US authorities has been more sporadic and dispersed. In 2001, the Food and Drug Administration (the 'FDA') asserted jurisdiction over human cells used in medicine, including mitochondrial material.[35] As a result, any clinical trials or clinical practice of MRTs are dependent on FDA approval.[36] In 2014, the Office of Cellular, Tissue and Gene Therapies of the Center for Biologics Evaluation and Research at the FDA considered MRTs but concluded that there was, at the time, insufficient evidence that the techniques were safe.[37] In 2016, the National Academies of Sciences, Engineering and Medicine published a report that focused on the ethics of the techniques (the '2016 NAS Report'). The report recommended that the FDA permit clinical investigation of MRTs, subject

[33] The Human Fertilisation and Embryology Authority.

[34] I Glenn Cohen, Julian Savulescu and Eli Y Adashi, 'Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy', (2015) 348(6231) Science 178; Rosa J Castro, 'Mitochondrial Replacement Therapy: the UK and US Regulatory Landscapes' (2016) 3(3) Journal of Law and the Biosciences 726.

[35] Department of Health and Human Services, Food and Drug Authority, 'Letter to Sponsors/Researchers – Human Cells Used in Therapy Involving the Transfer of Genetic Material by Means Other than the Union of Gamete Nuclei' (*Food and Drug Administration: Vaccines, Blood & Biologics*, 6 July 2001), <https://wayback.archive-it.org/7993/20170404210748/https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm> accessed 12 January 2019; Department of Health and Human Services, Food and Drug Authority, 'FDA Regulation of Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps) Product List' (*US Food and Drug Administration*, last updated 12 May 2009), https://www.fda.gov/biologicsbloodvaccines/tissuetissueproducts/regulationoftissues/ucm150485.htm accessed 15 January 2019; The FDA's jurisdiction over MRTs was confirmed in the National Academies of Sciences, Engineering and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations* (The National Academies Press, 2016), 64.

[36] Department of Health and Human Services, Food and Drug Authority (n 35).

[37] Cellular, Tissue, and Gene Therapies Advisory Committee, 'February 25, 2014: Cellular, Tissue and Gene Therapies Advisory Committee Meeting Summary Minutes' (25 February 2014) https://wayback.archive-it.org/7993/20170405194942/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm406412.htm accessed 15 January 2019.

to a number of risk-mitigation strategies.[38] However, the 2015/2016 federal budget[39] included a clause that prohibits the use of FDA funding to consider applications for trials 'in which a human embryo is intentionally created or modified to include a heritable genetic modification'.[40] This clause, which prevents the FDA considering applications for trials of MRTs, has been retained and remains in the 2018 federal budget.[41]

The Australian Senate Committee's Report on MRTs

In 2018, a Committee of the Australian Senate published a report on the science, ethics, and potential Australian regulation of MRTs.[42] It explored the techniques that have been developed, the ethical issues that were raised before the committee, and the legislative changes that would be required before MRTs could be permitted in Australia. The report took a generally positive view of MRTs. One of its key recommendations that a panel of Australian experts be convened to formally examine and endorse the UK's published findings on the safety and efficacy of MRTs[43] and that a public consultation be undertaken on the introduction of MRTs into Australian clinical practice.[44]

Part III: The Irish General Scheme and the Proposed Regulation of MRTs

The General Scheme of the Assisted Human Reproduction Bill (the 'General Scheme') was published by the Irish Minister for Health in late 2017.[45] At present, the General Scheme is still at the stage of 'pre-legislative scrutiny', and it is not clear when (or if), a finalised Bill will

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[38] The report recommends that clinical investigation of MRTs should be permitted, subject to the conditions that are that the technique be proven safe and effective, that the research be carried out in an ethical manner, than all risks be minimized, that all personnel involved have the requisite level of skill and expertise, that the trials take place only on women at risk of transmitting a mitochondrial disease that could lead to a child's early death or substantial impairment, and that only male embryos be implanted (since mitochondria are only passed down the female line, any unforeseen, deleterious consequences of MRTs would not enter the broader gene pool). See The National Academies of Sciences, Engineering and Medicine, 'Clinical Investigations of Mitochondrial Replacement Techniques are 'Ethically Permissible' If Significant Conditions Are Met, Says New Report' (3 February 2016), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=21871 (accessed 12 January 2019); I Glenn Cohen and Eli Y Adashi, 'Mitochondrial Replacement Therapy: the IOM report and its aftermath' (2016) 17(4) Nature Reviews: Genetics 189.

[39] The Consolidated Appropriations Act, PL 114-113.

[40] Consolidated Appropriations Act, PL 114-113, 114th Congress, HR 2029, Section 749.

[41] Consolidated Appropriations Act, PL 115-141, 115th Congress, HR 1625, Section 735.

[42] The Senate of Australia, Community Affairs References Committee, 'Science of mitochondrial donation and related matters' (27 June 2018) <https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report> accessed 12 January 2019 (hereinafter the 'Australian Senate Report').

[43] The Australian Senate Report (n 42), 52 (para 3.100).

[44] The Australian Senate Report (n 42), Recommendation 1, ix, (para 5.99).

[45] The publication of the General Scheme in this manner allows the Minister to invite public comment before the Bill is finalised and brought before the Irish parliament for a vote.

be brought to a vote.[46] Although public and media attention has largely been focused on the provisions relating to surrogacy and IVF, the General Scheme also deals with genetic modification and MRTs. The tone of the General Scheme in this regard is cautious and its approach is largely restrictive.

Head 61 of the General Scheme addresses human genome modification and MRTs. Section (1) regulates 'germline genetic modification.' Where a gamete or an embryo has been modified in a way that is heritable, section (1) prohibits the use of that embryo or gamete in an attempt to achieve a pregnancy. However, the Explanatory Note clarifies that, under section (1), 'basic and clinical research' involving germline genome editing or modification would be permissible, provided the cells, gametes or embryos involved were not subsequently used in an attempt to achieve a pregnancy.[47] Sections (2) and (3) of Head 61 of the General Scheme address MRTs. Section (2) expressly prohibits mitochondrial donation or mitochondrial replacement in human gametes and embryos, while section (3) prohibits the use of gametes or embryos which have been subject to mitochondrial donation in an attempt to achieve a pregnancy. Together, sections (2) and (3) effectively prohibit any use of MRTs, whether done in Ireland or abroad. Importantly, the Explanatory Note confirms that while 'basic and clinical research' may be done on 'germline genetic editing', there is a complete prohibition on any research on, or practice of, MRTs.

The Ambiguous Characterisation and Framing of MRTs

The first critique of the General Scheme relates to its characterisation or definition of MRTs, in relation to 'germline genetic modification'. The question of how MRTs should be characterised has played a significant role in the public debate elsewhere.

In the US, the question arose of whether MRTs were genetic editing or germline editing. The 2016 NAS Report concluded that MRTs are *always* genetic editing, because they always involve a modification of the genetic information within a cell,[48] while MRTs *become* germline editing when they produce genetic changes that are *heritable*. Since mitochondria are only passed via the maternal line, germline editing only takes place where mitochondrial replacement is performed on female embryos that are brought to term.[49] The report notes that the ethical, social, and policy issues involved in genetic modifications are different to (and by implication, less significant than) those involved in germline modifications because 'whatever modifications have been introduced into the germline have effects potentially in perpetuity',

[46] A 'General Scheme', in the Irish context, is a near-final draft of a Bill. Once the text of a Bill has been agreed, it must be passed by both houses of parliament, the Dáil and the Oireachtas. Houses of the Oireachtas, 'How laws are made' (*Oireachtas*) https://www.oireachtas.ie/en/visit-and-learn/how-parliament-works/how-laws-are-made/ accessed 12 January 2019.

[47] The General Scheme (n 6), Head 61, Explanatory Note. The Explanatory Note also specifically notes the General Scheme does not prohibit making non-inheritable genetic modifications to embryos in research or in future medical practice.

[48] National Academies of Sciences, Engineering and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations* (The National Academies Press, 2016) (hereinafter 'The 2016 NAS Report') 88.

[49] ibid 89.

while 'genetic modifications… do not survive beyond the life of the affected individual'.[50] The report takes the view that the ethical and safety concerns posed by MRTs could therefore be significantly mitigated if they were initially used only to create male embryos, thereby creating only genetic, not germline changes.[51]

In contrast to the US's stance, the position taken by the UK government, in a published response to a public consultation on MRTs, is that MRTs *always* produce germline modifications, because 'the result of mitochondrial donation – the avoidance of the transmission of a serious mitochondrial disease – will be passed down to future generations'.[52] Contrary to the cautious approach of the US to germline editing, it appears that the UK sees the fact that MRTs acts on the germline as a net positive. However, the UK publication continues by stating that MRTs do *not* create genetic modifications because they do not 'alter personal characteristics and traits of the person'. The UK government decided to adopt a 'working definition' of genetic modification that covers only 'the germline modification of *nuclear* DNA… that can be passed on to future generations'.[53] MRTs are not included in that definition. Instead, MRTs are framed as analogous to less controversial medical interventions like organ transplants or blood donation and compared to simply changing the 'battery pack' of a human cell.[54]

Meanwhile, the characterisation of MRTs is still an open question in Australia. The Australian Senate Report took a broadly positive view of the medical potential of MRTs and recommended that the government move forward with a public consultation on the introduction of MRTs into clinical practice.[55] However, they were unable to conclude, on the

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[50] ibid.

[51] ibid 108, 120-121.

[52] Department of Health, Public Health Directorate/Health Science and Bioethics Division (UK) *Mitochondrial Donation: Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child* (July 2014) 15. <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf> accessed 15 January 2019 (hereinafter the 'UK Government Response').

[53] ibid.

[54] The 2016 NAS Report took a similar position, finding that modifications to mitochondrial DNA 'represents a qualitatively different form of heritable genetic change from that resulting from any approach for modifying' nuclear DNA. The 2016 NAS Report (n 48) 107. Some commentators have argued that the 'battery' metaphor is not appropriate, given the possibility of interaction between nuclear DNA and mtDNA and the effect of MRTs on the identity of the resulting child. Neill Gemmell and Jonci N Wolff, 'Mitochondrial Replacement Therapy: Cautiously replace the master manipulator' (2015) 37(6) Bioessays 584; Katherine Drabiak, 'Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes' (2018) 20(1) DePaul Journal of Health Care Law. Others have argued, in support of the metaphor, that it was a necessary simplification of the science in the context of public debate. Lyndsay Craven, Julie Murphy et al, 'Scientific and Ethical Issues in Mitochondrial Donation' (2018) 24(1) The New Bioethics 57.

[55] The Australian Senate Report (n 42), Recommendation 1, ix, 52 (paras 3.97-3.106).

basis of the submissions to the Committee, whether mitochondrial donation is distinct from germline editing and recommended that a panel of expert scientists and bioethicists be convened on the subject.[56]

It is not clear from the General Scheme what position Ireland takes on the characterisation of MRTs. As noted above, the General Scheme deals with MRTs and 'germline genetic modification' in separate provisions and subjects MRTs to a broader prohibition. Viewed in the context of the broader global debate, there are two major ambiguities. By discussing 'germline genetic modifications', instead of 'germline modifications' and 'genetic modifications', the General Scheme appears to see one category of intervention where public bodies in the US and the UK see two. Furthermore, the fact that the General Scheme pertains to MRTs and 'germline genetic modification' in separate provisions, and subjects MRTs to a broader prohibition, suggests that the General Scheme sees 'germline genetic editing' and MRTs as distinct processes, which should be treated differently. However, that separation is undermined by the Explanatory Note, which seems to refer to MRTs as a 'specific case' of 'germline genetic editing'.

Whether there is a clear legal distinction between MRTs and other germline or genetic technologies is a significant question in the context of a global consensus that we should be extremely cautious in our approach to modifying the human genome.[57] Under that consensus, 'genetic editing' and 'germline editing'[58] are often negatively loaded phrases. In other jurisdictions, the proposition that MRTs are a form of germline and/or genetic editing has founded many objections to its use and efforts to downplay or deny a link are discernible in the positive public assessments of MRTs in the UK and the US.[59] In other words, framing

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[56] ibid ix; 71-73 (paras 4.78-4.89)

[57] See, for example, The Parliamentary Assembly of the Council of Europe, *Genetic Engineering* (text adopted on 26 January 1982), Paragraph 4a, which argues for an implied 'right to inherit a genetic pattern which has not been artificially changed'; See also the 2015 call for a moratorium on research on the editing of human DNA using CRISPR/Cas9: 'UNESCO panel of experts calls for ban on "editing" of human DNA to avoid unethical tampering with hereditary traits', *UNESCO* <https://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits> last accessed 15 January 2019. For an excellent survey of the international regulatory landscape on germline genetic editing as it stood in 2014, see Tetsuya Ishii, 'Potential impact of human mitochondrial replacement on global policy regarding germline gene modification' (2014) 29 Reproductive Biomedicine Online 150.

[58] As well as related phrases like 'genetic modification', 'genetic engineering', and 'genetic manipulation'.

[59] Department of Health, Public Health Directorate/Health Science and Bioethics Division (UK) *Mitochondrial Donation: Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child* (July 2014)<https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf> accessed 15 January 2019, (hereinafter the 'UK Government Response'), 15; The Australian Senate Report (n 42), 71 (para 4.78); The 2012 Nuffield Report (n 11), 58 (paras 4.33-4.35); National Academies of Sciences, Engineering and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations* (The National

MRTs as either closely linked to or completely distinct from genetic editing or germline editing may tend to decrease or increase its public acceptability.

Many commentators have argued that MRTs have already benefited from a positive framing in other respects. For example, as MRTs involve the extraction of the 'healthy' nucleus from the egg or the embryo of the intending mother or parents, and the transfer of that nucleus to a donated egg (from which the nucleus has been removed), it has been argued that it may be more accurate to speak of 'nuclear transfer' instead of 'mitochondrial replacement'.[60] Others have pointed out that the term 'mitochondrial replacement *therapies*' is often used in the debate and media.[61] Again, this is arguably a mischaracterisation as MRTs are a preventative measure, modifying a gamete before fertilisation. However, the use of the word 'therapy' adds a positive emotional sentiment to arguments in favour of MRTs.

Nisker argues that the use of the term 'mitochondrial replacement', instead of 'nuclear transfer' is the most recent example of a general trend of 'euphemisms' being used in debates on reproductive genetics, 'to open prickly barn doors into human research, as well as to gain clinical and public acceptance'.[62] He notes, for example, that the term 'pre-embryo' was created in the late 1980s to describe human embryos before they had reached 14 days post-fertilisation.[63] This was done to draw a distinction between embryos at different stages, so that research performed on these 'pre-embryos' might be made more publicly acceptable. He also notes that the term 'pre-implantation genetic diagnosis' is misleading, since the technique is primarily used to *screen* embryos.[64] Again, he argues, the word 'diagnosis' is used to make the technique more socially acceptable. In both instances, a deliberate use of language and the passage of time was enough to re-frame an ethically controversial scientific technique and make it publicly acceptable.

As noted in the introduction, this paper intends to remain neutral about the ethics of using MRTs in research or clinical practice. Similarly, this paper does not take a strong stance on how MRTs should be framed or characterised in relation to germline or genetic editing. Rather, the intention here is to argue that the General Scheme's provisions in relation to MRT and 'germline genetic modification' are poorly drafted. They lack precision and clarity of meaning in a context where subtle changes in legal characterisation or framing can change what research is permitted and what medical interventions are available. The ambiguous

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Academies Press, 2016), 88; Jeff Nisker, 'The Latest Thorn by Any Other Name: Germ-Line Nuclear Transfer in the Name of "Mitochondrial Replacement"' (2015) 37(9) Journal of Obstetrics and Gynaecology Canada 829.

[60] See, for example, Jeff Nisker, 'The Latest Thorn by Any Other Name: Germ-Line Nuclear Transfer in the Name of "Mitochondrial Replacement"' (2015) 37(9) Journal of Obstetrics and Gynaecology Canada 829; Francoise Baylis, 'Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush' (2017) 31(1) Bioethics 7.

[61] See, for example, Giulia Cavaliere and César Palacios-González, 'Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship' (2018) 44 Journal of Medical Ethics 835.

[62] Nisker (n 59) 829.

[63] ibid 830.

[64] ibid.

characterisation of MRTs in the General Scheme might have unintended consequences in the future. It is clear that the Irish government intended to prohibit MRTs, but the ambiguity leaves the legislation open to challenge and poses a risk to legal certainty.[65] Whatever position one takes on MRTs, a commitment to the principle of legal certainty requires that, insofar as possible, that ambiguity be reduced. Through public discussion papers, expert reports or official guidance documents, the Irish government should follow the lead of the UK, the US and Australia, engage in public debate and take an official position on the characterisation of MRTs. These steps will be addressed in Part IV below.

The Ethical and Safety Concerns Behind Ireland's Prohibition

The second critique of the General Scheme is based on the reasoning behind the prohibitions on germline genetic editing and MRTs. According to the Explanatory Note, genetic editing of gametes or embryos constitutes germline modification and could become a permanent, heritable part of the human genome.[66] It refers to the 'serious ethical and safety concerns' which have been raised about such modifications, both around the short-term impact on individuals and the long-term impact on future generations. It acknowledges that MRTs are used in a limited number of jurisdictions (and specifically refers to the UK). However, it also points out that, given the uncertainty surrounding their effects, and the availability of 'alternative options' such as PGD, gamete donation or adoption, many other countries have prohibited mitochondrial replacement.

The Explanatory Note echoes a broad global debate on the ethics of MRTs. The Nuffield Council's report is illustrative: it divides the chapter on 'Ethical Considerations' into a summary of key issues and eight separate chapter sub-headings, each of which contain detailed discussions of a particular set of ethical problems, with nuanced arguments and responses.[67] The concerns raised in the public and academic debate over MRTs are diverse, and cover deep and difficult questions, including the impact of MRTs on the genetic identity of the resulting child, the impact of having three people involved in a child's conception on society and relationships, the physical dangers posed by the techniques and the fundamental ethics of genetic and germline modifications.[68]

The issue with the approach of the General Scheme and the Explanatory Note is that the 'serious ethical and safety concerns' are not particularised the text and remain vague and

[65] The prohibition seems likely to be effective when the legislation is first brought into force, particularly since the express prohibition would be reinforced by Head 16 (4)(a), which prohibits the use of any assisted human reproduction method which, as part of a single procedure, involves 'eggs provided by more than one woman'. This would, in effect, prohibit the clinical practice of MRTs.

[66] The General Scheme (n 6), Head 61, Explanatory Note.

[67] The 2012 Nuffield Report (n 11), Chapter 4 – Ethical Considerations, 52-87.

[68] See, for example, The 2012 Nuffield Report (n 11); The 2016 NAS Report (n 48); Tetsuya Ishii, 'Reproductive Medicine Involving Mitochondrial DNA Modification: Evolution, Legality and Ethics' (2018) 4(1) European Medical Journal of Reproductive Health 88; Lyndsay Craven, Julie Murphy et al, 'Scientific and Ethical Issues in Mitochondrial Donation' (2018) 24(1) The New Bioethics 57; Giulia Cavaliere and César Palacios-González, 'Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship' (2018) 44 Journal of Medical Ethics 835.

undefined in the context of the broader public debate. To draw a comparison, the UK's Human Fertilisation and Embryology (Mitochondrial Donation) Regulations (the 'UK regulations')[69] are set in the context of several years and hundreds of pages of official public debate and academic commentary. The ethical and safety concerns considered by the UK government, and their responses to them, are well-documented. As such, there is no great need for the Explanatory Memorandum to the UK regulations to discuss the underlying ethical considerations in detail.[70] However, there was no comparable public debate in Ireland and the public debate on adjacent issues is sparse. This dearth of public debate and legislative guidance is not confined to MRTs; there has been a longstanding lack across many aspects of the public debate on assisted human reproduction, research on human embryos and related fields.[71] The paucity of public debate is reflected in the paucity of legislation. A 2009 Supreme Court decision described Ireland as an 'unregulated environment'[72] for this kind of research and the Introduction to General Scheme itself refers to a 'legal vacuum'.[73] Whilst two expert reports were published in 2005 and 2008 on assisted human reproduction and stem cell research respectively[74] and many of the provisions in the General Scheme relating to those subjects seem to be based on those reports,[75] the reports do not discuss MRTs or germline genetic editing in any great detail.[76] In short, it is very difficult to know which specific ethical and safety concerns are behind the proposed Irish prohibition on MRTs.[77]

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[69] The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, SI 2015/572.

[70] Explanatory Memorandum to the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations, SI 2015/572, <http://www.legislation.gov.uk/uksi/2015/572/pdfs/uksiem_20150572_en.pdf> accessed 15 January 2019.

[71] Fionnuala Gough, 'Human Embryonic Stem Cell Research in Ireland: Ethical and Legal Issues' (2011) 11(4) Medical Law International 262.

[72] *Roche v Roche & Ors* [2009] IESC 82.

[73] The General Scheme (n 6), 6

[74] The Commission on Assisted Human Reproduction, 'Report of the Commission on Assisted Human Reproduction' (2005); The Irish Council for Bioethics, 'Opinion of the Irish Council for Bioethics on the Ethical, Scientific and Legal Issues Concerning Stem Cell Research' (2008).

[75] The 2005 Report of the Commission on Assisted Human Reproduction (n 74) was referred to in the press release that announced the General Scheme. Department of Health, 'Press Release: Government approves the drafting of the Assisted Human Reproduction Bill' (*Department of Health*, 3 October 2017) https://health.gov.ie/blog/press-release/government-approves-the-drafting-of-the-assisted-human-reproduction-bill/ accessed 12 January 2019.

[76] The Report of the Commission on Assisted Human Reproduction does address the possibility of 'ooplasmic transplantation' to 'be used in the treatment of developmentally compromised ova', in the context of a discussion of the manipulation of gametes. However, it provides only the general recommendation that such research be permitted provided it is subject to strict regulatory oversight and informed consent. Report of the Commission on Assisted Human Reproduction, 62-63 (para 8.4).

[77] The public debate which precipitated the General Scheme focussed largely on issues of in-vitro fertilisation, surrogacy and parentage, precipitated by cases such as *Roche v Roche & Ors* [2009] IESC 82, and *MR and DR & ors v An t-Ard Chláraitheoir & ors* [2014] IESC 60.

The fact that the Irish government is proposing a prohibition is not particularly surprising. In fact, given Ireland's historically conservative attitude towards technologies like assisted human reproduction[78] and abortion,[79] and the controversy over the UK's legalisation of MRTs,[80] a cautious approach to the technology might be the most appropriate one. However, this paper argues that the perseveration of public trust in the regulation of science provides a strong reason for Ireland to engage in public debate and explicit regulatory reasoning in this context, no matter what position is finally taken on MRTs.

Public debate and explicit regulatory reasoning are also important for the preservation of public trust in the regulation of science.[81] For there to be public trust in the regulation of science, the public must believe that the governance and practice of science will be based on thorough and unbiased review of the scientific data, a deep and reasoned consideration of the ethics, a pragmatic assessment of the legal and social situation and a proper consideration of the public opinion.[82] The General Scheme itself appears to recognise this need. In the Introduction, it refers to the 'legitimate expectation' of the 'general public' that 'all AHR practices and related research is regulated and carefully monitored'.[83] When discussing the research ethics committee approvals that would be required for research involving human embryos, the General Scheme also refers to the need for 'public confidence that research in this area conforms to high ethical and scientific standards while also allowing a framework for scientific and clinical innovation'.[84] Maintaining this trust is crucial in part because progress in science is aided by public support[85] and in part as a general principle of

[78] David J Walsh and others, 'Irish public opinion on assisted human reproduction services: Contemporary assessments from national sample' (2013) 40 (4) CERM 169.

[79] Abortion in Ireland was restricted by the provisions of the Irish Constitution and only permitted in exceptional circumstances until those provisions were repealed by popular referendum in 2018. Thirty-Sixth Amendment of the Constitution Act 2018. Available at Irish Statute Book, 'Thirty-Sixth Amendment of the Constitution Act 2018' http://www.irishstatutebook.ie/eli/2018/ca/36/enacted/en/html accessed 17 January 2019.

[80] The UK's regulations, and the practice of MRTs, have been welcomed by many commentators and criticised by many others. See, for example, I Glenn Cohen, Julian Savulescu and Eli Y Adashi, 'Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy', (2015) 348 (6231) Science 178; The Australian Senate Report (n 42); Ian Sample, 'First UK licence to create three-person baby granted by fertility regulator' (*The Guardian,* 16 March 2017) <https://www.theguardian.com/science/2017/mar/16/first-licence-to-create-three-person-baby-granted-by-uk-fertility-regulator> accessed 15 April 2019; Nisker (n 59); Katherine Drabiak, 'Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes' (2018) 20(1) DePaul Journal of Health Care Law: The UK Government Response (n 52).

[81] David B. Resnik, 'Scientific Research and the Public Trust' (2011) 17(3) Science and Engineering Ethics 399; Onora O'Neill, 'A question of trust: the BBC Reith lectures 2002', (2002) Cambridge University Press.

[82] Resnick (n 81).

[83] The General Scheme (n 6), Introduction , 6.

[84] The General Scheme (n 6), Head 70, Explanatory Note: (4).

[85] Giulia Cavaliere, 'A 14-day limit for bioethics: the debate over human embryo research' (2017) 18 (38) BMC Medical Ethics, 9.

democratic governance. However, this trust may be damaged by the perception that legislative policies are not sufficiently explained and the lack of detailed explanation for the prohibition of MRTs may damage public trust in the Irish government's regulation of new scientific discovery. This mistrust may deepen if Ireland's prohibition remains unexplained and in place, given the warm reception that the UK's regulation of MRTs received in many quarters and the possibility that MRTs may soon enter clinical practice there and other jurisdictions.[86]

Part IV: Addressing the Problem

This final section will explore some steps that the Irish government should take to address the issues raised here.[87] First, the government should take an official position on the characterisation of MRTs in relation to germline editing or genetic editing. The existing draft of the General Scheme establishes an 'Assisted Human Reproduction Regulatory Authority' ('AHRRA') for matters related to assisted human reproduction.[88] The characterisation of MRTs should be addressed in a report undertaken by the AHRRA[89] (or by another body established specifically for the task).[90] The government should go a step further and

[86] Tetsuya Ishii, 'Potential impact of human mitochondrial replacement on global policy regarding germline gene modification' (2014) 29 Reproductive Biomedicine Online 150; Tetsuya Ishii and Yuri Hibino, 'Mitochondrial manipulation in fertility clinics: Regulation and Responsibility' (2018) 5 Reproductive Medicine and Society Online 93; Tetsuya Ishii, 'Reproductive Medicine Involving Mitochondrial DNA Modification: Evolution, Legality and Ethics' (2018) 4(1) European Medical Journal of Reproductive Health 88; Johanna Schandera and Tim K Mackey, 'Mitochondrial Replacement Techniques: Divergence in Global Policy' (2016) 32(7) Trends in Genetics 385.

[87] At the time of writing, the General Scheme was under 'pre-legislative scrutiny' before the Oireachtas Joint Committee on Health and the Minister for Health had stated that the Committee intended to publish a report on the bill in 'early 2019'. Formal assessment continued in December 2018. However, there was no definite timeline available for the finalisation of the Bill and its passage through the Irish parliament. See Written Answers to Parliamentary Questions, 'Assisted Human Reproduction Legislation – *Dáil Éireann* Debate, Thursday 8 November 2018' (*Oireactas.ie*, 8 November 2018) https://www.oireachtas.ie/en/debates/question/2018-11-08/136/ Accessed 14 January 2019; 'Health Committee to resume PLS on General Scheme of the Assisted Human Reproduction Bill' (*Oireachtas.ie*, 18 December 2018) https://www.oireachtas.ie/en/press-centre/press-releases/20181218-health-committee-to-resume-pls-on-general-scheme-of-the-assisted-human-reproduction-bill/ accessed 14 January 2018.

[88] The General Scheme (n 6), Head 65.

[89] The AHRRA is empowered to establish discrete committees for particular tasks. The General Scheme (n 6), Head 79.

[90] There is Irish precedent for this in the Commission on Assisted Human Reproduction, which prepared the 'Report of the Commission on Assisted Human Reproduction' (n 73). Perhaps the best course of action, and the one most likely to prevent similar problems arising in the future, would be to re-establish the Irish Council for Bioethics. Its terms of reference were to identify ethical questions raised by medical research; to investigate and report on those questions in the interests of promoting public understanding, informed discussion, and education; and to stimulate discussion through conferences, workshops, lectures, and published reports. However, it was defunded in 2010, as part of a cost-saving measure in the wake of the 2008 financial crisis. See Barry Lyons, 'The Irish Council for Bioethics: An Unaffordable Luxury?' (2012) 21 Cambridge Quarterly of Healthcare Ethics 375. A

commission a broad report on the safety, ethics and public acceptability of MRTs (and other, controversial gene-based technologies like CRISPR-Cas9[91]). Such a review should take into account the processes that are followed in the UK. This can be achieved through engaging in a broad consultation on the public acceptability of the technologies), as well as attempting a pragmatic assessment of the financial and social effects of their use and discussing the potential development of other new technologies and the legislative approaches that might be taken. Undertaking a wide review would allow the government to particularise the 'serious and ethical and safety concerns' underlying the current position on MRTs. This would additionally pre-empt the issues that will likely arise as these technologies are developed and to explore the general principles of governance that might be relevant to a broad range of other biotechnologies. This could also further the establishment of a more active national conversation around MRTs and other emerging biotechnologies.

Next, the government should redraft Head 61 of the General Scheme. This redraft should remove the definitional ambiguity, while keeping the framing and characterisation of MRTs within the government's control. For this to be effective, the government must establish a firm position on the characterisation of MRTs, whether through a public report or otherwise. For example, if section (2) and section (3) of Head 61 were removed, there would be no explicit reference to MRTs in the body of the General Scheme. However, in the context of the global debate, it would remain unclear whether the reference to 'germline genetic modification' in section (1) covers MRTs. In the absence of an official position on characterisation, the ambiguity would remain and framing, or reframing, MRTs would still be possible. Therefore, if sections (2) and (3) are removed or modified, the Explanatory Note should expressly include, or exclude, MRTS from the coverage of section (1). If the government continues to treat MRTs separately, the Explanatory Note should to make the reason for the separation clear. Another way to approach the issue, that would also account for new applications of gene editing technologies, would be to make any research or clinical practice of any techniques which deliberately modify the human genome subject to specific and case-by-case approval by the AHRRA.

As it stands, the General Scheme already sets out a framework for governing research and clinical practice. Under the General Scheme, research involving human embryos cannot done without approval from a research ethics committee and a licence from the AHRRA.[92] If the

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National Advisory Committee on Bioethics was established in 2008, and tasked with providing expert advice on priority issues, including recommendations on the development of policy and legislation, and representing Ireland in international bioethics fora. However, the last available minutes of the committee date from 2015. Department of Health, 'National Advisory Committee on Bioethics' (*Department of Health*) https://health.gov.ie/national-advisory-committee-on-bioethics/.

[91] CRISPR stands for 'clusters of regularly interspaced short palindromic repeats'. It is a specialised pattern of DNA. Cas9 is a protein that can make precise cuts to DNA. CRISPR-Cas9 refers to a mechanism, developed from natural mechanisms observed in bacteria, which allows scientists to make efficient, targeted edits to DNA. It has attracted attention, in part because of Its potential applications to human genome editing. See Patrick Hsu, Eric S Lander and Feng Zhang, 'Development and Applications of CRISPR-Cas9 for Genome Engineering' (2014) 157(6) Cell 1262.

[92] The General Scheme (n 6), Head 63, Head 67 (2), Head 70.

government's position on MRTs were to shift, applications for a licence to engage in research or practice would be granted or denied based on the redrafted provisions of the General Scheme, any public review of the issues, and any other conditions the AHRRA might impose.[93] Research on MRTs, therefore, would be subject to strict limitations that could evolve with the science. Under the General Scheme, the AHRRA is also the licensing authority for assisted human reproduction and related procedures. A clinic wishing to practice MRTs – or practice the implantation of an embryo created through MRTs in another jurisdiction – also requires a licence.[94] By assessing research on a case-by-case basis, this approach has the added advantage, in the Irish context, of balancing scientific progress and the relatively conservative cultural and legal environment.

There are further provisions of the current General Scheme that impede research on, or the practice of, MRTs. If the government's position on research or practice were to change following a review, these other provisions would have to be modified. For example, Head 59 prohibits the creation of an embryo specifically for use in research, regardless of how that embryo is created[95] and Head 13 confines research on human embryos to surplus (or 'supernumerary') embryos donated after assisted human reproduction treatment.[96] The General Scheme might therefore be interpreted as prohibiting research which uses either technique permitted under the UK legislation, as both techniques arguably create a new embryo.[97] The AAHRA's position in this respect should be clarified by issuing a guidance note or code of practice.[98]

With regards to the clinical practice of MRTs, Head 16 (4)(a) prohibits any AHR treatment or procedure which, as part of the same procedure, involves 'eggs provided by more than one

[93] ibid Head 63 (2)(1)(e).

[94] ibid Head 65 (1), Head 69.

[95] ibid Head 59.

[96] ibid Head 13.

[97] One of the techniques, Maternal Spindle Transfer, is performed on an unfertilised oocyte which is subsequently fertilised. It would, therefore, be prohibited by Head 59 of the General Scheme. The other, Pronuclear Transfer, uses two existing embryos. The pronuclei from one are transferred to the other. Lyndsay Craven, Julie Murphy et al, 'Scientific and Ethical Issues in Mitochondrial Donation' (2018) 24 (1) The New Bioethics 57. Whether this results in a new, third embryo depends on the resolution of a complex set of questions around the numerical identity of the resulting embryo. See The 2012 Nuffield Report (n 11), 55 (para 4.18-4.19); Anthony Wrigley, Stephen Wilkinson and John B. Appleby, 'Mitochondrial Replacement: Ethics and Identity' (2015) 29(9) Bioethics 631; S Matthew Liao, 'Do Mitochondrial Techniques Affect Qualitative or Numerical Identity' (2017) 31(1) 20; Rosamund Scott and Stephen Wilkinson, 'Germline Genetic Modification and Identity: The Mitochondrial and Nuclear Genomes' (2017) 37(4) The Oxford Journal of Legal Studies 886. A full answer is beyond the scope of this paper, but it is a question that the AHRRA could take a position on. As it stands, the General Scheme defines 'embryo' as 'a human embryo formed by the fertilisation of a human egg by a human sperm' but allows that an embryo might be created 'through some other process'. The General Scheme (n 6), p 6 and Head 59. This certainly leaves open the possibility that the ban on the creation of embryos specifically for use in research would prohibit research into Pronuclear Transfer.

[98] The General Scheme (n 6), Head 65 (7).

woman'.[99] This prevents the clinical practice of the UK's methods of MRTs, all of which involve the use of an egg from the intending mother and an egg from a donor in the same procedure. It also appears to (subject again to a guidance note or code of practice) prevent the importation of embryos which had been created through MRTs in another jurisdiction.

Conclusion

This paper has argued that there are a number of problems in the proposed General Scheme and that leaving them unresolved heightens the risk of greater problems developing over time. These bigger problems might be a reframing of MRTs, a lack of public trust in the proposed governance regime for assisted human reproduction, or damage to the public's trust in the general ability of the Irish government to assess and regulate new technology. While many other countries are currently unwilling to permit MRTs,[100] the UK, the US and Australia have spoken out in favour and it has been argued that the use and clinical practice of MRTs is likely to spread.[101] In this context, it is important that Ireland establish a clear and unambiguous policy on the topic. Furthermore, this General Scheme, if enacted, will be the most significant piece of government intervention to enter the sparse landscape of Irish technological regulation in recent memory and may set a strong precedent for how the Irish government will deal with technological assessment and regulation in the future. Thus, it is prudent to set this precedent carefully and support it with robust and public reasoning.

[99] ibid Head 16.

[100] ibid.

[101] Tetsuya Ishii, 'Potential impact of human mitochondrial replacement on global policy regarding germline gene modification' (2014) 29 Reproductive Biomedicine Online 150; Tetsuya Ishii and Yuri Hibino, 'Mitochondrial manipulation in fertility clinics: Regulation and Responsibility' (2018) 5 Reproductive Medicine and Society Online 93; Tetsuya Ishii, 'Reproductive Medicine Involving Mitochondrial DNA Modification: Evolution, Legality and Ethics' (2018) 4(1) European Medical Journal of Reproductive Health 88.