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New Developments

Mitochondrial replacement therapy: the UK and US regulatory landscapes

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1. INTRODUCTION

On October 29, 2015, the United Kingdom's regulations on mitochondrial donation (UK 2015 Regulations) came into force.[1] This amendment to the UK Human Fertilisation and Embryology Act (the 'HFE Act') allows the use of mitochondrial donation techniques as part of *in vitro* fertilization (IVF) treatments. Mitochondrial replacement therapies (MRT) aim at preventing the transmission of mitochondrial disease from a mother to her genetically related children. In the USA, the use of MRT falls under the oversight of the US Food and Drug Administration (FDA), and its approval, which would require clinical trials under an investigational new drug application, has been currently halted through a rider included in the 2016 Congressional Appropriations Act.[2]

This note discusses the UK regulatory framework for MRT and compares it to the US landscape. It focuses on the regulatory and ethical discussions in both countries to find some lessons for debates about editing human germ cells.[3] The first section introduces some biological characteristics of mitochondria and their implications for mitochondrial diseases, medical interventions and ethical and regulatory questions. The second section discusses the regulatory pathway leading to the adoption of the UK 2015 regulations and the main features of the approved text. The third section considers the current regulatory landscape in the USA. The fourth section discusses some regulatory and bioethical questions raised by MRT.

1 The Human Fertilisation and Embriology (Mitochondrial Donation) Regulations 2015, N. 572 (2015), http://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents (accessed Sept. 6, 2016).

2 See I. Glenn Cohen & Eli Y. Adashi, *Mitochondrial Replacement Therapy: the IOM Report and Its Aftermath*, 17 Nat. Rev. Genet. 189, 190 (2016), citing the Consolidated Appropriations Act 2016 (2015), Sec. 749, https://www.congress.gov/bill/114th-congress/house-bill/2029/text (accessed Sept. 6, 2016).

3 Germ cells are involved in the reproduction of humans (as well as all other multicellular eukaryotes with sexual reproduction). In their mature form, germ cells are known as gametes (ovum or egg and sperm).

2. THE BIOLOGY OF MITOCHONDRIA AND MITOCHONDRIAL DISEASES

Mitochondria are essential organelles of nucleated cells, including those of humans. While most of the DNA contained in a cell is located in its nucleus, mitochondria, which are located in the cytoplasm of the cell, also contain a small fraction of an organism's DNA. This fraction, called mitochondrial DNA (mtDNA), counts for less than 0.1 per cent of the total amount of DNA contained in the cell and for a small fraction of the total DNA that codes for proteins contributing to the function of mitochondria.[4] In spite of this, defects in mtDNA can cause devastating diseases as mitochondria are in charge of providing the energy that a cell needs to function.

Mitochondrial DNA differs from nuclear DNA in several ways. One of them is the fact that mtDNA are present in multiple copies within a single cell.[5] The number of such copies carrying mutated mtDNA significantly affects the way mitochondrial disease is expressed; some mutations can affect all the copies of mtDNA and others selectively affect only some of the copies. As a result, individuals with faulty mtDNA are affected in highly variable ways according to the number of affected mtDNA copies.[6] Depending on the extent of the problem and the organs involved, people with mitochondrial diseases can be mildly or severely affected. Estimates of the prevalence of mitochondrial disease are variable, mainly due to the different clinical presentations and difficulties in diagnosing patients, but estimations suggest that approximately 152 births per year in the UK and 778 in the USA involve women at risk for transmitting faulty mtDNA.[7]

During the process of fertilization, a woman's egg provides all the cytoplasm for the embryo. As a consequence, mitochondrial diseases are only inherited from the maternal line.[8] There are no current cures and only a few available therapies exist to alleviate the symptoms of these diseases. Researchers have developed alternatives to prevent the transmission of faulty mitochondria from an affected mother to her children. In the 1990s, a technique called cytoplasmic transfer was developed to help women having difficulty becoming pregnant through IVF. This technique involved all the cytoplasm of an egg.[9] However, in 2001, the FDA halted the use of this technique in the USA.[10] More recently developed MRT techniques have been suggested as alternatives

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4 See Robert W. Taylor & Doug M. Turnbull, *Mitochondrial DNA Mutations in Human Disease*, 6 NAT. REV. GENET. 389 (2005). However, see Eli Y. Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832, 833 (2016), highlighting evidence that the role of mitochondria can also extend to vital cell functions such as (eg apoptosis or programmed cell death, calcium homeostasis, and steroidogenesis) and that the interactions between nuclear DNA and mtDNA can be multiple and complex.

5 Taylor and Turnbull, *supra* note 4, at 390.

6 *Id.* at 391, 392, describing homoplasmy and heteroplasmy and warning that the dividing line between the two might be more apparent than real and that in some individuals, even without heteroplasmy, mtDNA is still constantly changing.

7 Gráinne S. Gorman et al., *Mitochondrial Donation—How Many Women Could Benefit*? 372 NEW ENG. J. MED. 885 (2015).

8 For anecdotic evidence about the transmission of mitochondrial diseases from the paternal line, see Marianne Schwartz & John Vissing, *Paternal Inheritance of Mitochondrial DNA,* 347 NEW ENG. J. MED. 576 (2002).

9 Cytoplasmic transfer is a technique that involves the injection of cytoplasm from a donor oocyte into a recipient oocyte before IVF. Since mitochondria are contained in the cytoplasm, a donation of mitochondria might occur but the exact number actually transferred would not necessarily be sufficient to avoid the transmission of mitochondrial diseases.

10 See *infra* note 24 and 25 and accompanying text.

for women carrying mutated mtDNA to have genetically related children without passing their mtDNA.

MRT uses healthy mitochondria from an egg donor and can be performed by two different processes. In the first, called maternal spindle transfer, the healthy nucleus of an egg with affected mitochondria is removed and then transferred to the egg of a donor containing healthy mitochondria, which has been previously deprived of its nucleus. In the second method, pronuclear transfer, the transfer happens 'after' fertilization of the oocyte. Two oocytes are fertilized with the father's or another donor's sperm (one oocyte from the intending mother and one from the donor). Shortly after, the pronuclei of the embryo containing the mother's mitochondria are transferred to a previously enucleated embryo containing healthy mitochondria.

3. THE UK MITOCHONDRIAL DONATION REGULATIONS OF 2015

The UK Human Fertilisation and Embryology Authority (HFEA), which was created in 1990, oversees different reproductive technologies, including IVF, commercial surrogacy, and now mitochondrial donation.[11] The same parliamentary act that created the HFEA gives power to the government to regulate what is 'permitted' in the field of assisted reproduction. In 2015, the UK Parliament expanded the definition of 'permitted eggs and embryos' to include those 'where unhealthy mitochondrial DNA is replaced by healthy mitochondrial DNA from a donor'.[12]

The UK has been praised for developing the first regulatory framework that explicitly allows the use of MRT. Regulating assisted reproduction under the umbrella of a single legislative act—the 1990 HFE Act—and a specialized authority—the HFEA—seems to have been fundamental for the UK's pioneering role in allowing clinical trials for MRT[13] and more recently for gene editing in embryos.[14]

The UK's 2015 regulations reformed the 1990 HFE Act in four important ways that allowed the use of MRT. First, the Act expanded the definitions of permitted 'eggs and embryos'. Second, the Act denied any parental rights to mitochondrial donors and made clear that the legal status of parent—under a parental order[15]—cannot be sought on the basis of mitochondrial donation only. Third, it established that children born with the help of MRT can have access to limited non-identifying information about the donor but no information about other children who share the same donor, while mitochondrial donors can also access limited non-identifying information about children born from their donations. Lastly, the Act established that the resulting egg or embryo following MRT is not to be treated as the egg or embryo of the mitochondrial DNA donor for the purposes of consent, and that after providing informed consent, a donor cannot withdraw it.

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[11] HFEA, *Mitochondrial Donation*, http://www.hfea.gov.uk/9933.html (accessed Oct. 18, 2016).

[12] See UK Regulations 2015, *supra* note 1.

[13] See I. Glenn Cohen, Julian Savulescu & Eli Y. Adashi, *Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy*, 348 SCIENCE 178, 179 (2015), arguing that a 'narrow framing' has allowed the UK to advance its regulatory framework in order to keep pace with current technological developments in the area of assisted reproduction.

[14] HFEA, *HFEA Approves Licence Application to Use Gene Editing in Research*, Feb. 1, 2016, http://www.hfea.gov.uk/10187.html (accessed Oct. 18, 2016).

[15] A parental order is a statement allowing non-genetically related parents to have legal status as parents within surrogacy agreements.

3.1. Historical and regulatory background

History can partly explain why the UK was the first country to allow clinical trials of MRT. It was in the UK that a baby was first born with the help of IVF in 1978. The UK responded to the emerging challenges of IVF and research with human embryos by establishing a Committee of Inquiry into Human Fertilisation and Embryology. This Committee produced a landmark report in 1984, addressing potential future applications of research and development of therapies as well as their social and legal implications. The report was followed by a 1987 white paper calling for the development of a legislative framework, which was then codified in the 1990 HFE Act. Research on mitochondrial diseases and mitochondrial transfer began alongside: in 1981, scientists sequenced the whole human mitochondrial genome and in 1985 techniques were developed to prevent faulty mtDNA transmission by nuclear transplantation.[16]

The 1990 Act also created the HFEA in charge of the regulatory oversight of reproductive technologies. The UK legislative framework and the appointment of a regulatory authority in the field facilitated the regulation of assisted reproduction. The HFEA gathered experts and led consultations with the public, producing several amendments to the 1990 HFE Act, the most recent of which allowed clinical trials for MRT.[17]

Of particular relevance to the process leading to the UK 2015 regulations was the 1998 Report of the HFEA and the Human Genetics Advisory Commission, which recognized that the 1990 HFE Act had not considered certain applications of human embryo research, including the development of mitochondrial therapies. In 2001, the HFE Act of 1990 was amended to extend the possibilities of research on early human embryos. In 2004, a group of Newcastle-based researchers applied for an HFEA license to do research on pronuclear transfer, which was granted in 2005. In 2008, the HFE Act was amended to allow the government to permit clinical application of MRT.[18]

3.2. The 2015 Amendment to the HFE Act

The process that concluded with the 2015 amendment to the 1990 HFE Act combined a wide amount of debate starting in 2010, when researchers asked the UK Department of Health to amend the regulations under section 3 ZA of the Human Fertilisation and Embryology Act of 1990, in order to allow mitochondrial donation. The proposal was advanced to the Department of Health and then sent to the HFEA. What followed was an intensive period of consultation with expert panels (2011), the release of the Nuffield Council on Bioethics Report in 2012 and a public consultation through Sciencewise.[19]

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[16] Lyndsey Craven et al., *Research into Policy: A Brief History of Mitochondrial Donation*, 34 STEM CELLS 265, 265 (2015).

[17] *Id.* at 266.

[18] *Id.*

[19] The Sciencewise program, funded by the Department of Business, Innovation and Skills, is in charge of supporting policymakers in the UK to engage into public dialogue in science and technology issues. See Sciencewise, *Tracing the Impacts of Public Dialogue Projects Supported by Sciencewise: Mitochondrial Replacement,* March 2016, http://www.sciencewise-erc.org.uk/cms/assets/Publications/Sciencewise-HFEA-Mito-dialogue-impacts-March2016.pdf (accessed Sept. 6, 2016).

In 2013, the Department of Health announced its intention to propose regulations to allow mitochondrial donation to prevent the transmission of serious mitochondrial disease. Draft regulations were published and a period of public consultation followed from February to May 2014.

The Department of Health developed an impact assessment, which gauged costs and benefits. Costs to the government and the provider clinics were considered. Benefits to families with mitochondrial disease were estimated using quality-adjusted life years, assuming 20 individuals a year born free of mitochondrial disease. This assessment estimated that allowing mitochondrial donation to be used in treatment would yield a total annual net benefit of approximately £32 million per year and £318 million over 10 years.[20] This exercise reflects best regulatory practices used by the most industrialized countries belonging to the Organization of Economic Cooperation and Development (OECD) and is meant to help countries in producing 'better' regulations.[21] These practices require governments to assess the impact of regulatory proposals as early as possible, consult with stakeholders, and also evaluate the impacts of regulation *ex post*. The process that preceded the enactment of the 2015 amendment largely illustrates the *ex ante* phase of regulatory policy but this regulation is also expected to be reviewed *ex post* in 2019.

In February 2015, the proposal was approved by both houses and entered into force on October 29, 2015. The HFEA then decided to wait for the results of further safety and efficacy tests to provide sufficient evidence as requested by an independent expert panel convened in 2014 before starting to examine applications from clinics planning to obtain licenses for MRT.[22] In June 2016, the HFEA decided to reconvene the independent expert panel in the light of new publications showing progress in terms of safety and efficacy.[23]

4. THE USA

Several factors have contributed to the current regulatory landscape of MRT in the USA. Research in the area of mitochondrial transfer has been influenced by the (negative) US experience with the use of cytoplasmic transfer during the 1990s. This technology was developed to help women having recurrent implantation failure and consisted in injecting a small amount of cytoplasm, including mitochondria, from a healthy young

[20] See UK Department of Health, *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*, Impact Assessment, http://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf (accessed Sept. 6, 2016), comparing two policies: policy 1, or 'do nothing', which was not further elaborated as to costs and benefits, and policy 2, which consisted in modifying the regulations to allow mitochondrial therapy.

[21] See Organization for Economic Cooperation and Development Regulatory Policy Outlook, OECD Publishing, Paris (2015), http://dx.doi.org/10.1787/9789264238770-en (accessed Sept. 6, 2016).

[22] See HFEA, *World First As Mitochondrial Donation Regulations Come into Force*, http://www.hfea.gov.uk/9946.html (accessed Sept. 6, 2016). See also Louise A. Hyslop et al., *Towards Clinical Application of Pronuclear Transfer to Prevent Mitochondrial DNA Disease*, NATURE (2016), DOI:10.1038/nature18303 (accessed Sept. 6, 2016), concluding that pronuclear transplantation 'has the potential to reduce the risk of mtDNA disease, but it may not guarantee prevention'. Using a different technique, another recent study found that even minor amounts of defective mitochondria might revert and affect the stability of the mtDNA and the efficacy of the therapy. Mitsutoshi Yamada et al., *Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes*, 18 CELL STEM CELL 749 (2016).

[23] HFEA, *HFEA Reconvenes Independent Expert Panel and Launches Call for Evidence*, http://www.hfea.gov.uk/10363.html (accessed Sept. 6, 2016).

donor to the intending mother's egg. Although the exact number of children born with the help of this technique is unknown and they have been lost to follow up, the use of this technique was halted after two children were born with a chromosomal anomaly and one was diagnosed with pervasive developmental disorder.[24]

Unlike the UK, the USA does not have a specialized agency in charge of dealing with of assisted reproduction. In 2001, the FDA asserted jurisdiction over the use of cytoplasmic transfer and effectively banned clinical trials at least until the filling of an investigational new drug application. In 2014, the Office of Cellular, Tissue and Gene Therapies of the Center for Biologics Evaluation and Research of the FDA convened a meeting to discuss mitochondrial transfer, but found insufficient evidence that the techniques were safe.[25] Compared with the UK, the USA has put less emphasis on public consultation and has mostly relied on expert meetings.[26] A partial explanation for the absence of public consultation could be that in the USA, the controversial nature of research with human embryos has conflated discussions about MRT with controversies about abortion.[27]

Following the FDA meeting in 2014, which left aside ethical issues, the agency requested the Institute of Medicine of the National Academies of Science, Engineering and Medicine to address these broader concerns. The report (hereinafter the 'NAS report'), which was published in February 2016,[28] concluded that subject to some limitations, MRT could be ethically justifiable. The main reasons were the potential benefits, in terms of increasing the reproductive choices for women carrying defective mtDNA and the different consequences of the modification of mtDNA compared to nuclear DNA.

However, the report recommended to move cautiously, limiting future clinical trials to (i) women with serious risks of transmitting mtDNA disease and for which the mtDNA mutation is pathogenic and highly likely to be manifested in a severe clinical way and (ii) only to the transfer of male embryos. While the first condition reflects similar UK requirements, the limitation to male embryos was rejected in the UK.

Experts have described the choice of limiting MRT initially to male embryos as 'an elegant solution to concerns over the germline transmission', [29] yet one that raises 'a series of altogether new ethical and legal questions'[30] that were not fully explored by the NAS report. Limiting MRT to male embryos takes away fears related to the transmission of undesired side effects from MRT to future generations since mitochondria are only transmitted through the maternal line. However, among the thorny questions

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[24] Nuffield Council on Bioethics, Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review 37, 38 (2012).

[25] Cellular, Tissue, and Gene Therapies Advisory Committee, FDA Briefing Document, Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility, Feb. 25–26, 2014, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM385461.pdf (accessed Oct. 6, 2016).

[26] See Cohen et al., *supra* note 13, at 180.

[27] *Id.*

[28] National Academies of Sciences, Engineering, and Medicine, Mitochondrial Replacement Techniques: Ethical, Social, And Policy Considerations (2016).

[29] See Cohen and Adashi, *supra* note 2, at 190.

[30] *Id.*

raised by this solution are the fate of female embryos and the consequences of a 'call for the FDA to require parents to engage in sex selection'.[31]

It is unlikely that MRT trials will be initiated in the USA, at least until two conditions are met. First, the FDA must change its opinion regarding safety concerns.[32] Second, Congress will have to unleash the current ban included in the 2016 Appropriations Act, which prohibits the FDA from considering applications for an exemption for investigational use in research involving the intentional creation of human embryos 'to include a heritable genetic modification'.[33]

5. BIOETHICAL AND REGULATORY QUESTIONS ABOUT MRT

5.1. Germ cell modification

MRT has been surrounded by a broader controversy about the modification of germ cells that would produce heritable changes, with many arguments grounded in the fear of eugenics.[34] However, at least according to some experts, MRT should not give raise to this type of concerns. First, mtDNA constitutes a very low fraction of the total DNA in a cell. Second, genetic traits that most people would associate with visible human characteristics are contained in the nuclear DNA rather than in the mtDNA, which targets a limited number of proteins related to the function of mitochondria and a few other cell functions.[35] Moreover, the purpose of MRT is to replace faulty mtDNA with healthy mtDNA rather than enhancing any genetic trait, which is what most people fear about eugenics and presumptive 'designer babies'.

Both the reports commissioned in the UK and the USA to examine the ethical aspects of MRT found significant distinctions between modifications to nuclear genes and those directed to mtDNA. The Nuffield Council based its decision to support MRT, *inter alia*, in 'the fact that there is a distinct material boundary between mitochondrial and nuclear genes [which] allows regulators to establish an equally clear legal distinction between modifications to the different genomes'.[36] The NAS report emphasized that MRT allows the replacement rather than the modification or editing of mtDNA; mtDNA is not associated with the common characteristics that the general public associates with genetic connection; and the potential for MRT to be used for enhancement is currently limited.[37]

Closely related to the differences between nuclear and mtDNA is the question of whether MRT should be considered as a germline modification. The Nuffield Council classified MRT as germline therapies, yet recognizing that the effects produced by these techniques are quite different than those produced by the modification of

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[31] *Id.*

[32] See Gretchen Vogel, *For Boys Only? Panel Endorses Mitochondrial Therapy, But Says Start With Male Embryos*, Feb. 3, 2016, http://www.sciencemag.org/news/2016/02/boys-only-panel-endorses-mitochondrial-therapy-says-start-male-embryos.

[33] Cohen and Adashi, *supra* note 2, at 190, discussing the 2016 Consolidated Appropriations Act.

[34] See NAS report, *supra* note 28, at 108.

[35] But see Adashi and Cohen, *supra* note 4 at 833, commenting that the 'essence of being human need not be viewed as the sole domain of the nuclear genome'.

[36] See Nuffield Council, *supra* note 24 at 65.

[37] See NAS report, *supra* note 28 at 8.

nuclear genes.[38] A slightly different reasoning, yet with similar results, was adopted by the NAS report. While recognizing that 'genetic modification' alludes to 'changes to the genetic material within a cell,[39] the NAS adopted a definition of germline modification as that entailing 'inheritable modifications'.[40] As a result, the use of MRT to produce male offspring—what the NAS recommended as a first step—'would not constitute genetic or germline modification'.[41]

The UK regulations seemed to have opened the door for limited therapeutic interventions directed at avoiding the transmission of severe mitochondrial diseases. Similarly, strict limitations could help move clinical trials for gene editing forward in cases of severe and unmet medical needs. As pointed out by the Nuffield Council, in the wake of Parliament's 2015 approval of MRT trials, the case for differentiating between techniques aiming at modifying mtDNA and those to modify and prevent the transmission of diseases linked to nuclear DNA is diluted.[42] Once the 2015 UK regulations allowed germline modifications to prevent mtDNA disease, going forward it will be harder to stop other germ cell modifications for therapeutic uses. But far from being an undesirable outcome, this means the MRT precedent could inform both the development and regulation of future gene editing technologies.

5.2. Less harmful alternatives

Some experts have argued against the use of MRT on the basis that safer alternatives exist. These alternatives, however, are limited to using oocyte (egg) donation, prenatal or pre-implantation diagnosis of mitochondrial disorders. Oocyte donation has been regarded as limiting the preferences of parents wanting a genetic relationship with their offspring.[43] Techniques to diagnose mitochondrial disorders in fetuses through the use of prenatal tests or pre-implantation genetic diagnosis are not completely accurate and do not offer any alternative solution apart from abortion or selective disposal of embryos carrying mtDNA disorders.[44]

5.3. The rights and interests of egg donors

Another criticism of the use of MRT is that it could increase the demand for egg donors, thereby increasing the frequency adverse effects and leading to undue inducement and exploitation of egg donors. In addition, the use of donors also raises the question of what information should be available about them to the children born from their eggs and vice versa. According to some experts, the debate about the ethics of egg

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38 See Nuffield Council, *supra* note 24, at 58, mentioning that MRT are not intended to modify nuclear genes, change the donor's mitochondria (but rather replace the donor's mitochondria) and that these changes would be passed to future generations only if used in female offspring.

39 See NAS report, *supra* note 28 at 6.

40 *Id.* at 6, 7.

41 *Id.* at 7.

42 See Nuffield Council, *supra* note 24, at 45, arguing that 'UK policymakers might need to consider their reasons for only permitting therapies pertaining to mtDNA mutation if, in the future, somewhere in the world a potential germline gene therapy treatment was developed which acted on the nucleus and would prevent mitochondrial disorders caused by genes in the nucleus' and providing similar arguments for potential germline gene therapy treatments.

43 See Appleby, *The Ethical Challenges of the Clinical Introduction of Mitochondrial Replacement Techniques,* 18 Med. Health Care & Philos. 501, 504–505 (2015).

44 *Id.* at 505.

donation was largely absent in the UK discussion of the 2015 regulations.[45] However, the limited number of women who might be candidates for MRT in the UK and the willingness of women to donate eggs for the Newcastle group runs counter to some of these concerns.[46]

5.4. Unintended consequences

The Nuffield Council report acknowledged the possibility that once the use of MRT was authorized, couples would come to the UK to have access to therapies not available in their countries. The possibility of 'medical tourism' from the USA to the UK has been heightened by current limitations on MRT clinical trials in the USA.[47] Potential problems could arise because the solutions developed by UK law regarding parentage, consent and access to information would not apply to children born outside of the UK. Different countries of origin of prospective parents could have different and contradictory legal solutions to these questions. Further, medical tourism might limit research and clinical follow-up of children born through the use of MRT and the eventual identification of any safety issues.[48]

The potential use of mitochondrial donation as a means to enhance fertility or for lesbian couples wishing to have children related to both also seems to have played a role in the eligibility requirements of the UK regulations of 2015.[49] Those regulations require proof that women are at risk of transmitting mitochondrial disease to their children, although such findings are not as clear cut as they might seem.[50]

5.5. Safety and efficacy

Apart from ethical questions, the most pressing issues for regulators are the safety and efficacy of MRT. Potential risks could affect the individual born with the help of MRT as well as future generations. The UK HFEA undertook three scientific reviews, which raised some potential concerns. A first concern relates to potential adverse effects from the interaction of mtDNA and nuclear DNA coming from two different persons (the donor and the intending mother). A second concern is that some of the faulty mitochondria from the mother could remain in the embryo after the transfer process.

The HFEA report concluded that MRT was 'not unsafe' and that it could potentially benefit women having a risk of transmitting a severe mitochondrial disease who want a genetically related child.[51] The FDA, however, has maintained a different opinion. In 2014, the FDA Committee concluded that there was 'not enough data in animals…to

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45 Rebecca Dimond, *Social and Ethical Issues in Mitochondrial Donation,* 115 Brit. Med. Bull. 173, 179 (2015).

46 *Id*. at 179.

47 Cohen and Adashi, *supra* note 2, at 190.

48 These questions are still open after the announcement of the first baby born with the help of MRT, which is the apparently the son of a Jordanian couple that traveled to Mexico in order to avoid US regulations. See Michelle Roberts, *First 'Three Person Baby' Born Using New Method*, BBC News Online, http://www.bbc.com/news/health-37485263 (accessed Sept. 27, 2016).

49 Dimond, *supra* note 45, at 178.

50 Biological phenomena such as the bottle-neck distribution of mitochondria and the presence of homoplasmy and heteroplasmy could further complicate the implementation of this section.

51 For a contrary opinion, see Taylor Philippa, *Three Parent Babies: Unethical, Unnecessary, Unsafe*, BioNews, 2015, http://www.bionews.org.uk/page_497347.asp (accessed Sept. 6, 2016).

move on to human trials without answering a few additional questions'.[52] As research continues to advance, the safety and efficacy of these treatments are subject to change.[53] MRT represents one example of the increasingly significant challenge for regulatory authorities all over the world -devising regulatory regimes that are both responsive to new scientific evidence and changing public attitudes.

6. CONCLUSIONS

The UK undertook a long regulatory process to approve the use of MRT. This process entailed consultation with experts and stakeholders as well as an *ex ante* assessment of the proposed regulations. While the processes to produce and assess new regulations are not so dissimilar to those used in the USA,[54] and while safety and bioethical concerns are similar on both sides of the Atlantic, their interpretations have widely differed.

The different stances of the UK and the USA with regard to MRT can probably be explained as the result of a combination of (i) historical events, including the adverse reports from cytoplasmic transfer treatments in the USA, (ii) the lack of a broader dialogue with experts and the public, (iii) the lack of a specialized authority in charge of reproductive technologies, and (iv) the deeply polarized abortion and 'personhood' debates.

At the closing of this note, news broke about the first baby born with the help of MRT. As usual, technologies are evolving faster than legal and ethical debates. In spite of this, it is worth continuing to explore the lessons from current and past technologies to inform the ethical and policy appraisals for future ones.[55]

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[52] Absent an official statement of the Committee, the chair was quoted by Sharon Begley, *U.S. FDA Weighs Evidence on Producing 'Three-Parent' Embryos,* Reuters, 25 Feb. 2014, http://uk.reuters.com/article/2014/02/25/us-usa-health-ivf-idUKBREA1O1WL20140225 (accessed Sept. 6, 2016).

[53] See John Zhang et al., *Pregnancy Derived From Human Zygote Pronuclear Transfer in a Patient Who Had Arrested Embryos After IVF*, Reprod. BioMed. Online (2016), http://dx.doi.org/10.1016/j.rbmo.2016.07.008 (accessed Oct. 6, 2016).

[54] See OECD, *supra* note 21. But see Adashi and Cohen, *supra* note 4, at 834, highlighting the different regulatory and legal paradigms in the USA and the UK.

[55] See Roberts *supra* note 48.