



Department
of Health

Mitochondrial Donation

A 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

February 2014

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Mitochondrial Donation

A 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

Prepared by the Health Science and Bioethics Division, Department of Health

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Executive summary

This consultation seeks the views of stakeholders and the wider public about draft regulations to allow newly developed treatment techniques to prevent the transfer of a serious mitochondrial disease from a mother to her child. The techniques would involve the donation of healthy mitochondria. The draft regulations in this document are solely for consultation, after which a decision will be made about the regulations to put before Parliament.

Mitochondrial disease is caused by unhealthy mitochondria, passed from mother to child through faults in the mitochondrial DNA or by faults in nuclear DNA. It is estimated that 1 in 200 children are born every year in the United Kingdom with some kind of mitochondrial DNA disorder. Serious mitochondrial disease can have a devastating effect on families, including the premature death of children, painful debilitating and disabling suffering, long-term ill-health and low quality of life.

The Human Fertilisation and Embryology Act 1990 is the primary legislation that governs assisted reproduction and embryology procedures in the UK. In 2009, following a review of the Act, a power was introduced to enable the Government to make regulations to allow treatment using eggs and embryos in which unhealthy mitochondria had been replaced by healthy mitochondria. The intention is that this would prevent the transfer of serious mitochondrial disease from mother to child while allowing the mother to have her own genetically related child. At that time, the Government of the day gave an assurance that such regulations would not be made until any proposed techniques were considered to be effective and safe for use in treatment.

In 2010, the Government was asked by researchers working in this field to use the power to make regulations. This request was supported by a number of medical research bodies. Two treatment techniques were proposed:

- **Maternal spindle transfer (MST).** The “maternal spindle” is the group of maternal chromosomes within the egg, which are shaped in a spindle. MST involves removing the spindle from the mother’s egg before it is fertilised by the father’s sperm. The spindle is then placed into a donor egg with healthy mitochondria (from which the donor’s spindle, and therefore her nuclear material, has been removed).
- **Pro-nuclear transfer (PNT).** The pro-nucleus is the nucleus of a sperm or an egg cell during the process of fertilisation after the sperm enters the egg, but before they fuse. PNT involves removing the pro-nuclei (nuclear material) from a newly fertilised egg (which is regarded as an embryo under the Human Fertilisation and Embryology Act 1990) that has unhealthy mitochondria. The pro-nuclei are then

transferred into a donated embryo, with healthy mitochondria, that has had its own, original pro-nuclei removed.

Following this request, in 2011 Ministers from the Department of Health (DH) and Department of Business, Innovation and Skills (BIS) asked the UK's national fertility regulator, the Human Fertilisation and Embryology Authority (HFEA), to convene an Expert Panel to consider the safety and efficacy of the two techniques. The Panel concluded that both techniques had merit but that there was insufficient evidence to recommend one technique over the other. The Panel also considered that, while there was no evidence that either technique was unsafe, there was a need for further experiments.

While this additional experimental work was undertaken, DH and BIS asked the HFEA to conduct a public dialogue and consultation exercise that focused on the ethical issues that these treatments raise. The HFEA reported the outcome of this exercise in March 2013. Overall, the balance of views from stakeholders and the members of public who took part was that the treatment techniques should be allowed but their use should be carefully controlled. The HFEA also recognised that there was a body of opposition to allowing these procedures.

At the request of the DH, the Expert Panel was reconvened by the HFEA to provide an updated view on the science to support the assessment of the efficacy and safety of MST and PNT techniques, including any recently published findings and the extent to which the Panel's recommendations had been addressed. In March 2013, the Expert Panel expressed the view that there remained insufficient research currently available to recommend one particular technique over the other. The Panel also concluded that, although there was still nothing to indicate that the techniques were unsafe, further research on some specific aspects should be undertaken. The Panel also recommended long-term follow-up monitoring of any children born as a result of the use of these techniques in treatment.

In June 2013, the Government announced that, based on the findings of the HFEA's public dialogue and consultation exercise and the views of the Expert Panel, it would move forward with draft regulations for public consultation. This document therefore contains a draft of regulations that would allow the mitochondrial donation techniques described above to be used in treatment.

The draft regulations set out which eggs and embryos will be permitted for use in mitochondrial donation treatment. The regulations describe the process which the eggs or embryos must have undergone and the circumstances in which the process must have been applied. The regulations also make transitional provision so that treatment licences cannot be used to provide mitochondrial donation treatment until the HFEA has approved clinics to do so. The regulations also contain provisions relating to information-sharing in cases involving mitochondrial donation.

The legislative provisions in the regulations would sit alongside the practical measures the HFEA would put in place in order to regulate the techniques.

This consultation document sets out a number of key questions on which we invite responses. The answers to these questions and any other comments received will be considered carefully by the Government, after which a decision will be made about the regulations to be put before Parliament.

The consultation document also includes a Regulatory Triage Assessment (RTA) at Annex C. The RTA sets out the Government's initial assessment of the potential impact of new regulatory requirements on businesses. This includes an assessment of the potential costs resulting from the regulations based on initial estimates of how many families might be helped. Comments on the RTA are also welcomed and will be considered by the Government in determining how to take forward the regulations.

Chapter 1: Background

Introduction

1.1 One of the key principles of the Human Fertilisation and Embryology Act 1990 (“the 1990 Act”)¹, which regulates the use of human sperm, eggs and embryos, is that for sperm, eggs and embryos to be used in fertility treatment they must be naturally derived from the human body and not genetically altered in any way. These sperm, eggs and embryos are described in the legislation as ‘permitted’. Section 3ZA (2)–(4) sets out:

(2) A permitted egg is one – a) which has been produced by or extracted from the ovaries of a woman and b) whose nuclear or mitochondrial DNA has not been altered.

(3) Permitted sperm are sperm – a) which have been produced by or extracted from the testes of a man, and b) whose nuclear or mitochondrial DNA has not been altered.

(4) An embryo is a permitted embryo if – a) it has been created by the fertilisation of a permitted egg by a permitted sperm, b) no nuclear or mitochondrial DNA of any cell of the embryo has been altered, and c) no cell has been added to it other than by division of the embryo’s own cells.

1.2 The 1990 Act allows for just one exception to this principle, to be established by regulations, Section 3ZA (5):

(5) Regulations may provide that – a) an egg can be a permitted egg, or b) an embryo can be a permitted embryo, even though the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease.

1.3 In 2010 the Government was asked by medical researchers and national medical research bodies to use this power to introduce regulations to allow newly developed techniques to be used in treatment for mitochondrial disease in the UK for the first time. This consultation document seeks the views of stakeholders and the wider public on the content of the draft regulations.

¹ The Human Fertilisation and Embryology Act 1990 (c.37) as amended by the Human Fertilisation and Embryology Act 2008 (c.22).

What is mitochondrial disease?

- 1.4 Mitochondria are present in almost all human cells. They are often referred to as the cell's batteries, as they generate most of a cell's energy supply.² For any cell to work properly, the mitochondria need to be healthy. Unhealthy mitochondria can cause genetic disorders known as mitochondrial disease.
- 1.5 Mitochondrial DNA comprises a very small proportion of total DNA (0.1% – only 37 of 20,000–30,000 genes)³ and its role is concerned with energy production in the cell. It is generally agreed by scientists that it is genes in our nuclear DNA, together with environmental factors, rather than mitochondrial DNA, that shape our personal characteristics and traits.
- 1.6 It is estimated that 1 in 200 children⁴ born every year in the UK have some form of mitochondrial DNA disorder. These disorders can range from mild and asymptomatic to severe enough to be fatal.
- 1.7 Mitochondrial diseases take on unique elements both because of the way the mitochondria are inherited from the mother and because mitochondria are so critical to cell function. Each individual affected will have a different combination of mitochondria that are working or not working within each cell, so every person's symptoms are different. There is wide variation in the symptoms and severity of mitochondrial disease, dependent on the number of cells affected and their location within the body. Among known symptoms are: poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction and dementia.
- 1.8 A range of disorders can be caused by unhealthy mitochondria. Some of the most serious disorders that can arise from unhealthy mitochondria include some forms of muscular dystrophy, Leber hereditary optic neuropathy and Leigh syndrome. Annex D sets out a table listing these disorders.

² Adenosine triphosphate, more commonly referred to as "ATP".

³ Nuffield Council on Bioethics: *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*

⁴ Nuffield Council on Bioethics: *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*

- 1.9 There is no cure for mitochondrial disease and treatment options are severely limited. This means that some people who inherit the condition may live with debilitating illness. In its most severe form, as indicated above, it can result in the death at an early age of the child who inherits it. Some children might also spend a lot of time in hospital and have a poor quality of life.
- 1.10 Serious mitochondrial disease can have a devastating impact on family life, both on any child with the disease and on their parents. Where inherited mitochondrial disease is diagnosed, parents will have difficult choices to make about future family life. This may also be of concern to female relatives of affected mothers, who would now be aware of the risks for them of having children with serious mitochondrial disease.
- 1.11 The initial estimate by researchers at Newcastle Centre for Life is that the proposed mitochondrial donation techniques would prevent around 10 children a year suffering from serious mitochondrial disease. This is being kept under review. Researchers also believe that being able to undertake the techniques in treatment would provide a greater understanding of the way in which mitochondrial DNA mutations are passed down from mother to child. They believe it will provide better understanding of how the mutations vary in different cells, which may lead to the development of new treatments.

How will the new treatment techniques work?

- 1.12 The techniques would not treat or cure a person who already has a mitochondrial disorder. The intention is that the techniques will enable women who are the carriers of the disorder to have their own genetically related children, who would be free of serious mitochondrial disease.
- 1.13 To date, two techniques have been developed to prevent transmission of serious mitochondrial disease: maternal spindle transfer and pro-nuclear transfer.

Maternal spindle transfer

- 1.14 **Maternal spindle transfer (MST)** involves removing the spindle (chromosomes, the nuclear DNA material, in the mother's egg which is found in a group which looks "spindle shaped") from the mother's egg. The spindle is then placed into a donor egg with healthy mitochondria, from which the donor's spindle, and therefore her nuclear DNA, has been removed. The egg is then fertilised by the father's sperm and the resulting embryo is then placed in the prospective mother at between 2 and 6 days of development.

Pro-nuclear transfer

1.15 **Pro-nuclear transfer (PNT)** involves removing pro-nuclei from a fertilised egg (which is regarded as an embryo under the Human Fertilisation and Embryology Act 1990) that has unhealthy mitochondria (there are two pro-nuclei present during the initial fertilisation stage – one derived from the egg and another from the sperm that were used to create the embryo). The pro-nuclei are then transferred into a donated early-stage embryo that has healthy mitochondria and has had its original pro-nuclei removed.

1.16 A more detailed explanation of the techniques and associated science is available at:

<http://mitochondria.hfea.gov.uk/mitochondria/what-is-mitochondrial-disease/new-techniques-to-prevent-mitochondrial-disease/>

and

http://nuffieldbioethics.org/sites/default/files/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf

Safety and efficacy of the proposed techniques

1.17 When the Government was first approached to make regulations it asked the HFEA to coordinate an Expert Panel to look at the state of the science in this area, including the safety and efficacy of the two proposed treatment techniques. The Expert Panel reported in April 2011⁵ that both techniques had the potential to be used to prevent the transfer of mitochondrial disease, although there was no evidence to recommend one technique over the other. The Panel was also recommended that while there was no evidence that either technique was unsafe, a minimum set of further experiments should be undertaken.

1.18 The Panel was reconvened in December 2012 to consider the progress made since its first report was published. It concluded⁶ that, although there was still no evidence to indicate that either technique was unsafe, further research on some specific aspects should be undertaken. The Panel again expressed the view that there remained insufficient research to recommend one particular technique above the other. It also recommended that there should be long-term follow-up monitoring of any children born as a result of the use of these techniques.

⁵ Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, report to the Human Fertilisation and Embryology Authority, April 2011.

⁶ Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, report to the Human Fertilisation and Embryology Authority, March 2013.

1.19 The Government has decided to proceed with regulations. However, before taking the decision to submit regulations for the scrutiny and approval of Parliament, we will ask the HFEA to reconvene the Expert Panel a further time to provide an updated assessment of the safety and efficacy of these techniques.

UK legislation in this area

1.20 The 1990 Act specifically prohibits placing any egg or embryo in a woman if the nuclear or mitochondrial DNA of any cell of the egg or embryo has been altered (section 3(2) read with section 3ZA). This prohibition makes the use of mitochondrial donation currently unlawful in the UK.

1.21 In October 2009, the 1990 Act was amended to introduce a regulation-making power⁷ that, if enacted, would enable mitochondrial donation to take place. When the amendment was made no commitment was given on a timescale for making regulations.

1.22 During the passage of the amending Bill,⁸ the regulation-making power was opposed by a number of organisations. The response of the Government of the day to those concerns was that the power would only be used once the techniques involved were considered to be effective and safe for use in treatment.

Concerns that have been raised

1.23 Although much support has been expressed for the introduction of mitochondrial donation in treatment, concerns have also been expressed. These include: that a child created in this way would have three genetic contributors; that the techniques might be regarded as being similar to cloning; and that some people might regard mitochondrial donation as the genetic modification of a human being, which would also have implications for successive generations. These concerns have been raised with the Department of Health (DH) and were considered in the HFEA's public dialogue and consultation. Below are particular areas of concern that have been taken into account in developing the draft regulations.

⁷ Subsection 3ZA(5) and section 35A of the Human Fertilisation and Embryology Act 1990, as amended.

⁸ The Bill became the Human Fertilisation and Embryology Act 2008 (c.22).

Three person IVF

- 1.24 The dominant DNA (the nuclear DNA) in any child born from these new techniques would be that of the mother and the man providing the sperm (usually the father). Although it would be the case that DNA from three people (the mother, the man providing the sperm and the egg donor) would be present in the child, only a tiny percentage of the child's DNA would come from the egg donor. Most importantly, the residual DNA from the donor would only be mitochondrial DNA so would not affect the resulting child's personal characteristics and traits. This is because mitochondrial DNA only contains genes that are essential for normal mitochondrial function; personal characteristics and traits are derived from the nuclear material.
- 1.25 This was reflected in the HFEA's report of its public dialogue, in which most contributors rejected the "three parent IVF" idea for these reasons. The Nuffield Council on Bioethics report similarly said that "mitochondrial donation does not indicate, either biologically or legally, any notion of the child having either a third parent or a second mother".

Reproductive cloning

- 1.26 Some consider that the techniques would be, in effect, reproductive cloning. However, the Government agrees with the views of the Expert Panel convened by the HFEA and the Nuffield Council of Bioethics that, although a similar methodology is used, these techniques are not reproductive cloning. Any children resulting from these new techniques would have arisen from fertilisation and would be genetically unique, rather than a copy of an existing person. They would be the genetic child of the woman receiving treatment and her partner (or a sperm donor if one is used).

Genetic modification

- 1.27 The proposed mitochondrial donation techniques only allow for unaltered nuclear DNA to be transferred to an egg or embryo that has unaltered healthy mitochondria. The key consideration is that these techniques only substitute, rather than alter, a very limited number of unhealthy genes in the "battery pack" of the cells with healthy ones. Most importantly, mitochondrial donation techniques do not alter personal characteristics and traits. As the aim is that children born as a result of mitochondrial donation, and their offspring, would be free of serious mitochondrial disease, it would though be a form of germ line modification or germ line gene therapy, as recognised by reports produced by the HFEA and the Nuffield Council on Bioethics.

International law

- 1.28 Some commentators have suggested that the introduction of mitochondrial donation might conflict with some provisions of international law.
- 1.29 In bringing forward regulations to enable mitochondrial donation we have been mindful of the UK's obligations under international law. We do not consider that permitting mitochondrial donation, aimed at preventing serious hereditary conditions, would be contrary to human dignity as envisaged by Article 24 of the UNESCO declaration.
- 1.30 It is important to note that the UK Parliament has expressly provided for the possibility of regulations enabling mitochondrial donation and that it is our view that this power is compatible with the European Convention of Human Rights.

Public and stakeholder opinion

- 1.31 In 2012 the Government asked the HFEA to conduct a public dialogue/consultation exercise on the ethical and social issues that mitochondrial donation raises. These specifically included:
- Modification of embryos
 - Changing the germ line
 - Implications for identity
 - Status of the mitochondria donor
 - Permissibility of the two mitochondrial donation techniques, and
 - Models for regulation.
- 1.32 With support from the Sciencewise Expert Resource Centre, the HFEA undertook a comprehensive public dialogue exercise from July to December 2012, involving a survey, focus group, workshops, an open consultation questionnaire and open consultation meetings. The HFEA reported to the Government in March 2013.⁹ In summary, the outcome was:
- The public deliberative workshops, which had time to consider the issues and arguments in detail, were largely in favour of allowing the use of these techniques in treatment, subject to strict regulation.
 - The open consultation questionnaire, the result of which represents views from a self-selected sample, was unique in terms

⁹ Mitochondrial replacement consultation; Advice to Government, published March 2013.

of slightly more people opposing than supporting the techniques, often arguing that their use would amount to inappropriate interference with the natural or spiritual aspect of reproduction, or that any artificial or in vitro manipulation of embryos is unethical.

- 1.33 When taken across the board, the overall view was that the treatment techniques should be used but be subject to strict regulatory controls.
- 1.34 The HFEA also set out the issues it considered should be taken into consideration in introducing an appropriate regulatory framework. Additionally, it arranged for its Expert Panel to provide an update on the safety and efficacy of the techniques.
- 1.35 The overall outcome of the HFEA's public dialogue and consultation exercise was consistent with a six-month inquiry that the Nuffield Council on Bioethics conducted in 2012 on mitochondrial donation. This exercise concluded that if these techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them.¹⁰

Next steps

- 1.36 On the basis of the range of evidence available, the Government announced on 28 June 2013 that it would proceed with draft regulations to allow mitochondrial donation to prevent the transmission of serious mitochondrial disease.

¹⁰ *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*, Nuffield Council on Bioethics, published June 2012.

Chapter 2: The regulations

Introduction

- 2.1 On 28 June 2013 the Government announced that it intended to move forward with regulations to allow mitochondrial donation to prevent the transmission of serious mitochondrial disease between mother and child. The Chief Medical Officer for England, Professor Dame Sally Davies, said:

Scientists have developed ground-breaking new procedures which could stop these diseases being passed on, bringing hope to many families seeking to prevent their future children inheriting them. It is only right that we look to introduce this life-saving treatment as soon as we can.

- 2.2 This announcement followed a consultation and public dialogue between June and December 2012 that the Government asked the HFEA to undertake. The HFEA concluded that *'there is general support for permitting mitochondrial replacement in the UK, so long as it is safe enough to offer in a treatment setting and is done so within a regulatory framework.'*
- 2.3 The Government also took note of the report by the Nuffield Council of Bioethics in June 2012 on novel techniques for the prevention of mitochondrial DNA disorders, which concluded *'on balance we believe that if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them, if they wish to do so and have been offered an appropriate level of information and support.'*
- 2.4 This consultation is therefore not about whether mitochondrial donation to prevent the transmission of serious mitochondrial disease should be *allowed*, but concerns the detail of the regulations that would put into effect the Government's intention to allow it. The draft regulations contain a number of policies and intentions on which we welcome comments and views. A draft version of the regulations is at Annex B.
- 2.5 The regulations describe the process and circumstances in which eggs or embryos created using donated mitochondria can be used in assisted conception services and make modifications to the Human Fertilisation and Embryology Acts 1990 and 2008 in relation to access to information around mitochondrial donation and eligibility for parental orders. The amendments clarify that a mitochondrial donor does not have the same status as a generic gamete donor. These regulations also make transitional provision to clarify that clinics will need to seek authorisation from the HFEA to be able to carry out mitochondrial donation.

- 2.6 This chapter provides an overview of the regulations under the following headings and poses specific questions on which we would welcome your views. We also welcome any additional comments on any aspect of the regulations if you consider there are other issues that we need to consider.

Nuclear material

- 2.7 Mitochondrial donation techniques involve the transfer of nuclear material between eggs and embryos, and the detail in the regulations describing this process reflects discussions the DH has held with expert scientists and researchers working in the field.
- 2.8 In defining “nuclear DNA” for the purposes of the regulations, regulation 2 refers to ‘*material which is necessarily removed or inserted along with that DNA, and may include any associated organelles*’. This reflects that some material closely associated with the nucleus sits outside it in the cytoplasm of the cell, and that close association means that it may need to be transferred as part of the transfer of the nuclear material.

Question 1: Regulation 2 defines the removal or insertion of nuclear DNA involved in mitochondrial donation. Do you agree with this definition?

“Permitted” eggs and embryos: definitions and the process by which they are created

- 2.9 As explained in Chapter 1, the 1990 Act only allows sperm, eggs and embryos to be used in treatment services if they are “permitted” under the Act. This includes provision to ensure that their nuclear and mitochondrial DNA has not been altered.
- 2.10 Regulations 3 (eggs) and 6 (embryos) of the draft regulations qualify that restriction by enabling eggs and embryos created following mitochondrial donation by particular processes to be recognised as permitted eggs or embryos under the Act in certain limited circumstances.
- 2.11 Regulations 4 and 7 set out those processes. Two techniques – maternal spindle transfer (MST) involving the use of eggs, and pro-nuclear transfer (PNT) involving the use of embryos – have been proposed for clinical practice. In both cases, the procedure involves removing the nucleus from an affected patient’s egg or embryo and placing it into a donated egg or embryo that is free of a mitochondrial disorder, where that egg or embryo has had its own original nuclear material removed.
- 2.12 Both the patient’s egg or embryo from which the nuclear DNA is to be removed, and the donated egg or embryo must, at the outset, already be considered to be “permitted” within the current meaning of the 1990 Act.

2.13 Regulations 4 and 7 also provide *only* for this specific replacement process, which reflects both the MST and PNT techniques. If a new mitochondrial donation technique is developed in the future, the draft regulations would not permit its use. It could only be used if new regulations were made, which would be subject to the Parliamentary approval process.

Question 2: Regulations 4 (eggs) and 7 (embryos) only allow mitochondrial donation where all the nuclear DNA is transferred from an egg or embryo to another egg or embryo from which all the nuclear DNA has been removed. Do you agree with this description and restriction?

“Permitted” eggs and embryos: the circumstances in which they can be used

2.14 Regulations 5 and 8 reflect the requirement in the 1990 Act that mitochondrial donation may only be used in cases to avoid the transmission of serious mitochondrial disease. The regulations set two tests that must be satisfied before an egg or embryo will be considered to be permitted for use in treatment:

- that the HFEA has determined that there is a particular risk that the egg or embryo of the patient has a mitochondrial abnormality, and
- that the HFEA has determined that there is a significant risk that a person with that abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition.

2.15 The regulations only set out the type of eggs or embryos which can be permitted for use in treatment. To actually use eggs or embryos in treatment a licence is required from the HFEA. Therefore it will be for the HFEA to determine how to consider any applications for use of mitochondrial donation. The HFEA said in their report to the Government that given the novel nature of these treatments they recommended that the HFEA approve the use of mitochondrial donation on a case by case basis.

Question 3: Regulations 5 (eggs) and 8 (embryos) require that, in order for mitochondrial donation to go ahead, the HFEA must decide that there is both a particular risk that the egg or embryo of the patient has a mitochondrial abnormality and a significant risk that a person with the particular mitochondrial abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition. Do you agree that the HFEA should have this role?

Supplemental provision

2.16 Regulation 9 makes provision to ensure that HFEA treatment licences, which allow clinics to provide treatment, such as IVF, using permitted embryos and eggs, do not extend to authorising mitochondrial donation treatment services without the further specific approval of the HFEA.

Question 4: Do you agree with the principle that licensed clinics should not be permitted to undertake mitochondrial donation without first obtaining authorisation to do so from the HFEA?

Applications for the use of the new procedure

2.17 The regulations set out the process for mitochondrial donation and the circumstances where that process can be applied to create eggs or embryos for use in treatment. Whether a clinic is authorised to carry out such techniques is a matter for the HFEA.

2.18 The draft regulations do not set out the protocols that the HFEA must follow in assessing an application. These are matters for the HFEA, as the statutory regulator, to determine. It will be for the HFEA to decide how to assess the merits of an application, including obtaining whatever external expert advice it considers to be necessary.

2.19 However, as a general indication, we envisage that the considerations and decision making process would be on the lines of:

- a consideration of why the patient's egg or embryo would pass the statutory test of being at particular risk of having a mitochondrial disorder (i.e. a risk greater than the general population),
- an assessment by the HFEA of why there is a significant risk that the mitochondrial disorder would be a serious one, and
- the provision of assurance by the applicant that staff have the necessary expertise, skills and environment to perform the replacement technique(s).

2.20 We envisage that the HFEA would convene an HFEA committee to consider the application, taking account of any additional expert advice it may seek, and to determine if the tests at Regulations 5 and 8 are satisfied.

Status of the mitochondrial donor

- 2.21 In terms of how the clinics handle mitochondrial donation patients and donors, the medical process and consents will be similar to that for sperm and egg donation in fertility treatment. However, we have taken account of the recommendations from the HFEA's consultation and public dialogue that mitochondrial donors should be treated more like organ donors than gamete donors in respect of information to be collected and made available. As already explained in Chapter 1, while the donors' mitochondrial DNA will be present in the resulting child, it will not impact on their personal characteristics and traits as these come from the nuclear DNA (all the donor's nuclear DNA will have been removed from the egg or embryo).
- 2.22 Mitochondrial DNA comprises a very small proportion of total DNA (0.1%, i.e. only 37 of 20,000–30,000 genes). When compared to the shared genetic material involved in gamete donation (50%) or even to DNA that might be shared between first cousins (12.85%), this puts into perspective the completely different nature of the genetic relationship between a mitochondrial donor and a child born from that donor's mitochondrial donation. This reflects views expressed in the HFEA's report of their public dialogue and consultation, and in the Nuffield Council of Bioethics' 2012 report, *Novel techniques for the prevention of mitochondrial DNA disorders*.
- 2.23 The nature of the genetic relationship between the mitochondrial donor and a child born from that donor's mitochondrial donation is reflected in the draft regulations in the provisions relating to access to information and availability of parental orders. The regulations clarify that a mitochondrial donor is *not* to be treated as a person who would or might be the parent of a resulting child if it was not for the provisions in the 1990 and 2008 Act removing parenthood. This is in contrast to the legal position for sperm and egg donors, who *are* treated as people who would or might be the legal parent of a child born from their donation but for the provisions in the 1990 and 2008 Acts. Provision is made in the regulations to reflect this different status by only allowing mitochondria-conceived people access to limited non-identifying information about mitochondrial donors and by clarifying that mitochondrial donation alone is not sufficient to allow a person to obtain a parental order.

Question 5: Do you agree that people donating eggs and embryos for the purposes of mitochondrial donation should *not* have the same status as those donating eggs and embryos for use in fertility treatment, but rather be regarded more like organ or tissue donors?

Information available to mitochondrial donation conceived persons

- 2.24 The 1990 Act requires the HFEA to keep a register of treatment cycles carried out in the UK that involve the creation of embryos outside the body and the use of donated sperm, egg or embryos.¹¹ This provision will encompass mitochondrial donation treatment cycles.
- 2.25 Regulation 10 enables a person, on reaching the age 16, who thinks they may have been born as the result of mitochondrial donation, to apply to the HFEA to see if it holds any information about this on its register.
- 2.26 The Government is of the view that if the HFEA's register does show that the applicant was born as a result of the use of mitochondrial donation, the applicant should be able to access *non-identifying* information about the donor. This reflects the HFEA's public dialogue and consultation and feedback from the Nuffield Council of Bioethics 2012 report, *Novel techniques for the prevention of mitochondrial DNA disorders*.
- 2.27 Regulation 10 specifies the non-identifying information that can be disclosed. This is:
- screening tests carried out on the mitochondrial donor and information on the donor's personal and family medical history – this reflects recommendations in the HFEA's public dialogue and consultation
 - matters contained in any description of the mitochondrial donor as a person which the donor has provided, and any additional matter which the mitochondrial donor has provided with the intention that it be made available to a person who requests information under this section – in a similar way to how organ donors can provide a pen picture for the organ recipient.
- 2.28 Any or all of these items may be disclosed to the applicant providing they do not, either individually or together, result in the identification of the donor.

¹¹ Section 31 of the Human Fertilisation and Embryology Act 1990, as amended.

- 2.29 Regulation 11 provides that if a person born following mitochondrial donation applies to the HFEA to find out if they are related to the person they are seeking to marry or enter into a civil partnership or intimate relationship with, they will not be treated as related to anyone who shares the same mitochondrial donor as them or to the donor themselves. This is because there is a very small (0.01%) genetic relationship between the mitochondrial donor and any child born through mitochondrial donation.
- 2.30 On the same basis, regulation 14 does not allow children born of mitochondrial donation to obtain information from the HFEA about other children conceived following mitochondrial donated by the same donor.
- 2.31 We note, however, that outside of the provisions of the draft regulations, clinics could facilitate a voluntary arrangement for mitochondrial donors and the families receiving treatment to exchange information.

Question 6: Regulation 10 provides that the HFEA should tell a person aged 16, on request, if they were born following mitochondrial donation. Do you agree with this?

Question 7: Regulation 10 also provides that the information that the HFEA should provide in response to such a request should not identify the mitochondrial donor and be limited to screening tests carried out on the donor and about her family medical history, and any other non-identifying information that the donor has provided with the intention that it is made available in these circumstances. Do you agree with this approach?

Information available to mitochondrial donors

- 2.32 The Government considers that mitochondrial donors should also be able to access non-identifying information on live births resulting from their donation. Regulation 13 will enable donors to request information on the number of children born plus the sex and year of birth of each child.

Question 8: Regulations 13 provides that the HFEA should tell a mitochondrial donor, on request, when a child has been born from their donation, how many and their sex. Do you agree with this approach?

Surrogacy cases

- 2.33 The regulations also make an amendment to the circumstances in which a Parental Order can be granted in cases where a child is born as a result of a surrogacy arrangement using eggs or embryos that contain donated mitochondria.

- 2.34 A Parental Order is granted by a Court to transfer the legal parentage of the child from the surrogate and her partner, if she has one, to the couple who commissioned the surrogacy arrangement.¹² There may be very rare occasions where the female partner of the commissioning couple is not only unable to carry a child but will also need the eggs or embryo used in the surrogacy arrangement to be subject to mitochondrial donation because she additionally carries a mitochondrial DNA disorder.
- 2.35 Were this to be the case, regulation 15 would ensure that a person cannot apply for a Parental Order if their only connection to a child is that they provided mitochondria. At least one of the couple applying must have provided genetic material which resulted in the child and this does not include donations of only mitochondria. This, again, reflects the fact that a mitochondrial donor cannot be considered to be the genetic parent of a child born as a result of their donation.

Monitoring and follow-up

- 2.36 The Government recognises that ongoing monitoring of the use of these techniques and the health of the children born as a result, and of successive generations, is vital. However, the regulation-making power does not provide the scope to include this within the regulations and, in any case, there would be difficulties around placing a legal obligation on families to participate in follow-up research.
- 2.37 While the Government does not believe that it would be acceptable to make participation in a research programme a condition for access to this treatment, it considers that clinics providing mitochondrial donation treatment should encourage their patients to participate in follow-up research involving their children.
- 2.38 It is recognised that both treatment techniques are akin to germ line therapy to the extent that mitochondrial donation may have implications not only for the children born as a result of the procedure but for their descendants. For this reason, it is essential that longer-term medical follow-up research is facilitated.
- 2.39 Once treatment is under way and continues, we envisage that the clinic would provide the HFEA with an annual report.

¹² Section 54 of the Human Fertilisation and Embryology Act 2008 set the criteria that must be satisfied for the Court to grant a Parental Order in a surrogacy case.

- 2.40 The Government has discussed this question with the HFEA, which also agrees that it is important that follow-up research needs to be carried out. The Government therefore envisages that as part of the broader regulation of allowing mitochondrial donation there would be an expectation that the clinic would conduct follow-up studies on children born as a result of mitochondrial donation and would discuss the issue of follow-up research, its benefits and the commitment it would require from patients and their children, with prospective patients before treatment commences. During the authorisation process, the HFEA would check the arrangements that clinics have in place for follow-up studies.
- 2.41 We also envisage that there would be an expectation that the treating clinic would maintain ongoing links with research centres specialising in research into mitochondrial disorders to enable longer-term studies to take place.

Any other comments

- 2.42 The above paragraphs highlight key provisions of the draft regulations but we would welcome any comments you may have on other aspects of the regulations and the accompanying impact assessment.

Question 9: Do you have comments on any other aspect of the draft regulations?

Chapter 3: Responding to the consultation

The consultation process

3.1 This document seeks views on the draft regulations to allow the use of newly developed treatment techniques to prevent the transfer of a serious mitochondrial disorder from mother to child.

3.2 The consultation is being run in accordance with the Cabinet Office guidance on Consultations, which is available at:

<https://www.gov.uk/government/publications/consultation-principles-guidance>

3.3 The closing date for the consultation is **21 May 2014**.

3.4 There is a full list of the questions we are asking in this consultation in Annex A. When responding, please state whether you are responding as an individual or representing the views of an organisation. If you are responding on behalf of an organisation, please make it clear who the organisation represents, and where applicable, how the views of members were assembled.

3.5 Please send your responses by post to:

Mitochondrial Donation Consultation
Department of Health
Room 109
Richmond House
79 Whitehall
London
SW1A 2NS

3.6 Alternatively, comments can be sent by email to:
mitochondrial.donation@dh.gsi.gov.uk

Comments on the consultation process itself

3.7 If you have concerns or comments which you would like to make relating specifically to the consultation process itself please contact:

Consultations Coordinator
Department of Health
2E08, Quarry House
Leeds
LS2 7UE

E-mail: consultations.co-ordinator@dh.gsi.gov.uk

Please do not send consultation responses to this address.

Confidentiality of information

3.8 We manage the information you provide in response to this consultation in accordance with the DH Information Charter, which can be found at:

www.dh.gov.uk/en/FreedomOfInformation/DH_088010

3.9 Information we receive, including personal information, may be published or disclosed in accordance with the access to information regimes, primarily the Freedom of Information Act 2000, the Freedom of Information (Scotland) Act 2002, the Data Protection Act 1998 and the Environmental Information Regulations 2004.

3.10 If you want the information that you provide to be treated as confidential, please be aware that, under the Freedom of Information Act, there is a statutory Code of Practice with which public authorities must comply and which deals, among other things, with obligations of confidence. In view of this, it would be helpful if you could explain to us why you regard the information you have provided as confidential. If we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. An automatic confidentiality disclaimer generated by your IT system will not, of itself, be regarded as binding on the DH.

3.11 The DH will process your personal data in accordance with the Data Protection Act and, in most circumstances, this will mean that your personal data will not be disclosed to third parties.

Summary of the consultation

3.12 A summary of the response to this consultation will be made available before or alongside any further action, such as laying legislation before Parliament, and will be placed on the Consultations website at:

https://www.gov.uk/government/publications?keywords=&publication_filter_option=consultations&topics%5B%5D=all&departments%5B%5D=all&world_locations%5B%5D=all&direction=before&date=2013-06-01

Annex A

List of questions

Question 1: Regulation 2 defines the removal or insertion of nuclear DNA involved in mitochondrial donation. Do you agree with this definition?

Question 2: Regulations 4 (eggs) and 7 (embryos) only allow mitochondrial donation where all the nuclear DNA is transferred from an egg or embryo to another egg or embryo from which all the nuclear DNA has been removed. Do you agree with this description and restriction?

Question 3: Regulations 5 (eggs) and 7 (embryos) require that, in order to agree that mitochondrial donation can go ahead, the HFEA must decide if there is both a particular risk that the egg or embryo of the patient has a mitochondrial abnormality and a significant risk that a person with the particular mitochondrial abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition. Do you agree that the HFEA should have this role?

Question 4: Do you agree with the principle that centres should not be permitted to undertake mitochondrial donation without first obtaining authorisation to do so from the HFEA ?

Question 5: Do you agree that people donating eggs and embryos for the purposes of mitochondrial donation should *not* have the same status as those donating eggs and embryos for use in fertility treatment but rather regarded more like organ or tissue donors?

Question 6: Regulation 10 provides that the HFEA should tell a person aged 16, on request, if they were born following mitochondrial donation. Do you agree with this?

Question 7: Regulation 10 also provides that the information that the HFEA should provide in response to such a request should not identify the mitochondrial donor and be limited to screening tests carried out on the donor and about her family medical history, and any other non-identifying information that the donor has provided with the intention that it is made available in these circumstances. Do you agree with this approach?

Question 8: Regulation 13 provides that the HFEA should tell a mitochondrial donor, on request, when a child has been born from their donation, how many and their sex. Do you agree with this approach?

Question 9: Do you have comments on any other aspect of the draft regulations?

Draft regulations

1. Draft Regulations laid before Parliament under section 45(4) of the Human Fertilisation and Embryology Act 1990, for approval by resolution of each House of Parliament.

DRAFT STATUTORY INSTRUMENTS

[2014] No. XXX

HUMAN FERTILISATION AND EMBRYOLOGY

The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations XXX

Made - - - - - ***

Coming into force - - - - - ***

These Regulations are made by the Secretary of State in exercise of the powers conferred by sections 3ZA(5), 31ZA(2)(a), 35A and 45(1) and (3A) of the Human Fertilisation and Embryology Act 1990(a).

A draft of this instrument has been approved by resolution of each House of Parliament pursuant to section 45(4) of that Act.

PART 1

Introductory Provisions

Citation and commencement

1. These Regulations may be cited as the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations [2014] and shall come into force on [].

Interpretation

2.—(1) In these Regulations “the Act” means the Human Fertilisation and Embryology Act 1990(b).

^(a) 1990 c.37. Sections 3ZA(5), 31ZA(2)(a), 35A and 45(1A) and (3A) were inserted by sections 3(5), 24, 26 and 30 of the Human Fertilisation and Embryology Act 2008 (c.22).

^(b) 1990 (c.37).

(2) In these Regulations a reference to the removal or insertion of nuclear DNA includes a reference to the removal or insertion of any material which is necessarily removed or inserted along with that DNA, and may include any associated organelles.

PART 2

Permitted eggs and embryos

Permitted egg

3. An egg (“egg P”) is a permitted egg for the purposes of section 3(2)(b)(a) of the Act if—
- (a) egg P results from the application of the process specified in regulation 4 to two eggs, each provided by a different woman;
 - (b) that process has been applied to those eggs in the circumstances specified in regulation 5; and
 - (c) there have been no alterations in the nuclear or mitochondrial DNA of egg P since egg P was created by means of the process specified in regulation 4.

Permitted egg: process

- 4.—(1) The process referred to in regulation 3(a) is as follows.
- (2) All the nuclear DNA of an egg which is a permitted egg as defined in section 3ZA(2) of the Act (“egg A”) is removed.
- (3) Then all the nuclear DNA of another permitted egg as defined in that section of the Act (“egg B”) is removed from egg B and inserted into egg A.

Permitted egg: circumstances

5. The circumstances are that the Authority has issued a determination that—
- (a) there is a particular risk that egg B may have a mitochondrion abnormality caused by mitochondrial DNA; and
 - (b) there is a significant risk that a person with that abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition.

Permitted embryo

6. An embryo (“embryo P”) is a permitted embryo for the purposes of section 3(2)(a) of the Act if—
- (a) embryo P results from the application of the process specified in regulation 7 to two embryos, each containing material from a different woman;
 - (b) that process has been applied to those embryos in the circumstances specified in regulation 8; and
 - (c) embryo P satisfies both of these conditions—
 - (i) there have been no alterations in the nuclear or mitochondrial DNA of any cell of embryo P since embryo P was created by means of the process specified in regulation 7;

⁽⁴⁾ Section 3(2) was substituted by section 3(2) of the Human Fertilisation And Embryology Act 2008 (c.22).

- (ii) no cell has been added to embryo P other than by the division of embryo P’s own cells.

Permitted embryo: process

- 7. (1) The process referred to in regulation 6(a) is as follows.
 - (2) All the nuclear DNA of an embryo which is a permitted embryo as defined in section 3ZA(4)(a) of the Act (“embryo A”) is removed.
 - (3) Then all the nuclear DNA of another permitted embryo as defined in that section of the Act (“embryo B”) is removed from embryo B and inserted into embryo A.

Permitted embryo: circumstances

- 8. The circumstances are that the Authority has issued a determination that—
 - (a) there is a particular risk that embryo B may have a mitochondrion abnormality caused by mitochondrial DNA; and
 - (b) there is a significant risk that a person with that abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition.

Supplemental provision – licenses

- 9. –(1) Any reference to a permitted egg in a licence whenever issued does not include an egg which is a permitted egg for the purposes of section 3(2) of the Act by virtue of regulation 3 unless express provision is made in the licence to that effect.
 - (2) Any reference to a permitted embryo in a licence whenever issued does not include an embryo which is a permitted embryo for the purposes of section 3(2) of the Act by virtue of regulation 6 unless express provision is made in the licence to that effect.

PART 3

Information requests

Modification of section 31ZA of the Act

- 10. For the purposes of section 35A of the Act(b), section 31ZA of the Act(c) applies as if—
 - (a) for the heading there were submitted “Request for information as to mitochondrial donors”;
 - (b) for subsection (2) there were submitted—
 - “(2) The applicant may request the Authority to give the applicant notice stating whether or not the information contained in the register shows that a person is the applicant’s mitochondrial donor, and if it does show that, giving the applicant the following information—
 - (a) the screening tests carried out on the mitochondrial donor and information on that donor’s personal and family medical history,
 - (b) matters contained in any description of the mitochondrial donor as a person which that donor has provided, and

^(a) Section 3ZA was inserted by section 3(5) of the Human Fertilisation and Embryology Act 2008 (c.22).
^(b) Section 35A was inserted by section 26 of the Human Fertilisation and Embryology Act 2008 (c.22).
^(c) Section 31ZA was inserted by section 24 of the Human Fertilisation and Embryology Act 2008 (c.22).

- (c) any additional matter which the mitochondrial donor has provided with the intention that it be made available to a person who requests information under this section,

but not giving any information which may identify the mitochondrial donor or any person who was or may have been born in consequence of treatment services using genetic material from the applicant's mitochondrial donor, by itself or in combination with any other information which is in, or is likely to come into, the possession of the applicant.”;

(c) for subsection (3) there were substituted—

“(3) The Authority must comply with a request under subsection (2) if—

- (a) the information contained in the register shows that the applicant is a mitochondrial donor-conceived person, and
- (b) the applicant has been given a suitable opportunity to receive proper counselling about the implications of compliance with the request.”;

(d) subsections (4) to (7) were omitted; and

(e) after subsection (7) there were inserted—

“(8) The definitions in subsections (9) and (10) apply for the purposes of this section and sections 31ZB to 31ZE, as modified by regulations under section 35A(1).

(9) “Mitochondrial donor-conceived person” means a person who was or may have been born in consequence of treatment services using—

- (a) an egg which is a permitted egg for the purposes of section 3(2) by virtue of regulations under section 3ZA(5), or
- (b) an embryo which is a permitted embryo for those purposes by virtue of such regulations.

(10) The “mitochondrial donor” in respect of a person who was or may have been born in consequence of treatment services using an egg or embryo of a kind described in subsection (9) is the person whose mitochondrial DNA (but not nuclear DNA) was used to create that egg or embryo.”.

Modification of section 31ZB of the Act

11. For the purposes of section 35A of the Act, section 31ZB of the Act(**a**) applies as if after subsection (6) there were inserted—

“(6A) For the purposes of this section, in a case where the information contained in the register shows that the applicant is a mitochondrial donor-conceived person, the applicant is not a person who, but for the relevant statutory provisions, would or might be related to—

- (a) the applicant's mitochondrial donor, or
- (b) any person who was or may have been born in consequence of treatment services using genetic material from the applicant's mitochondrial donor.”.

Modification of section 31ZC of the Act

12. For the purposes of section 35A of the Act, section 31ZC of the Act(**b**) applies as if—

- (a) for the heading there were substituted “Duty of Authority not to inform mitochondrial donor of request for information”;

^(a) Section 31ZB was inserted by section 24 of the Human Fertilisation and Embryology Act 2008 (c.22).

^(b) Section 31ZC was inserted by section 24 of the Human Fertilisation and Embryology Act 2008 (c.22).

(b) for subsection (1) there were substituted—

“(1) Where—

- (a) the Authority has received from a person (“the applicant”) a notice containing a request under section 31ZA(2) as modified by regulations under section 35A(1), and
- (b) compliance by the Authority with its duty under that section as so modified has involved or will involve giving the applicant information relating to the applicant’s mitochondrial donor,
the Authority may not notify the applicant’s mitochondrial donor that the request has been made.”; and
- (c) subsection (2) were omitted.

Modification of section 31ZD of the Act

13. For the purposes of section 35A of the Act, section 31ZD of the Act(a) applies as if—

- (a) subsections (1)(b), (2)(b), (7), (8)(b) and (9) were omitted; and
- (b) for subsections (3)(a) there were substituted—

“(a) the number of persons in respect of whom the donor is a mitochondrial donor.”.

Modification of section 31ZE of the Act

14. For the purposes of section 35A of the Act, section 31ZE(b) of the Act applies as if—

- (a) after subsection (1) there were inserted—

“(1A) Subsection (1B) applies in respect of a mitochondrial donor-conceived person (“P”) and P’s mitochondrial donor (“D”).

(1B) For the purposes of this section, D is not a person who would or might, but for the relevant statutory provisions, be the parent of P.”; and

- (b) subsections (2) to (4) were omitted.

Modification of section 54 of the Human Fertilisation and Embryology Act 2008

15. For the purposes of section 35A of the Act, section 54 of the Human Fertilisation and Embryology Act 2008(c) applies as if—

- (a) in subsection (1), paragraph (c) were omitted;
- (b) after subsection (1) there were inserted—

“(1A) Subsection (1B) applies if—

- (a) the child was or may have been born in consequence of treatment services using—
 - (i) an egg which is a permitted egg for the purposes of section 3(2) of the 1990 Act by virtue of regulations under section 3ZA(5) of that Act (which relate to mitochondrial donation), or
 - (ii) an embryo which is a permitted embryo for those purposes by virtue of such regulations; and

^(a) Section 31ZD was inserted by section 24 of the Human Fertilisation Act 2008 (c.22).

^(b) Section 31ZE was inserted by section 24 of the Human Fertilisation Act 2008 (c.22).

^(c) c.22.

(b) one of the applicants (“D”) is the person whose mitochondrial DNA (but not nuclear DNA) was used to create that egg or embryo.

(1B) For the purposes of paragraph (b) of subsection (1), D’s gametes are not treated as having been used as required by that paragraph.”; and

(c) subsections (2) to (8), (10) and (11) were omitted.

PART 4

Final Provisions

Amendment of the Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004

16. In the Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004^(a)—

(a) in regulation 1(2), for the definition of “applicant” substitute—

““applicant” means a person who has requested information under section 31ZA of the Act, except a person who has requested information as to mitochondrial donors as set out in subsection (2) of that section as modified by regulations under section 35A of the Act (mitochondrial donation);”; and

(b) after regulation 1(2) insert—

“(3) References in these Regulations to sections 31ZA of the Act do not include references to that section as modified by regulations under section 35A of the Act.”.

Signatory text

Name

Parliamentary Under Secretary of State

Date

Department

^(a) S.I.2004/1511.

EXPLANATORY NOTE

(This note is not part of the Regulations)

These Regulations make provision to enable mitochondrial donation.

Part 2 provides for specified eggs and embryos, which contain donated mitochondria, to be permitted for use in assisted conception treatment under section 3(2) of the Human Fertilisation and Embryology Act 1990 (“the 1990 Act”) in certain circumstances. Regulations 4 and 7 prescribe the process that such embryos and eggs must have undergone, which involves the removal of the nucleus from an egg or embryo (egg or embryo “A”) and the insertion of this material into an enucleated egg or embryo (egg or embryo “B”). Regulations 3(c) and 6(c) ensure that no other alterations can be made to the resulting egg or embryo after this process has taken place. Regulations 5 and 8 provide that the Human Fertilisation and Embryology Authority must have issued a determination there is a particular risk that egg or embryo A may have a mitochondrion abnormality caused by mitochondrial DNA, and that there is a significant risk that a person with that abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition. Regulation 9 makes supplemental provision to provide that existing treatment licences do not enable the use of embryos and eggs permitted under the regulations and to clarify that any new licence issued will require express provision to enable the use of such eggs or embryos.

Part 3 of the Regulations applies the 1990 Act with modifications to provide for cases where mitochondrial donation has taken place. Regulations 10 to 14 modify the information provisions in the 1990 Act to enable children born following mitochondrial donation to access limited, non-identifying, information about their mitochondrial donor. Provision is also made for a mitochondrial donor to access limited, non-identifying, information about children born from their donation and to be notified about requests for information. The Regulations modify the 1990 Act to clarify that mitochondrial donors are not related to any children who were, or might have been, born following treatment services using their donation and therefore no provision is made to allow access to information in connection with entering into a marriage, civil partnership or intimate physical relationship, nor to access information about other children who share the same donor. Modifications are made to section 54 of the Human Fertilisation and Embryology Act 2008 to provide that where a child has been born following treatment services a person who donated mitochondria is not eligible to apply for a parental order on the basis of that donation alone.

Part 4 of the Regulations make amendments to the Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004 to clarify that they do not apply to information relating to mitochondrial donations.

Annex C

Regulatory Triage Assessment

Regulatory Triage Assessment	
Title of regulatory proposal	Deregulation of Mitochondria Donation Therapies for Clinical Use
Lead Department/Agency	DH
Expected date of implementation	01/10/2014 SNR 8
Origin	Domestic
Date	2/10/2013
Lead Departmental Contact	Edward Webb
Departmental Triage Assessment	Deregulation (fast track)

Rationale for intervention and intended effects

Currently, the use of mitochondria donation treatments to counteract mitochondrial disease is not permitted under the Human Fertilisation and Embryology Act 1990. However, the Act includes provisions for regulations to be introduced that would permit mitochondrial donation therapies to take place in order to prevent serious cases of mitochondrial disease.

The Government commissioned the Human Fertilisation and Embryology Authority (HFEA) to consult the public for their views on mitochondria donation techniques. The results of the consultation are published in '*Mitochondria replacement consultation: Advice to Government*' published by the HFEA in March 2013¹. The public were broadly supportive of mitochondrial donation techniques as long as appropriate safeguards were in place to ensure safety for all those involved, and that the procedure did not involve alteration of nuclear DNA (that would directly alter the personality and aesthetic characteristics of a child).

It has only been recently that research on mitochondrial donation therapies has advanced to a point where it is suitable for clinical use. The Government is moving to simultaneously permit the treatment for clinical use, as allowed by the HFE Act 1990, and create regulations that ensure considered and safe use of the procedure.

There are two rationales for Government intervention: only Government can intervene to remove the prohibition of mitochondrial donation treatment because the activity is currently illegal. The second rationale is based on reducing harm to patients born with mitochondrial

¹ http://www.hfea.gov.uk/docs/Mitochondria_replacement_consultation_-_advice_for_Government.pdf

defects as this restricts the health of the patient, increases costs of caring for the patient both privately and through the NHS.

The ultimate effect of the policy is to reduce the incidence of severe mitochondrial disease in newborn children, whilst ensuring the child has a strong genetic link to both the mother and father. It will also encourage inflows of foreign direct investment into the industry in the UK.

Viable policy options (including alternatives to regulation)

It would not be reasonable to remove the ban on mitochondria donation treatment, leave the resulting market to engage in self-regulation, and expect a satisfactory outcome (satisfactory as defined by the consensus of the survey respondents in the HFEA consultation). The only way that mitochondrial donation can lawfully take place is if the power under the Act to make regulations is exercised.

The option considered in this Regulatory Triage Assessment (RTA) is the Government using a regulation-making power in the HFE Act 1990. This power extends the definition of “permitted” eggs and embryos (for IVF treatment) to include eggs and embryos that have transferred mitochondrial DNA.

Initial assessment of business impact

Because a RTA only considers impacts on bodies outside the public sector (private and third-sector organisations), a substantial amount of the impact of the proposed regulations falls out of scope of the RTA (see Annex 1). This includes the impact of cost-savings on the NHS, the direct health benefits to children who are born as a result of the procedure, the benefit to the economy from these patients having a more productive use and the impact on the HFEA in terms of having its scope broadened. The potential impact on the NHS and the health and productivity benefits are discussed in Annex 2 of the RTA. The RTA only explicitly considers the benefit from increased revenue to providers of mitochondrial donation procedures. As providers will be complying with the existing system of regulations with regard to genetic treatment, the costs of compliance are not included as these would be a standard costs incurred as part of performing treatment.

We assume the market for mitochondrial donation treatment follows the same public/private split as that of standard IVF, which is two thirds private sector and one third NHS.

Revenue to providers for mitochondria donation procedures

Providers of mitochondrial donation procedures will gain a revenue stream from entering into this market. While it is not known what a provider would actually charge for a cycle of treatment, it can be estimated using current price lists from private IVF clinics.

Each cycle of mitochondrial donation treatment will use resources equivalent to:

- Two “rounds” of standard IVF (due to the need for a donor mother and the birth mother to have their eggs extracted)
- One round of Pre-implantation Genetic Diagnosis (PGD) to test for the presence of mitochondrial disease in the extracted embryos.

The costs of these procedures vary depending on provider. Using current costs, we estimate each cycle of mitochondrial donation should cost in the region of £20,000. On average we would expect four cycles of mitochondrial donation to generate a successful conception, using a success rate of 25% per cycle.

The table below compiles all the parameters so far and calculates the expected annual benefit of the policy.

Parameter	Value
Cost of one cycle of IVF	£5,000
Cost of one cycle of PGD	£10,000 (including drugs)
Estimated cost of one cycle of Mitochondria donation treatment	£20,000
Estimated Success Rate	25%
Estimated cost of successful Mitochondria donation treatment	£80,000
Assumed number of eligible applicants for mitochondria donation treatment per year	10
Estimated revenue stream to all providers	£800,000
Proportion of market that is wholly private sector	66%
Estimated revenue stream to private sector providers (benefit)	£533,000

It is possible that this is an under-estimate of the actual cost that providers will charge. There are two reasons why this may be the case:

1. Only embryologists with substantial experience would have the necessary skill to carry out this procedure, meaning that the labour cost of the procedure may be higher than in average IVF.
2. There are very few viable providers of mitochondrial donation procedures. Given that

demand for this procedure is likely to be price inelastic (because there are no substitutes that will offer the same result, and parents place a very high weighting on their child’s wellbeing), there may be some monopoly behaviour from the provider(s). This would take the form of inflated prices relative to that for standard IVF, where there is more competition.

Likewise, it is also possible that this may over-estimate costs. This is principally because of economies of scale resulting from performing all three procedures in-house. For example, one clinic cites the cost for a single cycle of IVF treatment to be £3,350, but a three-cycle package is £7,000, suggesting economies of scale in IVF are possible. This will depend on the resources needed for the procedure, and the logistics involved in having a third person be involved in the procedure.

The profile of benefits are identical for each year over the policy period, thus it follows the Equivalent Annual Net Cost to Business (EANCB) calculation is equal to the Benefit.

Parameter	Value
Estimated revenue streams to firms (benefit)	-£533,000
Estimated net benefit (EANCB)	-£533,000

Note: a negative EANCB figure indicates that the estimate provides a benefit to business.

One-in, One-out status

This policy involves writing regulations that fall within the scope of the One In Two Out Framework. The regulations will permit activities that are currently prohibited, albeit in a limited and prescribed way. It is on this basis that we consider the proposal to be an OUT in the One In Two Out Framework.

Rationale for Triage rating

Our expectation of the number of patients eligible for treatment is expected to be very low in the first instance, as discussed above. The benefits on the private sector are a sufficient size that a Regulatory Triage Assessment is the most appropriate route for consideration by the RPC and the RRC.

Departmental signoff (SCS): Ted Webb

Date: 9/10/2013

Economist signoff (senior analyst): John Henderson Date: 8/10/2013

Better Regulation Unit signoff: Frank Brown

Date: 9/10/2013

Supporting evidence

The policy issue and rationale for Government intervention

1. Mitochondrial disease is the mutation of mitochondrial DNA in humans. It affects the ability of cells to function and can cause a variety of diseases ranging from the relatively minor (lethargy) to severe (heart and kidney failure) – all of which have substantial impacts on both life expectancy and quality of life. Mitochondrial disease is passed on to future generations through faulty mitochondrial DNA in eggs. As these are mutations that affect the basic structure of human bodies, there is no cure.
2. Scientists in the UK have pioneered techniques that replace the faulty mitochondria of the mother with a healthy mitochondria extracted from a donor egg or embryo¹.
3. Currently, it is legal to engage in research pertaining to this field using human embryos or eggs, but it is illegal to provide treatment based on this technique. Regulations are sought under section 3ZA of the Human Fertilisation and Embryology Act 1990 (amended through HFE Act 2008).
4. The rationale for Government intervention is that it is the Government that sets the regulatory framework that encompasses medical treatment in the UK. It is intended to reduce the harm to individuals born with mitochondrial disease and reduce the impact of treatment on the NHS and personal care services.

Policy objectives and intended effects

5. The intended effects of the proposal are:
 - a. To enable safe and effective treatment for mitochondrial disease;
 - b. To ensure that only those mothers with a significant risk of having children with severe mitochondrial disease would be eligible for treatment;
 - c. To signal the UK's desire to be at the forefront of cutting edge of medical techniques.

¹ <http://www.wellcome.ac.uk/News/Media-office/Press-releases/2012/WTVM054145.htm>

Policy options considered, including alternatives to regulation

6. The use of eggs or embryos with donated mitochondria in treatment is currently illegal. Hence the only approach to achieving the objectives is by creating regulations to enable this activity. The Government has a regulation making power in the HFE Act 1990 to redefine what is a “permitted” egg/embryo for use in assisted reproduction techniques. The regulation considered in this RTA expands this definition to include eggs and embryos where mitochondrial DNA has been altered.
7. It would be unreasonable for the Government to pursue other regulatory approaches to achieve the same outcome when the Government has this regulation making ability already.

Expected level of business impact

Range of impact – demand for treatment

8. Mitochondrial disease currently affects around 12,000 people in the UK, with one in every 6,500 babies being born with a form of the disease². The technique being legalised here will apply to the most severe cases in the first instance. An estimate provided by the Wellcome Trust Centre for Mitochondrial Research at the University of Newcastle suggests mitochondria donation treatment could apply to up to 10 cases per year initially. As the treatment and follow-up of cases increases over time, there may be reasons to expand the number of cases per year. It would be inappropriate to estimate the size of this increase so we will assume a constant 10 cases per year.

Range of impact – supply of treatment

9. Presently, very few organisations in the UK are capable of offering treatment. We expect increased interest from the scientific community to set up research centres in the UK for these diseases. In the longer term we expect more providers coming forward offering treatment. Any such activity is dependent on their ability to prove the safety and efficacy of their methods.
10. Using data from the DH Audit of Regulations, approximately two thirds of HFEA business relates to the private sector whilst the other one third relates to the NHS.³

² <https://www.gov.uk/government/news/innovative-genetic-treatment-to-prevent-mitochondrial-disease>

³Source: page 89;

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/236741/dhregulations_impact_on_business.pdf

Benefit: Providing the treatment itself

11. Mitochondrial donation techniques cover pro-nuclear transfer (PNT) and maternal spindle transfer (MST) and have been used in the UK for many years for research purposes. To get an idea of the costs of providing mitochondrial donation treatment, we start with the costs of providing IVF treatment privately. We believe the resources required to perform PNT or MST would be roughly equivalent to IVF treatment. Costs may be higher when factoring in the complexity of PNT or MST over and above IVF. Internet research finds that IVF treatments cost around £3,000-3,500 per cycle⁴. When other costs are included as well, such as consultations, laboratory tests, the costs are likely to be closer to £5,000 per cycle.
12. The mitochondrial donation techniques will be performed on both the mother egg and the donated mitochondria egg. Therefore the costs stated above would be doubled, to around £10,000 per cycle.
13. Lastly, expert opinion explains performing the technique of extracting the donor's mitochondrial DNA and disposing of the mother's mitochondrial DNA would involve resources equivalent to Pre-implantation Genetic Diagnosis (PGD). PGD is a technique that allows embryos to be tested for genetic conditions before being placed in the woman. NHS Guy's and St Thomas' Centre for PGD quotes the cost of performing this test of around £8,000 excluding drugs, or around £10,000 in total⁵.
14. In total, a clinic might expect to get a revenue of around **£20,000** per cycle per patient.
15. Success rates for IVF treatment differ by age group and is more common amongst young women. Experts from the Wellcome Trust centre in Newcastle have advised us that success rates for mitochondrial donation are likely to mirror that of traditional IVF treatment. The table below uses data from a 2011 HFEA report⁶ to show the success rate by age group and percentage of all IVF attempts accounted for under that age group.

Age Group	< 35	35 – 37	38 – 39	40 – 42	43 – 44	45+
Success Rate (%)	32.2	27.7	20.8	13.6	5.0	1.9
Percentage of all IVF cycles performed (%)	41.6	23.1	16.3	13.6	3.5	1.9

⁴ See, for instance:

http://www.londonwomensclinic.com/index.php/london/treatment_costs

<http://www.lfc.org.uk/prices>

http://www.manchesterfertility.com/assets/img/content/fee_schedule.pdf

<http://www.nhs.uk/Conditions/IVF/Pages/Introduction.aspx>

⁵ http://www.pgd.org.uk/referral_funding/funding.aspx

⁶ http://www.hfea.gov.uk/docs/HFEA_Fertility_Trends_and_Figures_2011_-_Annual_Register_Report.pdf

16. Weighting the success rates by the percentage of all IVF cycles performed for each age group yields an average success rate of **25%**. This implies that, on average, it will take four cycles of IVF for one to be successful. Hence, the total cost of a successful conception for a patient with mitochondrial disease is estimated at £80,000.

17. As we expect 10 patients to be granted treatment each year, this gives a total benefit for the entire sector as £800,000 per year. As the sector is split roughly two thirds private sector and one third public sector, this gives the benefit to industry at **£533,000**.

Summary of benefits and EANCB

18. The table below gives the summary of total benefits and an estimate of the Equivalent Annual Net Cost to Business (EANCB).

Parameter	Value
Estimated revenue streams to firms (benefit)	-£533,000
Estimated net benefit (and EANCB)	-£533,000

Risks

19. Risks may occur on the benefits and cost side of mitochondrial treatment. The estimates are based on a number of assumptions which are expected given the uncertain nature of the regulatory framework in which mitochondrial donation operates.

20. The labour cost of providing mitochondrial replacement treatment may be higher than standard IVF as only trained embryologists would have the necessary skills to perform this procedure.

21. There are very few viable providers of this treatment that could operate on the first day of the implementation of the regulations. This means these providers could exploit its monopoly status in the early stages of this market opening up and raise the price of treatment.

22. Economies of scale exist for multiple cycles of IVF treatment and these could be used in this scenario. For instance, one clinic offers one cycle of IVF for £3,350 whereas three cycles cost £7,000.

23. The probability of success for mitochondrial replacement treatment could be substantially different to that for standard IVF. In the absence of other information, the statistics from standard IVF offer a reasonable proxy.

Annex 1: Scope of impacts covered in the RTA

	What is the impact?	In/out of scope of RTA?	If out of scope, why?
Patients	Will have healthy children born without mitochondrial disease	Out	Not a private sector or civil society organisation
	Personal cost savings from less care for children who would have had mitochondrial disease.	Out	Not a private sector or civil society organisation
NHS	Benefit from providing treatment for mitochondrial disease	Out	Not a private sector or civil society organisation
	Cost savings from treating fewer children with mitochondria disease	Out	Not a private sector or civil society organisation
Private sector	Compliance with HFEA regulations	Out	These are standard costs incurred from the extension of existing regulation. A provider would incur these costs in the same way they would have to comply with, for instance, Health and Safety regulations.
	Inward investment in mitochondrial donation techniques	Out	Indirect effect; and mitochondrial donation techniques are legal in the UK for research at present.
	Training and other fixed costs to perform treatment	Out	Indirect cost and voluntary; only incurred if provider enters market.
	Monetary benefit from performing treatment	In	
HFEA	Setting and monitoring regulatory framework	Out	Not a private sector or civil society organisation

Annex 2: Benefits to patients from mitochondrial donation treatments

1. The annex summarises the wider benefits, other than to businesses, of mitochondrial donation treatment on the patients themselves. Three methods of benefit calculation are considered: the social net benefit estimates; the lifetime earnings created; and the NHS costs alleviated.
2. The analysis assumes the change in regulation affects ten couples a year. A 50/50 split in gender is also assumed.
3. The first method used is the wider social benefit model. This model attempts to calculate the total productive use a person places upon society.
4. The most common symptoms associated with mitochondrial diseases are loss of motor or sensory functions. These symptoms suggest a quality of life measure of 0.4¹.
5. It is assumed mitochondrial donation will increase the quality of life of all patients to 1.0. This corresponds to a £2.1m social net benefit over 10 years.
6. The next measure of benefit created to be used is the lifetime earnings created. For this calculation it is assumed that those suffering from severe mitochondrial disease will not live into working age, as the life expectancy of many diseases associated with mitochondrial disease is only a few years (Orpha, 2006). It is also assumed that those effected will earn the median full-time gross weekly earnings (ONS, 2013)
7. This benefit will be created over 75 years, not the 10 year period used in other models
8. Assuming that the entire cohort is working when able within this 75 year period it is expected that £106m of lifetime earnings will be created across the 100 members of all 10 cohorts, but it is vital to note this is over 75 years.
9. The final method of benefit calculation used is the reduction in NHS costs. As an illustrative example we model the impact on primary care drug costs as these will be incurred on an ongoing basis. Only those drugs with dosage data and cost estimates were included here. These are thiamine, riboflavin, L-creatine and L-carnitine².
10. Over ten years the cost savings from not needing to provide these drugs is approximately £60,000. By applying this average cost per patient per year to each cohort over a 10 year

¹ Quality of life measures are bounded by 0 (equivalent to a state of death) and 1 (a patient in full health). The quality of life estimate corresponds to symptoms of MELAS and MERFF, epileptic seizures and strokes. Source: Wallace, 2010.

² These drugs are sufficient treatment options for MELAS and Leigh syndrome.

period this gives a total NHS cost of £61k.

11. With the introduction of this policy these costs will be removed therefore the benefit to the NHS as a reduction in costs is £61k

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Annex D

Some disorders caused by unhealthy mitochondrial DNA

Mitochondrial DNA disorder	Description	Prevalence	Life expectancy/morbidity
Kearns–Sayre syndrome	Progressive blindness and blocked heart	Rare disease	Onset before 15
CPEO (chronic progressive external ophthalmoplegia)	Progressive wastage of eyelids, eyes and sometimes facial muscles	Rare disease	Onset in young adulthood
Pearson syndrome	Anaemia, pancreatic failure, muscle wastage	Very rare (less than 100 worldwide)	Early death
MELAS (myopathy, encephalopathy, lactic acidosis and stroke)	Stroke like episodes; muscle spasm; early dementia	Rare disease	Death before 40
MERFF (myoclonic epilepsy and ragged-red fibres)	Epilepsy, hearing loss, lactic acidosis, short stature	1 in 400,000 across Europe	Childhood onset
NARP (neurogenic weakness, ataxia and retinitis pigmentosa)	Muscle weakness, vision loss, learning disabilities	Rare disease	Onset in early childhood. Early death
MILS (maternally inherited Leigh syndrome)	Muscle weakness, heart and kidney failure, delayed development	Very rare	Onset in infancy. Death in early childhood
MIDD (maternally inherited diabetes and deafness)	Combination of all types of diabetes with deafness	Rare disease	Adult onset
LHON (Leber hereditary optic neuropathy)	Rapid blindness	1 in 30,000 across Europe	Range from early childhood to 70s
Myopathy and diabetes	Covers forms of muscular dystrophy		From infancy. Early death
Sensorineural hearing loss	Covers a range of hearing loss through to deafness	Common condition but rarely caused by mitochondrial disease	Onset at any age
Exercise intolerance	Range from lethargy to muscle wastage	1 in 8,000 but symptoms often combine with others	Onset in early life
Fatal infantile encephalopathy (Leigh syndrome)	Brain and nervous system dysfunctions	Very rare	Onset in infancy. Death in early childhood