

Mitochondria replacement consultation: Advice to Government

Human Fertilisation and Embryology Authority, March 2013

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1 Summary of advice to Government

- 1.1 The Secretary of State for Health and the Secretary of State for Business, Innovation and Skills asked the Human Fertilisation and Embryology Authority (HFEA) in January 2012, to seek public views on emerging IVF-based techniques to prevent the transmission of mitochondrial disease, with support from Sciencewise Expert Resource Centre¹. These techniques, which are referred to as mitochondria replacement, are currently illegal in treatment in the UK.
- 1.2 Mitochondria are present in almost all human cells. They generate the majority of a cell's energy supply. For any cell to work properly, the mitochondria need to be healthy. Unhealthy mitochondria can cause genetic disorders known as mitochondrial disease.
- 1.3 There are many different conditions that can be described as mitochondrial disease. Many have not been given names because the symptoms vary from patient to patient, so cannot be grouped together as a specific condition. They range from mild to severe or life threatening, and can have devastating effects on the families that carry them. Currently there is no known cure and treatment options are limited. For many patients with mitochondrial diseases, preventing the transmission of the disease to their children is a key concern.
- 1.4 The evidence presented here is drawn from a multi-method research and engagement project conducted between July and December 2012 which looked at the social and ethical issues raised by mitochondria replacement. The evidence also addresses a range of practical regulatory issues.
- 1.5 In considering this evidence, and developing the analysis presented in this report, the HFEA has also brought to bear its experience of regulating IVF and research involving human embryos over the past 20 years.
- 1.6 It is not the task of the HFEA to advise the Government as to whether it should permit mitochondria replacement in treatment. That decision

¹ The Sciencewise Expert Resource Centre (Sciencewise-ERC) is funded by the Department for Business, Innovation and Skills (BIS). Sciencewise-ERC aims to improve policy making involving science and technology across Government by increasing the effectiveness with which public dialogue is used, and encouraging its wider use where appropriate to ensure public views are considered as part of the evidence base. It provides a wide range of information, advice, guidance and support services aimed at policy makers and all the different stakeholders involved in science and technology policy making, including the public. The Sciencewise-ERC also provides co-funding to Government departments and agencies to develop and commission public dialogue activities. www.sciencewise-erc.org.uk

would require a change in the law and is, quite properly, one which only Parliament can take. If the Government does wish to take steps to change the law, it must draft Regulations as provided by the Human Fertilisation and Embryology Act 1990 (as amended) ('the Act').

1.7 Our advice to Government, set out in this report, is that there is general support for permitting mitochondria 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. Despite the strong ethical concerns that some respondents to the consultation expressed, the overall view is that ethical concerns are outweighed by the arguments in favour of permitting mitochondria replacement.

1.8 We have therefore framed our advice so as to inform the Government's thinking, should it be minded to put Regulations forward to Parliament to make this possible. The advice we give below addresses the policies and safeguards that might guide those Regulations.

1.9 It is worth noting that there are also ethical issues associated with deciding not to seek Parliament's approval to permit mitochondria replacement. Such a move would restrict the reproductive options of people with serious mitochondrial disease, denying them access to a treatment which has clinical promise.

1.10 We set out our advice to Government in section 6, organised under the following themes:

- Modification of embryos and changing the germ line
- Implications for identity and the status of the mitochondria donor
- General views on the permissibility of the techniques
- Licensing models and further regulatory issues

Each theme discusses the issues and provides advice, in bold, at the end. That advice is reproduced here.

Modification of embryos and changing the germ line

1.11 In order to address concerns that permitting these techniques might open the door to other less desirable ones, the Authority advises that any Regulations allow for the specific germ line modifications proposed and consulted on (ie, the replacement of mitochondria) only. They should be drafted in such a way as to mirror the prohibition on modifying nuclear DNA in the Act and preclude in a treatment setting techniques which alter nuclear DNA, permit somatic cell nuclear

transfer, or allow use of the techniques for anything other than avoiding serious disease.

- 1.12 In order to address concerns about the safety implications of changing the germ line, the Authority advises that mechanisms are put in place to allow for further recommended research (as outlined by the expert scientific panel in its report at Annex viii). The Authority also advises that licensed centres carrying out mitochondria replacement are encouraged to conduct follow-up studies on any children born as a result and on future generations.

Implications for identity and the status of the mitochondria donor

- 1.13 The Authority advises that mitochondria donors should have a similar status to that of tissue donors. Children born of mitochondria replacement should not have a right to access identifying information about the donor when they reach the age of 18.
- 1.14 Existing systems for ensuring the traceability of gametes and embryos used in fertility treatment should be used in mitochondrial donation:
- licensed clinics should keep records to ensure they are able to trace all mitochondria donations from procurement to use and storage, including being able to identify the donor
 - the HFEA should keep a register of treatment cycles involving mitochondria replacement, resulting children and medical information about mitochondria donors.
- 1.15 The Authority advises that any Regulations should facilitate arrangements for disclosure of non-identifying information to mitochondria donors and children born as a result of their donation:
- parents and children conceived of mitochondria replacement should be entitled to find out non-identifying medical information about mitochondria donors once they reach the age of 16 (either from a licensed centre or the HFEA)
 - mitochondria donors should be entitled to find out basic non-identifying information about children resulting from their donation eg, the number, sex and year of birth (either from a licensed centre or the HFEA).
- 1.16 Local systems, based on mutual consent, should be put in place (eg, by clinics, in collaboration with appropriate charities or professional bodies) to facilitate voluntary exchange of information and contact between mitochondria donors and children resulting from their donation. These systems could reflect the voluntary systems in place for exchange of information following tissue donation.

General views on the permissibility of the techniques

- 1.17 The Authority advises that mechanisms be put in place to allow for further consideration of the safety and efficacy of the techniques, in light of further research suggested by the expert scientific panel (outlined in its report at Annex viii), in conjunction with HFEA consideration of a licence application. The techniques should only be carried out in clinical practice once experts advise the HFEA that these results are reassuring.

Licensing models and further regulatory issues

- 1.18 The Authority advises that any Regulations permitting mitochondria replacement, should:
- ensure the techniques are only used to avoid serious mitochondrial diseases in cases where clinical specialists have deemed it to be appropriate
 - require the HFEA to approve each licensed centre wishing to offer mitochondria replacement as a clinical treatment
- 1.19 In order to future-proof the Regulations, they should provide flexibility for the HFEA to design a process for approving the use of mitochondria replacement in individual cases. Given the novel nature of these treatments, we recommend that the HFEA approves the use of mitochondria replacement on a case-by-case basis. It may be appropriate in the future to move to a more localised, clinic-based approval process.

2 Introduction and background

- 2.1 The Secretary of State for Health and the Secretary of State for Business, Innovation and Skills asked the Human Fertilisation and Embryology Authority (HFEA) in January 2012 to seek public views on emerging IVF-based techniques to prevent the transmission of mitochondrial disease, with support from Sciencewise Expert Resource Centre. These techniques are referred to as mitochondria replacement.
- 2.2 The HFEA is the UK's independent regulator for IVF treatment and embryo research. Our role is to protect patients and the public interest, to drive improvement in the treatment and research sectors and to provide information to the public and policymakers about treatment and research. The HFEA is a public body with substantial expertise in public dialogue and consultation often on contentious ethical and scientific issues, recent examples being the licensing of human-animal hybrid embryos for research and policies regarding sperm, egg and embryo donation. The HFEA has long experience of regulation and policy in such difficult areas.
- 2.3 On considering advice from the HFEA, the Government will decide whether to seek Parliamentary approval to permit one or both of the procedures for treatment.
- 2.4 The HFEA, with support from Sciencewise Expert Resource Centre, commissioned OPM (in partnership with Forster and Dialogue by Design) to conduct a multi-method research and engagement project looking at the possible social and ethical issues and arguments relating to mitochondria replacement. The project consisted of five strands (the findings of which are summarised at Annex i):
- Deliberative public workshops (Annex ii)
 - Public representative survey (Annex iii)
 - Open consultation questionnaire (Annex iv)
 - Open consultation meetings (Annex v)
 - Patient focus group (Annex vi)
- 2.5 At the request of Government, the HFEA has also considered the practical implications of allowing these techniques within the existing regulatory regime. The report at Annex vii highlights some of the regulatory issues associated with permitting mitochondria replacement.
- 2.6 As outlined in section 5 below, in anticipation of the outcomes of the public dialogue work, the Secretary of State for Health asked the

HFEA, in December 2012, to provide an updated view of the science to support the assessment of the efficacy and safety of the two mitochondria replacement techniques: pro-nuclear transfer and maternal spindle transfer. The HFEA reconvened a small panel of experts to advise on this; their conclusions are outlined in the report at Annex viii.

The mitochondria replacement techniques

- 2.7 Mitochondria are present in almost all human cells. They generate the majority of a cell's energy supply. For any cell to work properly, the mitochondria need to be healthy. Unhealthy mitochondria can cause genetic disorders known as mitochondrial disease.
- 2.8 There are many different conditions that can be described as mitochondrial disease. Some are rarer than others, but they include conditions such as Leigh's disease, Barth syndrome and MERRF syndrome. However, many forms of mitochondrial disease have not been given names because the symptoms vary from patient to patient, so cannot be grouped together as a specific condition.
- 2.9 They range from mild to severe or life threatening, and can have devastating effects on the families that carry them. Currently there is no known cure and treatment options are limited. For many patients with mitochondrial diseases, preventing the transmission of the disease to their children is a key concern.
- 2.10 Mitochondrial disease can be caused by faults in the genes within a cell's nucleus that are required for mitochondrial function or by faults within the small amount of DNA that exists within the mitochondria themselves, which is inherited from the mother. It is the latter form of mitochondrial disease² that could be avoided using two new medical techniques, termed pro-nuclear transfer (PNT) and maternal spindle transfer (MST). These are currently at the laboratory stage, with active research programmes going on in the UK and the United States.
- 2.11 Mitochondria replacement holds great promise for women with mitochondrial disease who wish to have children who are genetically related to them. They are at the cutting edge, both of science and ethics and are currently only permitted in research. They involve removing the nuclear DNA from an egg or embryo with unhealthy mitochondria, and transferring it into an enucleated donor egg or embryo with healthy mitochondria.

² The term 'mitochondrial disease' is used throughout to describe the spectrum of diseases or conditions caused by mitochondrial DNA mutations.

2.12 If mitochondria replacement were to be made available for treatment in the UK, it would be the first time that modified embryos were used to make a child. The resulting child will have inherited nuclear DNA from its parents and mitochondrial DNA from a donor. These changes to a person’s mitochondria will be passed down the maternal line through the mitochondrial DNA to the next generation.

The legislation and regulatory context

2.13 The Human Fertilisation and Embryology Act (1990) (as amended) (‘the Act’) governs research and treatment involving human embryos and related clinical practices in the UK. The Act only permits eggs and embryos that have not had their nuclear or mitochondrial DNA altered to be used for treatment. However, in 2008 the Act was amended, introducing new powers which allow for Regulations to be passed by Parliament that will allow techniques that alter the DNA of an egg or embryo to be used in assisted conception, to prevent the transmission of serious mitochondrial disease.

3 Timeline

3.1 The table below sets out the key milestones regarding mitochondria replacement, relating both to the HFEA’s considerations and other related developments:

2005	Research licence for pronuclear transfer granted
May 2010	The Authority’s Scientific and Clinical Advances Advisory Committee considers research developments
June 2011	The Authority’s Ethics and Law Committee considers ethical issues
April 2011	Core panel of experts, co-ordinated by the HFEA, reports to the Secretary of State for Health on the safety and efficacy of methods to avoid mitochondrial disease
January 2012	The Secretary of State for Health and the Secretary of State for Business, Innovation and Skills ask the HFEA to carry out public dialogue work
January 2012 – June 2012	Public dialogue and consultation work planning and preparation
July – August 2012	Public dialogue work takes place (deliberative public workshops and public representative survey)
September – December 2012	Open consultation runs (open consultation questionnaire, open consultation meetings and patient focus group)

December 2012	The Secretary of State for Health asks the HFEA to provide an updated view of the science to support the assessment of the efficacy and safety of MST and PNT
January 2013	Core panel of experts reconvened and call for evidence issued

3.2 In 2012, the Nuffield Council on Bioethics conducted a six-month inquiry into the ethical issues raised by “new techniques that aim to prevent the transmission of maternally-inherited mitochondrial DNA disorders” and concluded 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”³.

4 Public dialogue and consultation

4.1 The overall aim of the public dialogue and consultation work was to identify:

- The process of deliberation people use to form views on mitochondria replacement
- The differences between informed and uninformed public views on these techniques
- Interested stakeholders’ arguments for and against the use of the techniques
- Analysis of the ethical and regulatory issues involved

4.2 The public dialogue work was designed to gain an insight into the views of members of the public on the ethical and social issues associated with the techniques. The public representative survey provides an indication of the views of the UK population by the sampling of a representative group. The deliberative work focuses on how people’s views change over time and develop when introduced to different information. The outcomes of the open consultation questionnaire and open meetings provide an insight into those with a specific interest in the issues, as the participants were self-selecting the findings from these strands of the consultation are not necessarily representative. Each strand is summarised below:

Deliberative public workshops: Workshops were held in Newcastle, Cardiff and London in July 2012 and participants met twice in each location. Participants were recruited to represent a broad spectrum of age, gender, socio-economic status and family circumstances. Thirty

³ ‘Novel techniques for the prevention of mitochondrial DNA disorders: an ethical view’ Nuffield Council on Bioethics, June 2012

people were recruited for each location. The aim of this strand of the consultation was to explore public attitudes in depth, and to understand participant viewpoints as they become increasingly engaged with, and knowledgeable about, mitochondrial disease and mitochondria replacement techniques. The first meetings focused on helping participants to understand the techniques – PNT and MST – while the second events focused on the social and ethical issues relating to the techniques.

Public representative survey: In August 2012, just under 1000 face-to-face interviews were carried out with members of the public across 175 random locations. For each location, demographic quotas were set to ensure the sample was representative. The aim of the survey was to benchmark public opinion on: general attitudes towards medical research and genetic treatments; awareness of IVF and mitochondrial disease; views on the genetic treatment of mitochondrial disease; and attitudes to the regulation of genetic treatments.

Open consultation meetings: Two public meetings were held in November 2012. The first of these was in London (53 self-selecting attendees) and the second in Manchester (39 self-selecting attendees). The meetings were open to anyone wishing to attend and were advertised on the HFEA consultation website, through HFEA networks, and promoted to stakeholders and the public in a number of ways. At each meeting, a panel of speakers shared their knowledge and views with audience members. Panellists were selected to reflect a range of different perspectives and areas of expertise, and to provoke discussion amongst participants. The events involved a combination of small group discussions around particular issues, whole group debates, and discussion between and across the panel and the floor.

Open consultation questionnaire: A public consultation was held between September and December 2012. Self-selecting respondents were invited to consider a range of information presented on the consultation website, and to respond to seven questions using the online questionnaire. Responses made via email or post were also accepted while the consultation was open. A total of 1,836 responses were received, the majority of which via the consultation website. Respondents included stakeholder organisations, individuals with personal experience of mitochondrial disease as well as a large number of members of the public.

Patient focus group: One focus group was held with six participants. The aim of the focus group was to create a forum where people affected by mitochondrial disease, either directly or indirectly, could give their in-depth views on mitochondria replacement techniques. The group was comprised mainly of parents who had children affected by mitochondrial disease and someone who had been diagnosed with

MELAS⁴. A telephone interview was also carried out with someone unable to attend the focus group.

4.3 In addition to HFEA-led events, there were also a number of other relevant conferences and meetings which coincided with the consultation period, which included the following:

- Progress Educational Trust debate, 25 September 2012: 'Freeing Us from Our Cells: Avoiding Inherited Mitochondrial Disease'
- The Cheltenham Literature Festival, 14 October 2012: 'The Modern Family'
- Science London debate, 19 November 2012: 'The great mitochondria transfer debate'
- 'Sixth form conference 2012: Decoding DNA', organised by Wales Gene Park and Techniquet, 21 November: HFEA presentation on 'Medical Frontiers: Debating Mitochondria Replacement'
- The Wales Gene Park in association with Techniquet offered a free session to schools/colleges that allowed more than 80 post-16 students the opportunity to respond to the open consultation questionnaire.

4.4 An Independent Oversight Group was set up to ensure the consultation was balanced and accessible. The Group was made up of a diverse range of experts who each brought a different perspective to the project. The role of the Group was to help ensure the dialogue material was comprehensive, balanced and accessible to a lay audience. It also ensured that the engagement process was far reaching, accessible and targeted all relevant stakeholder groups. The terms of reference and membership of the Group are available on the consultation website⁵.

4.5 The HFEA also considered the practical implications of allowing these techniques within the existing regulatory regime. The report at Annex vii highlights some of the regulatory issues associated with permitting mitochondria replacement. In order to inform this report, following discussion of issues with the Authority's Ethics and Law Committee and Scientific and Clinical Advances Advisory Committee, we consulted with fertility sector staff and other professionals who have

⁴ Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes – abbreviated to MELAS.

⁵ <http://mitochondria.hfea.gov.uk/mitochondria/about-the-consultation/independent-consultation-oversight-group/>.

direct experience of working with patients and donors in the clinic environment, rather than the general public.

5 Safety and efficacy of the techniques

- 5.1 The Secretary of State for Health asked the HFEA, in February 2011, to carry out a scientific review to scope “expert views on the effectiveness and safety of mitochondrial transfer”. In order to carry out this task, the HFEA established a small panel, with broad-ranging scientific and clinical expertise, to collate and summarise the current state of expert understanding on the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. The HFEA submitted a report⁶ of the panel’s findings to the Department of Health on 18 April 2011.
- 5.2 The panel concluded that evidence available at that time did not suggest that the techniques are unsafe. Nevertheless, the report stated that these techniques are relatively novel, especially when applied to human embryos, and there is relatively little data to provide robust evidence on safety. The panel therefore urged that additional research be undertaken to provide further safety information and knowledge about the biology of human mitochondria. The panel proposed a (minimum) set of experiments that it felt were critical.
- 5.3 The report concluded that PNT and MST are potentially useful for a specific and defined group of patients whose offspring may have severe or lethal genetic disease, and who have no other option of having their own genetic child. These techniques may be preferable for patients with high levels of abnormal mitochondria for whom PGD is not suitable and more broadly, given that PGD can only reduce, not eliminate, the risk of transmitting mitochondrial disease.
- 5.4 Following these recommendations, a new mitochondrial research centre⁷ was been set up in Newcastle, funded by the Wellcome Trust, which is carrying out the research as set out by the panel.
- 5.5 Subsequently, and in anticipation of the outcomes of the public dialogue work, the Secretary of State for Health asked the HFEA, in December 2012, to provide an updated view of the science to support the assessment of the efficacy and safety of pro-nuclear transfer and maternal spindle transfer techniques, including any recently published findings and the extent to which the panel’s recommendations of April 2011 have been addressed. This latest report can be found at Annex

⁶ <http://www.hfea.gov.uk/6372.html>

⁷ <http://www.ncl.ac.uk/iah/research/centres/wellcome/>

viii. The panel concluded that although the results with the two techniques are promising, further experiments need to be done before introducing either into clinical practice to provide further reassurance with respect to efficiency and safety. The panel updated its advice regarding critical and recommended experiments.

6 Analysis and advice

6.1 As outlined in section 4, a number of different methods were used to gauge public opinion in order to identify the differences between informed and uninformed views and to carry out a qualitative analysis of the key themes and views. General attitudes towards assisted reproductive technologies have not been explored; the conclusions reached and the advice offered start from the basis of regulated IVF and associated techniques being acceptable.

6.2 The analysis outlined below points out where views relate either to that of self-selected or randomly selected participants. Table 1 in Annex i outlines the selection methods and the number, type and knowledge level of participants for each strand of the public dialogue and consultation.

6.3 The questions put to respondents throughout the different strands of the public dialogue focussed around the following themes:

- Modification of embryos
- Changing the germ line
- Implications for identity
- The status of the mitochondria donor
- Permissibility of the two mitochondria replacement techniques
- Models for regulation

6.4 In all the strands, participants were given the opportunity to express thoughts and views which did not necessarily fit into these themes.

General comments

6.5 Our advice to Government, based on the evidence collected through the public dialogue and consultation, is that there is general support for permitting mitochondria 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. Despite the strong ethical concerns that some respondents to the consultation expressed, the overall view is that ethical concerns are outweighed by the arguments in favour of mitochondria replacement.

- 6.6 We have therefore framed our advice in order to inform the Government's thinking, should it be minded to put Regulations forward to Parliament to make this possible. The advice we give below addresses the policies and safeguards that might guide those Regulations.
- 6.7 It is worth noting that there are also ethical issues associated with deciding not to seek Parliament's approval to permit mitochondria replacement. Such a move would restrict the reproductive options of people with serious mitochondrial disease, denying them access to a treatment which has clinical promise.
- 6.8 The public dialogue and consultation work we undertook was focused on gathering and understanding public views on the social and ethical issues associated with mitochondria replacement. We wanted to explore their views independent of any questions of safety and efficacy. In practice, however, people's views on these issues tended to be linked to questions of safety; this was a strong theme through all the responses. Sometimes, safety concerns become a proxy for concerns about ethical and social issues, which are often hard to express. On other occasions, support for mitochondria replacement dipped when the scientific evidence was less clear.
- 6.9 The public expects questions of safety to be settled by the experts and that new treatments will not be made available until there is a consensus that it is safe to move from the laboratory to the clinic. The vast majority of people trust that someone will have the expertise to decide when the techniques are safe enough to use in humans and that mechanisms for robust follow-up research will be put in place.
- 6.10 However, safety is not a black and white issue. In reproductive medicine particularly, it is not possible to be absolutely certain about the consequences of a new treatment until children are born. Although such uncertainties are often difficult to accept, the evidence we have collected suggests that the public do understand this in the context of mitochondria replacement. For them, provided that there is further assessment of the safety of mitochondria replacement before it is offered in the clinic, and that it is properly regulated, it would be reasonable to proceed.

Modification of embryos and changing the germ line

- 6.11 We sought views - through all of the public dialogue and consultation strands - about the fact that mitochondria replacement techniques result in changes to a person's mitochondria which will be passed down the maternal line through the mitochondrial DNA to the next

generation. If the child is female, that change will be passed to their child and so on.

6.12 This passing down of a change from one generation to the next makes mitochondria replacement a form of germline modification. Given that this has never been permitted on human embryos in a treatment setting before, it would clearly be a significant step and may raise important social and ethical questions. Does modifying the germ line affect a child's right to an open future? Is germline modification a step too far into a natural biological process?

6.13 It should be noted that some respondents did not accept the idea that mitochondria replacement is germline modification in the sense that it is commonly understood. Given that the two techniques involve replacing a woman's mitochondria with that of a donor, her mitochondrial DNA is not being modified, but rather substituted. Although this procedure might not be without its consequences for the embryo created, it is not the same as altering the genes with a person's mitochondria.

Positive attitudes towards germline modification

6.14 The public was largely relaxed about changing the germ line. When randomly selected members of the public were presented with information about what is currently known about the risks and uncertainty of changing the germ line, the majority felt that the benefits would outweigh those risks. Their views were largely shaped by the importance they placed on individual and personal choice for parents. When asked for their initial reaction, just over half of the public said they were 'very' or 'fairly' positive about changing the germ line, assuming the technique was shown to be safe.

6.15 Self-selected respondents expressing their views through the open consultation questionnaire and meetings held a broader range of views of this issue. Those in favour of the techniques felt either that the only implication of changing the germ line is the removal of terrible disease from a family, that the germ line would be changed for the better, or that any negative implications would be outweighed by the positive ones. Some felt that the germ line would not be changed significantly and parents could 'ideally' choose a mitochondria donor with a mitochondrial DNA sequence very similar to that of the mother.

Concerns around safety

6.16 However, the main theme running through responses to the open consultation questionnaire was the uncertainty and risk involved with introducing a new technique and the extent to which any consequences can be predicted. Others argued that if negative

implications are identified, the consequences (once introduced to the germ line) would be so severe and far reaching that even a small risk should be considered carefully.

- 6.17 Some measures can be taken to address, as far as possible, these safety concerns. The panel of experts commissioned by the HFEA to examine the safety and efficacy of the mitochondria replacement techniques recommended a set of experiments (critical and recommended) to be undertaken before the techniques can be deemed safe enough for use in human treatment. These include experiments which focus on the possible impact of changing the germ line, in particular the derivation and examination of human embryonic stem cell lines (then primordial germ cells) from embryos created from the techniques. The panel also thought that there is no evidence for any mismatch between the nucleus and any mtDNA haplogroup⁸, at least within a species ie, the nucleus from one person should be compatible with the mitochondria of another person.
- 6.18 The scientific panel (in the 2011 report and the 2013 update – see Annex viii) and respondents feeding into the regulatory considerations report (Annex vii) also recommended that families using these techniques be encouraged to take part in long-term follow-up studies in order to monitor any possible effects on children born and future generations. This was also a recommendation made by the Nuffield Council on Bioethics⁹, in its examination of the ethical issues arising from mitochondria replacement. There are arguments for both this being recommended as best practice and it being a formal condition of use of the technique. Commitment would be needed from patients and their children for a number of years and, although it's thought they would probably want to take part, there could be no obligation. Practical suggestions for how this follow-up research could take place and what data might be held by the HFEA are outlined in section 5 of Annex vii.
- 6.19 Another potential means of avoiding any effects of mitochondria replacement on future generations was raised as part of the consideration of regulatory issues (Annex vii). It was suggested that only male embryos be used in treatment, as changes to their mitochondria would not be passed onto the next generation. However, using sex selection after mitochondria replacement would expose the embryos to additional intervention.

⁸ A population group who share a common ancestor on the maternal line.

⁹ 'Novel techniques for the prevention of mitochondrial DNA disorders: an ethical view' Nuffield Council on Bioethics, June 2012

Societal attitudes towards those born

- 6.20 One concern raised by a small number of respondents related to the way in which society would view those born using the proposed techniques, or indeed those born to parents who decide not to use them. A small number of respondents felt that if the techniques are made available there will be pressure on parents to use them and discrimination against those who chose not to. They also raised a possible knock-on effect on attitudes towards disabled people more generally. Others were concerned that those born as a result of the techniques might be treated differently because of it or that it might be difficult for the child to come to terms with how they came into being. This question is explored in the 'Implications for identity' section below.
- 6.21 These arguments could be – and have been - made in relation to other methods for avoiding the transmission of genetic diseases, be that prenatal diagnosis or PGD. It is beyond the scope of this piece of work to explore in detail the extent to which these techniques have served to devalue people with genetic diseases, but it is not a concern which has been significant enough for society to decide to deny people access to prenatal diagnosis or PGD.

Slippery slopes?

- 6.22 The predominant ethical issue raised by those with concerns about mitochondria replacement was that making changes to the germline for this purpose could lead to other germline modifications or, at least, to those modifications becoming more acceptable.
- 6.23 There are two dimensions to the idea of what is commonly called the slippery slope argument. The first is technical: is it possible that a change in legislation to permit one technique could inadvertently open the door to other, less desirable, techniques? The second is more conceptual: does social acceptance of one technique make it harder to argue against a further, more controversial, development? More specifically, will there be a demand, in future, for modification of nuclear DNA (germline gene therapy) and, if yes, will it be more difficult to resist this because modification of mitochondrial DNA is permitted?
- 6.24 The technical dimension of the slippery slope argument can be addressed through careful regulation and monitoring. The Act already prohibits the use in treatment of eggs, sperm or embryos which have had their nuclear or mitochondrial DNA modified¹⁰. It also prohibits the

¹⁰ Human Fertilisation and Embryology Act 1990 (as amended), section 3ZA, paragraphs (2)(b), (3)(b) and (4)(b)

use in treatment of eggs and sperm which have been created *in vitro* and embryos which have been created through somatic cell nuclear transfer (SCNT) ie, cloning. If Regulations permitting mitochondria replacement were enacted, they would need to reflect these prohibitions in the parent legislation.

6.25 The conceptual dimension is more difficult to address because it relies upon a future possibility. We do not know whether there will be a demand in the future for nuclear DNA modification. It may be unlikely, particularly as PGD is an existing, viable option for the avoidance of genetic diseases which arise from mutations in the nuclear DNA. If a method of replacing nuclear DNA were developed, it is possible that the existence of mitochondria replacement would weaken any arguments against it. After all, when considering a novel technique, it is often helpful to look to existing, comparable techniques to guide our thinking about its acceptability.

6.26 However, the prospect of modifying the nuclear DNA would be a distinct development requiring a change to the law and, therefore, public and parliamentary debate. It would entail different risks and might be of interest to families who already have reproductive options available to them. Similar concerns were raised when SCNT was permitted for research purposes in 2001, with some arguing that this would lead to reproductive cloning. More than a decade on, however, opposition to reproductive cloning has not softened. Whilst concerns about slippery slopes should not be ignored, we can take comfort from the fact that the UK has a sufficiently developed system of regulation and tradition of public debate to minimise the risk of such concerns materialising.

Is this a form of cloning?

6.27 Many of the respondents to the public consultation questionnaire who expressed concerns about germline modification did so because they associated it with eugenics and cloning. One of the panellists in the London open consultation meeting argued that PNT is in fact cloning, because it involves the creation of an embryo which is then destroyed when its nuclear material is transferred to an embryo with healthy mitochondria.

6.28 However, the overwhelming majority of the audience challenged this view, arguing that although a similar methodology is used in PNT (the nuclear material is transferred from one embryo to another), it is not equivalent to SCNT. Any children resulting from PNT would have arisen from fertilisation and be genetically unique, not a genetic copy of an existing person. They would be the genetic child of the woman receiving treatment and her partner. Furthermore, PNT does not involve reprogramming cells or nuclei, as SCNT does, which is a

relatively inefficient process and associated with significant risks of abnormal development.

Future generations

- 6.29 Some respondents to the public consultation questionnaire argued that any change to the germ line is inappropriate because there is no way for those affected to give consent. This view is contradicted by a few respondents, who regard making choices for subsequent generations as a very ordinary part of being a parent.
- 6.30 The few patients we spoke to expressed very little concern about this issue, mostly commenting that a change to the germ line would be 'preventing the disease' and that this is, in essence, a good thing.
- 6.31 Although some respondents, particularly those responding to the public consultation questionnaire, expressed concerns about modifying the germ line, the prevailing view of the majority of participants across all strands of the consultation was that the positive outcome of both mitochondria replacement techniques – a healthy child, free of faulty mitochondria – outweighs the possible negative consequences of changing the germ line.

Advice

- 6.32 **In order to address concerns that permitting these techniques might open the door to other less desirable ones, the Authority advises that any Regulations allow for the specific germ line modifications proposed and consulted on (ie, the replacement of mitochondria) only. They should be drafted in such a way as to mirror the prohibition on modifying nuclear DNA in the Act and preclude in a treatment setting techniques which alter nuclear DNA, permit somatic cell nuclear transfer, or allow use of the techniques for anything other than avoiding serious disease.**
- 6.33 **In order to address concerns about the safety implications of changing the germ line, the Authority advises that mechanisms are put in place to allow for further recommended research (as outlined by the expert scientific panel in its report at Annex viii). The Authority also advises that licensed centres carrying out mitochondria replacement are encouraged to conduct follow-up studies on any children born as a result and on future generations.**

Implications for identity and the status of the mitochondria donor

- 6.34 Children born following mitochondria replacement will have inherited nuclear DNA from their parents and mitochondrial DNA from a donor.

This would be a first for medical science and it raises the question of whether the contribution of mitochondrial DNA from a third person will impact on the future child's sense of identity or on our concepts of parenthood.

Three parent IVF?

- 6.35 Some media reports have referred to mitochondria replacement as 'three parent IVF', based on the fact that three individuals would be contributing DNA to create a child. Views on this issue amongst randomly selected members of the public, gleaned through the deliberative public workshops, were relatively balanced, although a slight majority were not concerned about this issue.
- 6.36 Most rejected the 'three parent IVF' idea, arguing that mitochondrial DNA contributes little or nothing to a child's personal characteristics and the donor should not therefore be regarded as a parent. A few participants felt that the donation of healthy mitochondria would have helped a child to exist free from mitochondrial disease and that this should be recognised by giving the donor some sort of parental status. Views were shaped by using a range of comparisons and analogies, such as to adoption, organ donation, sperm donation, blood transfusion and bone marrow donation and by information on the amount and role of mitochondrial DNA in a person's genetic makeup.
- 6.37 Views of the public gleaned through the public representative survey tended to be more positive than negative about the idea of DNA from three people. When asked for their initial reaction to the fact that eggs or embryos resulting from new treatments would contain small amounts of genetic information from a third person, 44% said they were 'very' or 'fairly' positive, whilst 15% were 'very' or 'fairly' negative.

What status should mitochondria donors have?

- 6.38 Views on how mitochondria contribute to a person's identity, or sense of identity, are closely linked to how people think about the status of the donor and what, if any, information (eg, personal, medical or contact details) should be available to the future child. The public hold varied views on whether a child born from mitochondria replacement should be able to access information about the mitochondria donor involved. About a third of the deliberative public workshops participants held to the view that a child should have the right to know about their donor. By contrast, the number of participants that did not, increased during this process, from 31% at the start to 45% at the end.
- 6.39 The outcomes of the open consultation questionnaire and meetings demonstrate that self-selected respondents' views on the social and ethical implications relating to a person's sense of identity are also

closely linked to their view on the status of the mitochondria donor. Respondents who referred to the donor as a third parent usually expressed concern about implications for identity. The concerns expressed about identity can be broadly grouped together as follows:

- Children being confused by knowing that they carry DNA from three people (some drawing comparisons to adopted or donor-conceived children, arguing they suffer from identity issues)
- Children born from PNT feeling unhappy about the creation and destruction of embryos
- General concerns about the potential emotional and psychological damage which children could experience

6.40 Those who regarded the social and/or genetic connection between donor and child as less significant mostly said they were not worried about the implications for identity, giving the following reasons:

- There is no connection between mitochondrial DNA and identity
- The genetic information important for identity is held in the nuclear DNA
- Identity is determined by more than genetic factors
- Mitochondria donation is comparable to organ, bone marrow or blood donation, which are not seen as influencing the recipient's sense of identity
- The impact on the child will be similar to or less significant than in sperm or egg donation (participants at the open consultation meetings felt that children born from mitochondria replacement might be 'happier' in the knowledge that they are genetically related to both their parents)

6.41 Views expressed through the open consultation questionnaire and meetings showed a roughly equally split between those who felt that mitochondria donation is similar to gamete donation and those who see it as different. Those who felt it is similar commonly took this view because mitochondria replacement involves procreation or genetic transfer. Those that saw it as different from gamete donation often said "it won't determine the characteristics of individuals; it will simply prevent them from inheriting a genetic disease".

6.42 It is clear that people's views on the importance and role of mitochondrial DNA determines their views on the status of the mitochondria donor and how they conceptualise the relationship between the donor and the child.

6.43 It is noteworthy that where respondents see the donation as making a genetic contribution of mitochondrial DNA, which has significance over and above the avoidance of mitochondrial disease (and therefore affecting personal characteristics), they tended to infer a role for the donor in the child's life (suggesting disclosure of identifying information). In contrast those who see the donation as having a minimal impact, tended to infer no role for the donor.

Views specifically relating to PNT

6.44 Many respondents suggested that mitochondrial donation for PNT differs from other donations, and is unacceptable because it involves the creation of an embryo with no intention of it being carried to term or born.

6.45 Embryos are often disposed of in fertility clinics, either because they are no longer needed for a patient's treatment, they are found to be affected by a genetic condition following PGD or they are found to be the wrong tissue type following pre-implantation tissue typing. From this point of view, the creation and subsequent destruction of an embryo for PNT is nothing new. Embryos are also created during licensed research and are destroyed during or after the study.

6.46 However, PNT would represent the first time embryos were created, in a treatment situation, with no intention of being used (albeit that either their nuclear material or everything other than their nuclear material will go on to be used in treatment).

What information should be available?

6.47 When asked about different models for the disclosure of information about the mitochondria donor to the child, a substantial number of respondents to the open consultation questionnaire felt that no information, or only non-identifying information, should be disclosed. These respondents often saw MST and PNT as more like blood or tissue donation than egg or sperm donation, and so concluded that the donor's identity need not be disclosed.

6.48 Respondents who favoured a model allowing the donor's information to be disclosed along with their identity once the child reaches 18 years of age, tended to feel more strongly about the consequences and significance of mitochondria replacement. Their main concern was the medical, emotional or legal rights of children born through the procedure, which are sometimes explained as potential conditions determining what information should be disclosed. Several respondents felt it was important that donor consent should be sought to clarify which information would be disclosed if a donor's identity were to be disclosed to the child.

6.49 Patients felt that, as no nuclear DNA would be used from a third party, the techniques are more akin to blood or tissue donation. On this view, the child's sense of self would be inherited from their parents. They felt strongly that donors should remain anonymous and, moreover, that donors should want to, because no nuclear DNA is being donated.

What do stakeholders think?

6.50 Fertility sector staff and other professionals who attended a workshop to discuss regulatory considerations relating to mitochondria replacement came to a greater consensus. The majority view was that mitochondria donors are akin to tissue donors and should not be identifiable, as their genetic contribution is less likely to affect a person's identity than gamete donation.

6.51 Some stakeholders referred to the basis for removing gamete donor anonymity in 2005 as a useful starting point. This change was based on the idea that a donor-conceived child had a right to know who made them who they are. The main policy objective was to enable donor-conceived children to have access to information about their genetic origins, similar to the right that adopted people have, for both health and personal history reasons.

6.52 In contrast, some stakeholders argued that current scientific evidence suggested that the role of mitochondria is limited to energy production and therefore, in their view, does not impact on a person's physical characteristics. They felt that if mitochondria donors were treated on a par with gamete donors then this could have the perverse effect of devaluing the status of gamete donation. And they felt that children born through mitochondria replacement may be curious to find out details of their donor - just as the recipient of a tissue donation might - but that curiosity is not enough to warrant providing identifying donor information.

6.53 The majority agreed that there may be benefit for some donor information being held as the science surrounding the role of mitochondria could change, and that there is a possibility that it may later come to light that a donor suffers from a previously unidentified heritable disorder. This point was echoed at one of the open consultation meetings. As outlined in Annex vii, the European Union Tissue and Cells Directive already requires HFEA-licensed centres to ensure they are able to trace all tissues and cells from procurement to use and storage, including being able to identify the donor.

6.54 There was also a consensus at the workshop to discuss regulatory considerations that mitochondria donors should be able to find out the same type of information about their donation as is currently available to gamete donors (ie, the number, sex, and year of birth of any child).

However, it is worth noting that when gamete donors were anonymous, they were initially unable to find out this type of information about their donation.

Analogies with other types of donation

- 6.55 In summary, views regarding the implications for identity and the status of the donor are shaped by using a range of comparisons and analogies to other types of donation and by views on information regarding the amount and role of mitochondrial DNA in a person's genetic makeup. Irrespective of the views on these issues, people generally think that mitochondria donors would play an important role – whether just to help ensure a child is free from disease or further – which should be recognised. The most common view was that a child should not have the right to know about their donor; therefore mitochondria donors should be anonymous.
- 6.56 There is a wide spectrum of information provision relating to different types of donation in the UK and the basis for this varies – some involve the donor making a genetic contribution to a child, some involve the saving of a life. For example, legislation entitles children born following gamete donation to find out non-identifying information about their donor when they reach the age of 16, and then identifying information once they reach the age of 18. The non-identifying information can include a goodwill message and personal description of the donor (pen portrait)¹¹. Although not based in statute, it is established practice for bone marrow donors to be provided with the recipient's gender and general age group, and there are systems in place for information exchange (eg, messages of luck or thanks) and contact between the donor and recipient, if mutual consent is in place¹². These systems are managed by transplant centres and donor registries.
- 6.57 The balance of public views suggests that mitochondria donors should not be treated in the same way as gamete donors. Instead, they should be given a status similar to tissue donors. As mitochondria are thought not to be responsible for a person's characteristics (beyond their health)¹³, information about a mitochondria donor's personal

¹¹ 'For donor conceived people – What can you find out if you were conceived after 1 April 2005': <http://www.hfea.gov.uk/5526.html>

¹² Information from The Anthony Nolan Trust <http://www.anthonynolan.org/>

¹³ "The small mtDNA genome encodes 13 genes essential for the ETC [energy production], the remaining components being encoded by about 67 genes residing on chromosomes in the nucleus. The mtDNA also carries transfer RNA (tRNA) genes required for mitochondrial protein synthesis. Mitochondria have other important roles in cellular physiology, notably in programmed cell death (apoptosis) and steroid synthesis, although these depend on genes encoded entirely within the nucleus." http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

details and identity should only be disclosed on a basis of mutual consent through a system without a statutory standing.

- 6.58 As the techniques involve the creation of embryos *in vitro*, and transfer to a woman, information about treatment cycles involving mitochondria replacement will be kept on the HFEA Register. As the state of mitochondrial DNA can have significant health consequences, children born following mitochondria replacement and their parents should be able to access medical information about the mitochondria donor.
- 6.59 The Authority thinks that good practice regarding gamete donation (for standard donor conception) should apply equally to mitochondria replacement. For example, patients should be encouraged to be open with their children from an early age about how they were conceived and implications counselling should be offered both to the patients and donors. Best practice around information provision regarding unsuspected heritable conditions in donors should also apply to mitochondria donors. This would mean that if a treatment centre learns, through the birth of an affected child, that a mitochondria donor carries a previously unsuspected mitochondrial disease, then the donor should be notified (if they have indicated that they wish to be notified).
- 6.60 The Authority carefully debated whether a child born from mitochondria donation should be able to find out the identity of their mitochondria donor. Some Members thought that children should be entitled to this information to answer any questions or to satisfy any curiosity they may have about their origins.
- 6.61 It is likely that many mitochondria donors will be known to the patients, as there are anecdotal reports that many will be family members. This will need to be taken into account when implementing systems for parents and children accessing information about their mitochondria donor. It should be ensured that information access rights apply equally to cases of known and unknown donation, as is the case for standard donor conception.
- 6.62 The Authority is of the view that the welfare of the child is a key consideration and this might suggest that follow-up work should include social research into how children born from mitochondria replacement feel about their origins.
- 6.63 On balance, the Authority felt that mitochondria donation is unique and is not directly comparable to any other form of donation. As a result, mitochondria donors should be treated differently from gamete donors. In taking this position, the Authority does not feel that the status of

the gamete donor (for standard donor conception) should change, but should remain identifiable.

Advice

- 6.64** The Authority advises that mitochondria donors should have a similar status to that of tissue donors. Children born of mitochondria replacement should not have a right to access identifying information about the donor when they reach the age of 18.
- 6.65** Existing systems for ensuring the traceability of gametes and embryos used in fertility treatment should be used in mitochondrial donation:
- licensed clinics should keep records to ensure they are able to trace all mitochondria donations from procurement to use and storage, including being able to identify the donor
 - the HFEA should keep a register of treatment cycles involving mitochondria replacement, resulting children and medical information about mitochondria donors.
- 6.66** The Authority advises that any Regulations should facilitate arrangements for disclosure of non-identifying information to mitochondria donors and children born as a result of their donation:
- parents and children conceived of mitochondria replacement should be entitled to find out non-identifying medical information about mitochondria donors once they reach the age of 16 (either from a licensed centre or the HFEA)
 - mitochondria donors should be entitled to find out basic non-identifying information about children resulting from their donation eg, the number, sex and year of birth (either from a licensed centre or the HFEA).
- 6.67** Local systems, based on mutual consent, should be put in place (eg, by clinics, in collaboration with appropriate charities or professional bodies) to facilitate voluntary exchange of information and contact between mitochondria donors and children resulting from their donation. These systems could reflect the voluntary systems in place for exchange of information following tissue donation.

General views on the permissibility of the techniques

- 6.68 General views on the permissibility or acceptability of the techniques were sought through all of the public dialogue and consultation strands. Randomly selected members of the public remain broadly in favour of the two new techniques during the process of finding out about them and the possible ethical and social issues. The principal reason given for this was because the techniques give parents the opportunity to have healthy children who are genetically their own, which is not possible using current lawful techniques.
- 6.69 Views are shaped by information on the amount and role of mitochondrial DNA in a person's genetic makeup and great importance is placed on individual and personal choice for patients. Views are also largely dependent on the safety of the techniques - the risks involved, long term safety and success rates. This was demonstrated by the fact that when, during one of the deliberative public workshops, support for the techniques dipped following questioning of the robustness of information regarding the scientific basis. Where opposition was expressed it was mainly because PNT involves manipulating and disposing embryos; the latter concern is applicable to all assisted reproduction techniques.
- 6.70 We know, from the representative survey of the public, that people are generally positive about the benefits of medical research. Almost nine out of 10 are in favour of providing people with serious genetic diseases with 'healthcare and treatment to manage their condition' and the majority are positive about embryo testing during IVF. Over half are 'very' or 'fairly' positive about mitochondria replacement when asked for an initial reaction, even though about half feel that 'the application of medical research leads to unforeseen negative side effects'.
- 6.71 It is important to bear in mind that the majority of the general public are unlikely to be aware of mitochondria replacement, as only just over a quarter of people know what mitochondrial disease is – awareness being strongly correlated to levels of education.
- 6.72 The open consultation questionnaire, the result of which represents views from a self-selected sample, was unique in terms 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.
- 6.73 Proponents again focused on the benefits they could offer to parents, children or society more broadly, particularly the potential to avoid

disease and allow parents the opportunity to have a healthy child. Some felt that, if the techniques were possible, there is a clear ethical obligation to implement them. Such views were echoed strongly at one of the open consultation meetings and the patient focus group. Patients also stressed the importance of individual parents and families having the choice about whether or not to use these techniques, whilst also being aware that use of these techniques would be a medical first and there may be a degree of risk involved.

- 6.74 In conclusion, there is considerable public support for mitochondria replacement and the majority of concerns relate to the safety rather than ethical issues associated with the techniques. As outlined in section 5, a panel of scientific experts has advised on the safety of the efficacy of the techniques and concluded that there is no evidence to suggest that the techniques are unsafe. The panel has recommended further experiments which need to be done before introducing either into clinical practice.

Advice

- 6.75 **The Authority advises that mechanisms be put in place to allow for further consideration of the safety and efficacy of the techniques, in light of further research suggested by the expert scientific panel (outlined in its report at Annex viii), in conjunction with HFEA consideration of a licence application. The techniques should only be carried out in clinical practice once experts advise the HFEA that these results are reassuring.**

Licensing models and further regulatory issues

- 6.76 If the Government was minded to draft Regulations permitting mitochondria replacement, it is likely that there will need to be some criteria to specify when these techniques can be used, bearing in mind how comparable activities are regulated.
- 6.77 Under the existing regulatory regime, clinics have to demonstrate competence before they can provide particular treatments. This is particularly important in the case of specialist services like pre-implantation genetic diagnosis (PGD). It is difficult to see why the same principles should not apply to MST and PNT.
- 6.78 Taking this model, the HFEA would only allow specialist clinics to offer these treatments if they had the relevant expertise and equipment to do so. We asked the public and stakeholders for their views on regulatory models, ie, when and how should patients be able to access mitochondria replacement and who should decide when the techniques are used. In all the consultation strands participants

argued that strong regulation is essential if the techniques are licensed for clinical use.

6.79 The following possible options for accessing treatment were discussed:

- Clinics and their patients to decide when mitochondria replacement is appropriate in individual cases.
- The regulator to decide which mitochondrial diseases are serious enough to require mitochondria replacement and, just for these diseases, permit clinics and patients to decide when it is appropriate in individual cases.
- The regulator to decide which mitochondrial diseases are serious enough to require mitochondria replacement and also decide, just for these diseases, when it is appropriate in individual cases.

6.80 Of the self-selected respondents to the open consultation questionnaire who expressed a preference for a particular regulatory model, close to half opted for the first system. This would involve clinics and individual patients being free to make a decision about whether or not to use mitochondria replacement in a particular case, without any regulatory stipulations regarding which conditions or cases it may be suitable for. This preference was often associated with a view that a central regulatory body may lack sensitivity to individual circumstances and a feeling that individual patients should be empowered to choose the best option for their own families. This was a view echoed strongly at the open consultation meeting in Manchester.

6.81 However, a similar number preferred an option that includes a role for the regulator. The majority of these respondents expressed a preference for a broad regulatory framework outlining those diseases that are deemed serious enough to warrant mitochondria replacement but which provides flexibility for patients and clinicians to reach individual decisions within this framework. This is currently how the HFEA authorises the availability of PGD for certain genetic conditions.

6.82 A minority of respondents expressed a preference regulatory a model in which a central regulator would maintain responsibility for making decisions about particular cases. This is currently how the HFEA regulates use of pre-implantation tissue typing (PTT). Reasons given in support of a regulatory framework, which were also echoed at the open consultation meeting in London, include:

- it would provide a buffer against abusive profiteering and a wide

range of 'slippery slope effects' or illegal use, which might otherwise ensue

- a central regulator would promote fairness by making sure that all applications for treatment would be judged according to the same criteria
- it could ensure that priority is given to those at risk of passing on the most severe forms of mitochondrial disease

- 6.83 The views of those who object to mitochondria replacement being offered as a treatment, under any circumstances, have not been outlined here.
- 6.84 Views of randomly selected members of the public, gleaned from the deliberative public workshops and the public representative survey, were mixed. Over a third of respondents (36%) favoured the option of couples being allowed to decide for themselves. A further 39% favoured some kind of involvement from a regulator, whilst one fifth (20%) favouring an expert regulator deciding on case-by-case basis (20%). A similar proportion (19%) favoured an expert regulator approving clinics, with medical specialists deciding who to offer it to (19%).
- 6.85 Deliberative workshop participants who supported regulation tended to do so because of the uncertainty of the risks associated with the techniques and the possibility of techniques becoming available in other countries with less stringent regulatory regimes (ie, where the techniques could be misused). Almost half of participants favoured some kind of regulation (43% at the start of the day to 48% by the end of their discussions). Although a large proportion of participants felt that couples themselves should make the decision about treatment (in consultation with their doctor), without the involvement of a regulator, reflecting the view that individual and personal choice for parents is paramount. This view rose from 35% at the start of the day to 40% by the end.
- 6.86 As outlined in section 3 of Annex vii, it is useful to make comparisons to other comparable techniques that have a basis in the HFE Act 1990 (as amended), in particular, the testing of embryos cannot take place unless the Authority is satisfied:
- “...that there is a significant risk that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition”
- 6.87 To ensure that the Authority is satisfied, authorisation processes are in place for PGD and PTT:

- In the case of PGD, embryo testing clinics apply to the HFEA for permission to test for a particular genetic condition which they believe meets the relevant criteria in the Act (as noted above). If approved, any clinic with the appropriate licence can test for this condition in the embryos of patients who they deem appropriate. PGD has already been approved for a number of specific and named mitochondrial diseases (mostly caused by nuclear DNA defects) and it is a reproductive option for some patients at risk of passing on mitochondrial disease. The HFEA processes the majority of applications for PGD within approximately four months; this process includes seeking views of a peer reviewer.
- In the case of PTT, the HFEA approves embryo testing on a case by case basis. Only conditions that have already been approved under the authorisation process for PGD can be considered for PTT. In making its decision, the HFEA will consider a referral from the child's treating clinician to ensure that the treatment is necessary and all other options have been considered. Applications are processed within 30 working days (approximately six weeks).

6.88 Some stakeholders, who expressed their views at a workshop, favoured mirroring the PGD approach, suggesting that the HFEA should approve conditions, and leave the judgement as to which patients receive the treatment with clinical staff.

6.89 However, the majority of workshop delegates agreed that the complexity and variable basis of mitochondrial disease, as outlined further in section 3 of Annex vii, would suggest an approach in which licensed clinics decided who should receive this treatment, according to criteria in the Regulations. This would determine if the disease was likely to develop into a serious condition, and whether mitochondria replacement is suitable for the patient. Fertility clinics would need to liaise with genetics teams and mitochondria specialists, to investigate how a disease may manifest (taking into account the level of unhealthy mitochondria and a patient's family history), before deciding the most appropriate treatment.

6.90 The majority agreed that the decision on who should receive the treatment should be made by clinicians, rather than the HFEA, and that patient referral from mitochondria expert centres (of which there are currently three¹⁴), could be worked into any new authorisation process.

¹⁴ <http://www.mitochondrialncg.nhs.uk/>

6.91 In conclusion, a large proportion of the public favour some kind of regulatory oversight of access to mitochondria replacement. Bearing in mind past experience regarding the introduction of new comparable techniques into clinical practice, it seems unlikely that Parliament would allow mitochondria replacement techniques to be permitted without a degree of oversight of access to these services.

6.92 The complex and variable nature of mitochondrial disease suggests a case-by-case approach to decision making. However, given the assurances of regulatory oversight that Parliament is likely to want, we suggest that mitochondria replacement techniques be authorised in a similar way to PTT. However, in order to future-proof any Regulations, such oversight might be better expressed in HFEA guidance and processes, rather than on the face of the Regulations themselves. Further detail regarding possible mechanisms for this is outlined at Annex vii.

Advice

6.93 **The Authority advises that any Regulations permitting mitochondria replacement, should:**

- **ensure the techniques are only used to avoid serious mitochondrial diseases in cases where clinical specialists have deemed it to be appropriate**
- **require the HFEA to approve each licensed centre wishing to offer mitochondria replacement as a clinical treatment**

6.94 **In order to future-proof the Regulations, they should provide flexibility for the HFEA to design a process for approving the use of mitochondria replacement in individual cases. Given the novel nature of these treatments, we recommend that the HFEA approves the use of mitochondria replacement on a case-by-case basis. It may be appropriate in the future to move to a more localised, clinic-based approval process.**

6.95 A number of other regulatory issues were considered, some of which may require further consideration should mitochondria replacement be permitted in clinical practice, which are outlined in section 7 of Annex vii.