Office for Public Management

Medical Frontiers: Debating mitochondria replacement

Annex V: Open consultation meetings: London and Manchester

Report to HFEA

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OPM
252B Gray's Inn Road,
London WC1X 8XG

tel: 0845 055 3900
fax: 0845 055 1700
email: info@opm.co.uk
web: www.opm.co.uk

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Author	Grace Trevelyan
Quality assurance by	Tim Vanson
Contact details	
Main point of contact	Robin Clarke
Telephone	0207 239 7871
Email	RClarke@opm.co.uk

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Executive Summary

The Office for Public Management (OPM), in partnership with Forster and Dialogue by Design, was commissioned by the Human Fertilisation and Embryology Authority (HFEA) to conduct a multi-method research and engagement project looking at the possible social and ethical issues relating to two techniques for the avoidance of mitochondrial disease: pronuclear transfer (PNT)[1] and maternal spindle transfer (MST)[2].

As part of this research and engagement, OPM ran two open consultation meetings which were held in November 2012 in London and Manchester. A broad range of channels were used to promote the meetings and participants were self selecting. A total of 53 people attended the London meeting and 39 people attended the Manchester meeting.

The meetings were designed to expose participants to the full spectrum of possible views about mitochondria replacement techniques and to provide a forum for informed debate about the issues. After being provided with an overview of the scientific and contextual details, participants had the chance to engage in small group discussions structured around the broad social and ethical themes, before posing questions to an invited panel in a whole group debate.

Key messages from London

The London meeting was characterised by a dynamic exchange of views on a range of social and ethical issues. The diverse set of perspectives and reference points that the audience members drew on to illustrate their points made for an animated and often heated debate. However, in terms of the balance of opinion throughout the discussions, there were more comments from people who were supportive of the techniques compared to those who opposed them.

Participants expressed different views around matters such as the moral status of embryos. While it was pointed out by several participants that the destruction of embryos already routinely takes place in IVF treatments, for some members of the audience the need to treat embryos with respect played a crucial role in determining their attitude towards mitochondria replacement. In the light of this, the feeling that embryos were being used as *'building blocks'* to create *'better'* embryos was viewed as particularly contentious. At several points during the meeting mitochondria replacement was likened to cloning. This fed into discussion of a potential slippery slope effect, a prospect which was a prominent concern for some but dismissed as highly unlikely by others.

There was also a great deal of discussion about the relative importance of *'genetic relatedness'*, with some identifying this outcome as a tangible advantage of the new techniques deemed important from the patients' and parents' perspective, while others put forward the view that it was a *'relatively minor'* benefit when compared with the potential risks

[1] Pronuclear transfer involves transferring the pronuclei from an embryo with unhealthy mitochondria and placing them into a donor embryo which contains healthy mitochondria and has had its pronuclei removed. A pronucleus is a small round structure containing nuclear DNA seen within an embryo following fertilisation. A normal embryo should contain two pronuclei, one from the egg (maternal pronucleus) and one from the sperm (paternal pronucleus).

[2] The maternal spindle is a structure within the egg containing the mother's nuclear DNA. Maternal spindle transfer involves transferring the spindle from the intended mother's egg, with unhealthy mitochondria, and placing it into a donor egg with healthy mitochondria.

and consequences which may not currently be understood. A number of different ways of conceptualising the role of the mitochondria donor were put forward at the London meeting. Some members of the audience spoke about the *'insignificance'* of the tiny amount of genetic material that any child born following the use of mitochondria replacement techniques would inherit from the donor. This line of argument was backed up with reference to distinctions between mitochondrial and nuclear DNA, with the former being seen playing no role in determining identity. Others complained that this DNA centric approach was reductionist and contended that the role of the donor should not be down played. A number of participants supported the techniques in principle but suggested that any children born following mitochondria replacement should have the right to access information about the mitochondria donor.

Key messages from Manchester

While a diversity of perspectives were aired at the London meeting, the Manchester meeting was characterised by a strongly 'pro' mitochondria replacement tone. Throughout the proceedings, particular weight was given to the views expressed by those who had been personally affected by mitochondrial disease. For the participants who expressed their support for the techniques, two important and recurring themes underscored many of the arguments:

- There is an ethical imperative to intervene to prevent suffering where the capability to do so exists.
- Individual families should be empowered to make an informed choice about whether or not mitochondria replacement is right for them.

A great deal of floor time was devoted to safety considerations and scientific details, particularly in relation to mitochondrial function and its perceived lack of significance in determining characteristics. For many participants the balance and role of mitochondrial and nuclear DNA appeared to be fundamental when reflecting on and discussing the ethical significance of the new techniques. Having considered the available scientific evidence many participants concluded that terms such as 'three parent families', which have sometimes been associated with mitochondria replacement, were highly misleading. Most of the participants did not feel that mitochondria replacement would have a significant negative effect on a child's sense of identity, and some suggested that from a child's point of view it would present less identity issues than egg donation. The participants were also very influenced by the findings of a relevant report by the Nuffield Council on Bioethics[3]. Many agreed with the report's conclusion that if mitochondria replacement techniques can be proved to be safe then they do not present any significant ethical concerns.

[3] Nuffield Council on Bioethics, 2012. *Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review.* London: Nuffield Council on Bioethics on Bioethics

Available at: http://www.nuffieldbioethics.org

1. Introduction

Mitochondria are present in almost all human cells. They are often referred to as the cell's 'batteries' as 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.

There are many different conditions that are linked to mitochondrial disease. They can 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 disease preventing the transmission of the disease to their children is a key concern.

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. It is the latter form of mitochondrial disease that could be avoided using two new medical techniques, termed pro-nuclear transfer (PNT)[1] and maternal spindle transfer (MST)[2] which UK researchers are working on.

These techniques 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.

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 currently prevents the clinical use of these techniques (or any other technique that involves genetic modification of gametes and embryos to treat patients). However, in 2008 the Act was amended, introducing new powers which enable the Secretary of State for Health to permit techniques which prevent the transmission of serious mitochondrial disease. The Secretary of State for Health and the Secretary of State for Business, Innovation and Skills asked the Human Fertilisation and Embryology Authority (HFEA) to seek public views on these emerging techniques. On considering advice from the HFEA the Government will decide whether to propose regulations legalising one or both of the procedures for treatment.

The HFEA, together with the Sciencewise Expert Resource Centre[4], therefore 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 the techniques. The project consisted of five strands:

1. Deliberative public workshops
2. Public representative survey
3. Patient focus group
4. Open consultation meetings
5. Open consultation questionnaire

This research provides the evidence base that will inform the HFEA's advice to the Secretary of State.

The two **open consultation meetings** were held in November 2012 in London and Manchester. The objectives of the meetings were:

[4] The Sciencewise Expert Resource Centre (Sciencewise-ERC) is the UK's national centre for public dialogue in policy making involving science and technology issues

1. To provide participants with detailed information about the context and science behind the development of mitochondria replacement techniques.

2. To highlight some of the key issues which have been raised in support of and in opposition to the proposed procedures, thereby exposing participants to a range of different perspectives.

3. To provide a forum for informed debate about key social and ethical issues associated with mitochondria replacement techniques.

4. To allow the HFEA to gather information about people's views on the matter, and to observe the ways in which they respond to particular arguments.

This report provides an overview of the themes and issues that were raised by the panellists and audience members at each of the meetings.

2. Meeting design

The open consultation meetings were designed to engage a wide range of different stakeholders and members of the public. At each of the events the audience was made up of a group of self selecting people. The meetings were widely promoted and interested parties were targeted through the following channels:

- Email invitations were sent to the HFEA stakeholder database (patient groups, government departments, relevant charities, foundations and trusts, academics, scientists and research groups).
- Meetings listings were placed on the main HFEA website, the mitochondria consultation website and an independent meetings websites.
- The HFEA's Twitter account was used to promote the meetings. Others who followed the HFEA then spread the word by retweeting the invitation.
- Email invitations were sent to people who had registered to complete the online consultation, to people who had signed up to receive email alerts about the consultation, and to people who had attended the Deliberative public workshops in London, Cardiff and Newcastle.
- Oversight group members and panellists were asked to make the members of their relevant networks aware of the open invitation for the event.
- The meetings were promoted in HFEA publications and during speaking slots at public meetings.
- The press were informed about the consultation and meeting dates.

Participants were asked to state any affiliations when they registered to attend the meeting. This information was used to allocate participants with a mix of backgrounds and areas of expertise to each table.

A panel of speakers was invited to both consultation meetings to share their knowledge and views on mitochondria replacement with the audience and answer specific questions from participants. As mentioned above, one of the key objectives of the open consultation meetings was to highlight the most contentious issues surrounding mitochondria replacement and expose audience members to the full range of views. The panellists in both Manchester and London were therefore carefully selected for the range of different perspectives and areas of expertise that they brought. It was hoped that their divergent outlooks would help to

stimulate discussion from members of the audience. It should be noted that the HFEA did not endorse any of the views put forward by the panellists.

Format and structure of the meetings

Each of the meetings began with a short animated film that introduced audience members to the background and science behind the two techniques; this film had also been used at the Deliberative public workshops and was available on the consultation website. The scientific information was complemented by brief presentations from each of the panellists explaining the science and outlining some of the issues and views that exist in order to trigger discussion and elicit participants' views. This was followed by an opportunity for participants to discuss the key issues in small groups for approximately 30 minutes. The discussions were structured around five pre-identified themes[5] and participants were provided with handouts for each (see Appendix 1). The themes discussed were:

a. Avoiding mitochondrial disease
b. Affecting future generations: changing the germ line
c. Implications for identity: DNA from three people
d. The status of the mitochondria donor
e. Regulation of mitochondria replacement

So as to ensure that each of the themes was covered, each table began by discussing a particular theme before being invited to choose a remaining theme, or themes, that they would like to cover. Most of the small groups discussed two themes within the allocated time. An audio recorder captured the dialogue on each table, and key points were recorded by a self-selected 'scribe'. The key points to emerge in this part of the meeting are discussed in the 'Small group discussion' section below.

The third and final part of the open consultation meetings was a 55 minute 'question time' style debate, where audience members were able to air their own views, seek clarification on particular issues and direct questions or comments at panellists. The content of this third section has been thematically discussed. The agenda for both meetings can be found in Appendix 2.

Meeting summaries

London

The London meeting took place on 13th November 2012 and was held at Hamilton House in Euston. It was chaired by **Professor Bobbie Farsides**, professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School.

The panel was comprised of:

> **Dr Helen Watt:** Senior Research Fellow at the Anscombe Bioethics Centre. The Anscombe Bioethics Centre, an independent charity, is a Roman Catholic academic institute that engages with moral questions arising in clinical practice and biomedical research.

[5] The five themes used to structure table discussions are broadly in line with the themes and questions that were used in the other strands of the consultation and deliberative public workshops.

Alison Maguire: Research Director at The Lily Foundation. The Lily Foundation is a patient charity set up to support those affected by mitochondrial disease and supports research into such disorders. Alison provided a patient perspective having had a child who suffered from a mitochondrial disease.

Professor Mike Parker: Professor of Bioethics and Director of the Ethox Centre at the University of Oxford.[6]

Hannah Darby: Senior Policy Manager at the HFEA with an understanding of the scientific underpinnings of mitochondria replacement techniques.

The London meeting was attended by **53** people. This included a broad mix of stakeholders many of whom were highly engaged and knowledgeable about the key issues. This included:

- Representatives from research and medical charities
- Students of law and healthcare ethics
- Patients directly affected by mitochondrial disease and their parents
- Clinicians and academics working in relevant fields.

A wide range of topics were discussed in great detail, and the conversations which took place throughout the evening aired many of the pertinent social and ethical arguments for and against the use of two new mitochondria replacement techniques.

Manchester

The Manchester meeting was held on 22nd November 2012 at The Studio, a conference venue located in central Manchester. The proceedings were chaired by **Professor Margot Brazier**, a Professor of Law at the University of Manchester.

The panel was comprised of:

Dr Shamima Rahman – Reader in Paediatric Metabolic Medicine at the UCL Institute of Child Health within the Department of Clinical & Molecular Genetics.

Josephine Quintavalle: The Founder of 'Comment on Reproductive Ethics' (CORE), a public interest group focusing on ethical dilemmas surrounding human reproduction.

Dr Marita Pohlschmidt: Director of Research at the Muscular Dystrophy Campaign. The Muscular Dystrophy Campaign (MDC) is the leading UK charity focusing on muscular dystrophy and other related conditions. MDC have supported the scientific community to develop treatments and cures.

The Manchester meeting was attended by **39** people including a number of participants who were learning about mitochondria replacement for the first time.

[6] Arrangements had been made for a geneticist to sit on the panel but due to unforeseen circumstances she was unable to attend on the day. For this reason, Mike Parker and Hannah Darby stepped in to add to the range of knowledge on the panel.

As well as several clinicians and academics working in relevant fields, at the Manchester meeting there was good representation from:

- Families affected by mitochondrial disease
- Sixth form and university students - including several from a nearby sixth form as well as students on the Healthcare Ethics and Law MSc course at Manchester University.

In terms of the balance of opinion, the large majority of views expressed were supportive of the techniques and the mood in the room was more consensual when compared with the London meeting. For this reason the chair and panel played a role in encouraging participants to consider and debate the range of social and ethical issues around the introduction of the new techniques.

3. Small group discussions

a) Avoiding mitochondrial disease

London

The participants in London used the small group discussion time to debate the ethical implications of the science behind mitochondria replacement. Questions were asked about whether eggs would be *"cloned"* in the first technique (MST) and embryos *"killed"* in the second (PNT). Some participants expressed greater reservations about the latter techniques and explained that they had more concerns about manipulating an embryo than an egg.

The participants expressed a range of views about the extent to which the proposed mitochondria replacement techniques differ from existing approaches such as pre-implantation genetic diagnosis (PGD) and prenatal diagnosis (PND). In addition to this, a number of participants were insistent that options such as adoption and IVF with a donor egg were '*perfectly good*' ways for carriers to avoid passing mitochondrial disease onto their children. Some put forward the view that it would be *"better to focus on treatment for children who have already been born with mitochondrial disease"*. It was also suggested that there were '*perfectly valid'* forms of treatment available to sufferers, but no specific examples of these were given.

The conversations also revealed contrasting interpretations of the '*benefits*' that would be brought about by the introduction of mitochondria replacement techniques. The chance to offer a greater degree of choice to *"traumatised"* families with a history of the disease was put forward by some participants as a progressive step forward. Others, however, were not convinced by this argument and suggested that while the risks to children born as a result of the *"invasive manipulation of embryos"* would be high, the associated *"social"* benefits of allowing genetic parenthood were *"relatively minor*.*"* This line of argument was also to find expression during the debate.

Manchester

Many of the participants in Manchester felt that the lack of an available cure for mitochondrial disease created an imperative for exploring other options. It was noted that one course of action available to affected families was to *"just have a child and see"* but it was felt that this option was *"not a particularly good one*.*"*

The participants attributed particular significance to the fact many affected families appeared to support the introduction of mitochondria replacement techniques. It was suggested, for example, that the *"voices"* of those who have been *"most affected"* ought to be listened to. One participant who had lost a child to mitochondrial disease gave a rationale for his own perspective on the matter explaining *"I do not want any parent to go through what we have been through."*

The idea that affected families should have the right to make a personal judgement about whether or not to take advantage of mitochondria replacement techniques was repeated several times. On one table, for example, it was argued that:

> *"It is question of choice. A sufferer should not have to wait for postnatal options if prenatal choices are in development."*

Participants also wondered about the efficacy of gamete donation and questioned whether donors were screened for mitochondrial disease themselves. The possibility that mitochondria replacement techniques are *"just about scientists wanting to push boundaries"* was raised, but this point was closely followed by the suggestion that scientific curiosity is not a problem as long as it ultimately helps people. There was also repetition of the argument that the severity of the disease meant that there is a clear case for permitting the new techniques:

> *"There is a compelling reason why so much time and energy has been invested in these new techniques."*

b) Affecting future generations: changing the germ line

London

This issue elicited a number of strong responses which can be grouped into three broad categories.

The first type of response took the view that the germ line would not be significantly changed. It was argued that parents could *"ideally"* choose a mitochondria donor with a very similar mitochondrial DNA sequence to the intended mother. This line of argument was backed up with reference to scientific evidence that mitochondrial DNA variation is limited, particularly in individuals of the same ancestral origin (e.g. European, sub-Saharan African).

The second type of response was based on the idea that the intergenerational effects of mitochondria replacement techniques would be significant and negative. It was argued, for example, that mitochondria replacement *posed "serious risks to societies and individuals."* There was some concern about the *"unforeseen"* effects of mitochondria replacement, with participants on one table concluding that *"we are playing with something unknown and the full risks need to be understood."* On a separate table, meanwhile, statements were made about the danger of *"taking human embryos lightly."* Terms such as *"unnatural"*; *"genetic manipulation"* and *"violating the integrity of nature"* were also used.

A third type of response came from individuals who felt that mitochondria replacement techniques would have a significant but positive impact on future generations. These respondents felt that it would be *"more irresponsible"* for society to allow families with a history of the disease *"to have more children and face the risk of more affected children being born."*

A variety of views were recorded in response to the question of whether parents have the right to make a decision that will impact their child's future. Participants on one table felt that parents have a *"full right"* to make such a decision since the alternative is to risk their children *"suffering and living a short life."* Others agreed and argued that any child born following mitochondria replacement would be *"unlikely to think what their parents had done was wrong"*. Reference was made to the fact that parents are commonly expected to make decisions that will affect their children's future health and development, and it was suggested that there is *"little difference"* between mitochondria replacement and the choice to vaccinate a child. Others, however, claimed to disagree with the concept of making a life changing choice on behalf of an unborn child and suggested that there was some tension between the best interests of the child and the best interests of the parents.

Manchester

In Manchester this theme attracted less discussion. Those participants who did cover the subject felt that the new techniques would be changing the germ line *"for the better"* by creating a *"healthy cell."* They focussed on the fact that mitochondria replacement would not change characteristics and while they acknowledged that the impact on future families would be huge, they felt that the impact would be entirely positive: *"the child will go on to pass on healthy mitochondria and children will be free from mitochondrial disease."*

c) Implications for identity: DNA from three people

London

Many of the participants were comfortable with the concept of a child having genetic information from three people. On a number of tables the discussion dwelt on mitochondrial DNA's perceived lack of relevance in determining identity, with some participants concluding *"it's just like changing the battery in your laptop."* A participant at a separate table expressed a similar sentiment, explaining *"I don't think of my mitochondrial DNA in the same way as my nuclear DNA."* Others, however, suggested that genetic science may '*change*' and mitochondria may be discovered to have a greater impact on determining characteristics than has hitherto been assumed.

When discussing alternatives such as using a donor egg it was suggested that children born following mitochondria replacement may be *"happier"* in the knowledge that they are genetically related to both their parents. This comment introduced the possibility that mitochondria replacement techniques could raise fewer identity issues than existing procedures.

Manchester

Three tables used the small group discussions as an opportunity to debate the role played by genetics in determining identity. One table posed the question *"what do we mean by parents?"* On another table participants asked *"what is identity?"* and suggested that in the light of practices such as adoption, our concepts of family are socially constructed. On a third table, however, it was argued that while *"ideas about the significance of genetics"* may vary, genetic relatedness still holds great weight in society. A related area of concern was the influence of the media. The view that *"sensationalised headlines"* surrounding the technique might themselves have an impact on the way children thought about their identity was expressed.

Several references to the Nuffield report[3] were made and these were linked to the view that mitochondria replacement poses *"no ethical problems"* with regards to identity. As was the case in London, it was hypothesised by some participants that egg donation, where all maternal DNA is sourced from a donor, would result in *"greater implications on a sense of identity"* than mitochondria replacement, where most of a child's maternal DNA would be inherited from their mother. This point was developed further in the debate section of the Manchester meeting. On one table, however, it was claimed that adopted children '*crave*' information about their natural parents, a statement which could be interpreted as suggesting that children born following the use of the techniques would be at risk of experiencing a similar sense of curiosity about their mitochondria donor.

One participant whose son had been affected by mitochondrial disease shared the belief that the child's mitochondrial DNA had shaped his life but had not affected who he was. The implicit suggestion was that if he had had healthy mitochondria he would have been the exactly the same person but would simply not have been forced to cope with the debilitating symptoms of the disease.

Some participants explained their views by drawing comparisons between the new techniques and more familiar medical procedures such as blood transfusions and organ transplants, neither of which are commonly thought to have a significant impact on identity. It was noted that one potential counter to the argument that mitochondria can be likened to other transferable human tissue is the fact that mitochondria are present in every human cell. This point, however, was balanced by repetition of the accepted view that mitochondrial DNA does not play a role in determining an individual's identity or phenotype. Indeed, discussion about mitochondrial function emerged as an important theme and appeared to be of paramount importance in determining an individual's ethical stance on the matter. Some participants identified clear communication as a priority, arguing that explaining the science would help to distinguish mitochondria replacement from separate areas of genetics, such as cloning. They felt that the impact of mitochondrial disease on patients and their families should also be widely articulated.

d) The status of the mitochondria donor:

London

A number of participants in London expressed the view that records should be kept about mitochondria donors. This was linked to a suggestion that although there is currently no scientific indication that mitochondrial DNA has a determining influence of characteristics, this area of genetic science is *"new and could change"*. Some indicated that those willing to donate their mitochondria were *"making a choice to be a part of a child's life"* and referenced the importance of being *"upfront about what donor-ship means."*

It was claimed that having access to information about *"where you come from"* is recognised as a fundamental human right. This observation was followed up by one suggestion that any individual born following mitochondria replacement should be able to find out about their *"third parent"* and their *"genetic origins"* in the same way that children born from egg donors are able to access donor information once they reach the age of 18.

Manchester

While the participants in Manchester agreed that 'three parent' terminology was confusing, they had different views of exactly how the status of the mitochondria donor should be

understood. Most were emphatic that there *"is no relationship"* between the child and the donor, while a minority maintained that mitochondria donors were making a huge commitment.

A number of the participants acknowledged that people may want to know the *"origin of their mitochondria"*, but the general consensus within the small groups was that donors should be *"non-traceable."* There was concern that if mitochondria donors could be contacted it would not only *'limit donation'* but it would alter the public's perception of the process by fuelling the misleading notion of 'three parents'.

The opportunity for donors to give informed consent based on honest information about what would happen to their eggs was considered to be essential. Participants acknowledged that this was *"uncharted territory"*, and some followed up on earlier points by suggesting that mitochondria donation could not be satisfactorily compared with either tissue or egg donation, but should instead seen as existing in a category of its own.

e) Regulation of mitochondria replacement

London

The theme of the regulation of mitochondria replacement attracted less detailed and varied discussion compared with others however some clear messages emerged. Participants in London attributed a high degree of importance to regulation and felt that strict controls should be put in place to safeguard against illegal use of the techniques. Some felt that regulation was necessary because of a potential slippery slope effect and warned that *"once you breach a principle such as allowing hybrids it creates a precedent."*

On one table there was a reference to *"a lack of confidence in the HFEA"* as a result of unspecified cases in which licences were granted to clinics where research wasn't *"up to scratch"*. In light of this it was deemed essential that any regulator should earn a reputation as being trustworthy.

There was also some suggestion that mitochondria replacement programmes should be structured in a way that ensured treatment priority would be given to those at risk of passing on the most severe forms of mitochondrial disease.

Manchester

As in the London meeting this theme attracted less detailed discussion. Participants in Manchester again argued that regulation was essential within experimental science. It was suggested that mitochondria replacement should be administered and monitored in a similar way to egg donation and that licenses should be reserved for special HFEA approved centres.

The participants also recognised the need to regulate spending on clinical trials since it was felt that healthcare budgets could not absorb unlimited costs.

4. Whole room debate

a) Modifying and using embryos

London

A number of audience members and panellists at the London meeting held strong and opposing views about the ethical implications attached to the modification and use of human embryos. As such, this issue constituted an important and recurring theme which surfaced at a number of different points during the debate session.

The belief that human embryos must be treated with respect was forcefully articulated by one audience member:

> *"The HFEA is here because we believe there is something special about human embryos and sperm which we don't accord to mouse or monkey sperm and embryos…The important thing which we, as a society, have got to be very careful about, is not to begin treating embryos as instruments for us to do to what we like."*

The suggestion that there is a need for the HFEA to take into account '*important moral differences*' between the two proposed mitochondria replacement techniques (MST and PNT) was voiced early on in the debate. The implicit suggestion was that PNT, which relies on the creation of embryos that will never be implanted, is more ethically objectionable than MST, where the egg containing unhealthy mitochondria is not fertilised.

One of the strongest objections to PNT was the argument that embryos were being created and destroyed to provide 'spare parts'. Dr Helen Watt referred to the embryo as a 'child' and expressed grave concerns about the fact that one embryo is *"deliberately conceived solely to extract its pro-nuclei."* She used the following metaphor to elaborate on this point:

> *"This is no more prevention than killing a 20 year old with a condition so that 20 year old can't have children or grandchildren with that condition. That is not prevention but is eliminating someone."*

The above statement rests on the assumption that human embryos share the same human worth as adult human individuals. This line of argument prompted Alison Maguire of the Lily foundation to point out that *"we already destroy embryos in IVF, it is common place."* Dr. Watt's response was that *"two wrongs don't make a right".* ' She expressed further objections to the PNT technique, in terms of the deployment of embryos it would involve whenever it was used:

> *"It is bad enough that we destroy embryos through IVF but here the embryos are building blocks for new embryos."*

The discussion of embryo modification acted as a catalyst for a subsequent exchange of ideas about the likelihood that mitochondria replacement would leave other areas of genetic science more vulnerable by creating a 'slippery slope' effect. One audience member captured this concern by commenting that:

> *"In society we get used to certain things happening and we say, we are doing that already, so it would be alright to do this."*

Another participant voiced their disquiet at the wording of the 2008 amendment to the Human Fertilisation and Embryology Act, which they felt had created a *"loophole"* which *"could allow changes in nuclear DNA"* as part of future efforts to prevent other varieties of mitochondrial

disease. However, a fellow audience member offered a degree of reassurance on this matter by pointing out that such techniques wouldn't be needed because there are other legal diagnosis options available to people with the type of mitochondrial disease which is caused by mutations in the nuclear DNA.

Others at the meeting were keen to challenge the 'slippery slope' argument altogether by pointing out that the techniques would have a very specific application. One audience member who identified themselves as belonging to a patient campaign group explained:

> *"We are trying to tackle human suffering and misery in a way that has an ethical basis with carefully tested scientific research which might benefit no more than a few thousand people who may wish to choose to take advantage of this."*

Another audience member then attempted to demonstrate holes in the 'slippery slope' argument by pointing out that:

> *"The difference between these proposed techniques and other forms of genetic manipulation, is that in this instance the DNA molecules are intact, they are transferred whole – they are not interfered with."*

This prompted a response from Dr Watt who contended that:

> *"The same argument could be given in a few years time for Dolly style cloning. Where we are not doing anything to the nucleus, we are leaving it completely intact."*

The above comment led to a member of the audience to accuse Dr Watt of *"making pejorative statements all the time"* and complained that she was not paying due attention to *"the suffering of the children who are affected by this."*

Manchester

The use of embryos proved to be a less contentious issue at the Manchester meeting than it had been in London. For example, the logic behind 'slippery slope' arguments were swiftly dismissed by an audience member who contended that *"the same has been* [been argued about] *IVF, the same has been done with pretty much anything*."

Josephine Quintavalle voiced a number of concerns about the new techniques. For example, she implied that she had greater ethical objections to PNT than MST, when she announced:

> *"I've got a statement here from Professor Herbert where she is clearly opting for the embryo rather than the egg… It does seem that egg manipulation is being put into the back ground now."*

Dr Rahman confirmed that while experts were continuing to work on developing both techniques, in her view it did appear that PNT was the safer option. No follow up comments were made in relation to this matter.

Josephine later returned to this issue and described PNT as the *"disaggregation"* of one embryo to create a *"better"* embryo:

> *"Some will argue that when you are combining two embryos you have to accept that both of those individual embryos could have been implanted and developed into children so you're sort of getting into a big identity question for any offspring of 'who am I?"*

However, no similar sentiments were expressed by any audience members. This suggests that this particular line of argument did not achieve a great deal of traction with the Manchester audience.

b) Concepts of identity

London

A large section of the London audience was keen to learn more about the properties of mitochondrial DNA. Early on in the proceedings the panellists were asked how confident scientists are able to be about the role played by this genetic material. An answer to this question was provided by Hannah Darby of the HFEA, who spoke of a *"body of evidence"* which has informed the widely accepted scientific view that the function of mitochondrial DNA is to encode cell structures involved in energy production. She did acknowledge, however, that there are other [unknown] factors to take into account including the interaction between the mitochondrial and nuclear DNA. A number of audience members went on to add to this discussion by providing contextual scientific detail. For example, one participant ventured that the reason mitochondria replacement feels *"new"* and *"difficult"* is *"the DNA-centric and reductionist way we understand things."* They expanded on this point by suggesting that phenomena such as the human genome project and the widely known importance of DNA to forensic identification processes have helped to promote a *"fairly simplistic account of the role of DNA":*

> "*We were all taught that it is a very special thing and… it's very important for our personality… but mitochondria are not really part of that story."*

Later on another audience member explained that while nuclear DNA sequences are unique to each individual, people of similar ancestry often have mitochondrial DNA sequences that are *'essentially identical*.*'*

This scientific interpretation, however, was not popular with everyone in the room. Dr Helen Watt reminded audience members that *"mitochondria… do help us trace our maternal life history."* She drew on this fact to suggest that mitochondria play a *"very important social role"*, adding *"this is how we know about people thousands of years ago to whom we are connected by this maternal line."*

Indeed, Dr Watt went on to posit the view that mitochondria replacement could have wide reaching implications for identity. She made the suggestions that a child conceived using PNT, where two original embryos were used as 'building blocks', would not be the true genetic child of the couple but would be constructed artificially from two separate *'children*' – the couple's embryo and the donor embryo – whose genes the "*PNT child*" would inherit:

> *"Is that helping a parent conceive their own child? You are using their child and another woman's child to produce another child entirely."*

Some sympathy for this kind of thinking was expressed by other members of the audience (see sections on the modification of embryos above and the role of the donor below). Dr Watt also described PNT as a form of cloning, by which she meant cloning from an earlier embryo, where the resulting embryo would "*have no genetic parents in the normal sense*." She argued that *"we need to look at whether we are replacing parenthood by these techniques*.*"*

Manchester

At Manchester there appeared to be a broader degree of consensus amongst audience members about the function of mitochondrial DNA. For example, the following statement from an audience member went entirely unchallenged:

> *"We are not changing characteristics, we are not changing those things that make you, 'you' what we are changing is energy metabolism."*

It is important to note that a great deal of weight was attributed to the views of this particular participant (Participant A) who identified herself as *"one of these young women"* at risk of passing mitochondrial disease onto their children. Throughout the meeting she spoke eloquently about the dilemmas she faced and her personal experience of living with mitochondrial disease. She made a broader point about identity by referring to a newspaper article which had previously been referenced by Josephine Quintavalle and which recounted the stories of sufferers under headlines such as 'My Mother Loves Me the way I Am':

> *"Well, my mother loves me the way I am…but would she love it if I didn't have the disease? Of course she would! And would I love to have a child who didn't have this disease? More than anything"*

This statement achieved wide spread expressions of approval and was followed by enthusiastic applause.

Later on in the debate a Josephine Quintavalle's suggested that it would be morally preferable to accept a healthy embryo created using a donor egg (see discussion in regulation and choice section below) by echoing a point that had been made by several participants during the small group discussions:

> *"Doesn't that just leave the child with identity issues? … Don't they know their identity better if their DNA is from their parents who are going to raise them, rather than a donor egg?"*

A large portion of the audience seemed to agree that mitochondria replacement would actually *"resolve"* rather than *"generate"* identity dilemmas by making it possible for children who would otherwise have been born using donor eggs to be genetically related to both their parents. In fact, a number of questions from the floor were accompanied by laughter and phrased in a way that poked fun at the assumed irrationality of identity-based objections. One participant, for example, made the following point:

> *"There is talk of three parents, but the alternative is to have a debilitating illness. Why is that such a problem of mixed identity? Can you not explain to them that its not that you've got three parents, your main identity is your mum and dad, we've just altered a little bit of how the process works, your body works, and we've stopped you having a debilitating illness."*

Against this back drop Josephine Quintavalle found little support from the floor for her view that *"this is about creating human life. It's considerably different from blood donation."*

c) Safety

London

Safety was a prominent concern amongst audience members in London. Indeed, the very first question to the panellists was a request for more detail about the safety implications of

the proposed techniques. Hannah Darby of the HFEA responded by telling the audience members that there were robust tests being conducted. However, as she pointed out, this has to be balanced with the reality that *"we won't be sure* [that the techniques are safe] *until the first child is born*."

Some participants would go on to draw the conclusion that the potential health risk to *"the child"* and any subsequent decedents, combined with the broader notion or *"risks to society"* were so great as to outweigh any of the associated 'social' benefits (see discussion of this issue in the Regulation section below).

Manchester

A considerable portion of the debate section at Manchester was devoted to safety matters. Much of this was instigated by Josephine Quintavalle, who structured her safety related concerns around a *"similar"* American experiment which, she explained, had also involved an *"egg to egg kind of process."* She pointed out that this research was ultimately shut down due to a poor safety record and used this to argue that the process of combining genetic material from two different women *"is potentially very complicated and dangerous."* She added that *"to find that a process that we think is going to cure mitochondrial disease is actually causing other problems*' would be '*the last thing we would want to do*."

Dr Rahman later provided some more information about the experiments that had taken place in America, which had been designed to help *"older women"* have their own children. She agreed with Josephine that those procedures had not been safe but then went on to explain that the abnormalities in that case had been a consequence of duplication of mitochondria populations. She reassured the audience that when it came to developing the proposed techniques, the UK experts were carrying out rigorous tests to *"make sure there is as little carry over of the mitochondrial DNA from the genetic mother's structure, the nucleus, as possible"* and that they did not believe this would pose a problem.

Participant A contributed to this part of the discussion by arguing:

> *"Of course there are risks…this is what happened with the first organ transplant. This is what happened with the first egg donation. More information should be found. More research should be done, but that doesn't mean that it shouldn't move forward."*

She then added that she would be prepared to take on some of that risk herself:

> *"If they need to do an experiment, fine, I'll sign up. If people need to be aware of it, fine, I'll be aware of it and go for it."*

Dr Pohlschmidt agreed that a safe, regulated environment was very important, especially to the patients who she was there to represent. However, she argued that there is always going to be *"that scary step towards doing it in a human being."* This, she felt, was necessary for progress. For this reason she insisted that it remained imperative that individuals who volunteer for clinical trials *"are given the right information in a language that they understand."*

The chair of the debate summed up by concluding that while all could agree that it was necessary to identify a threshold of acceptable risk, it was unlikely that they were ever going to agree about where the line should be drawn.

d) Affecting future generations

London

At the London meeting this issue was tackled head on by an audience member who asked *"Are we experimenting with future generations and is this ethical?*"

Dr Watt responded in the affirmative to the first part of the question and in the negative to the latter part. She expressed a concern that *"this will go on and on and on if we make a mistake."*

It was also Dr Watt who introduced the matter of couples using new means of creating children who might then have moral objections to those means; *"There could be moral questions asked by a child conceived this way."*

This point prompted a strong response from one audience member who argued that *"as parents we are making decisions for our children all the time, some of which they may not agree with."* This audience member went on to express the view that *"as long as we did it in their best interest, fine. We can do no more than that*."

Alison Maguire concluded this part of the debate by drawing on her personal experience:

> *"I think it would be very easy, in the context of an affected family, for a child who was conceived this way to understand why this happened*."

Manchester

The impact that mitochondria replacement could have on future generations was very much the focus of the arguments put forward by Josephine Quintavalle at the Manchester meeting. She pointed out, for example, that *"there will be a lot of invasive charting of their health and their wellbeing etc… we need to look at the issue of children's rights from this perspective."*

She also expressed a concern that if something were to go wrong the child would have "*every right*" to ask:

> "W*hy did this happen to me?"* and *"Why have I got a slightly different type of genome from everybody else which I'm going to be passing on to my children as well?'"*

Participant A strongly objected to this suggestion and argued:

> *"I have no problem saying to my child 'because I love you'… and why has this happened to you? So you could live a long, healthy, fulfilling life without the obstacles that I've had to deal with."*

Other audience members agreed that the affect on future generations would be positive based on the potential for *"stopping next generations coming through with this illness*."

e) The status of the mitochondria donor:

London

In London a number of audience members took the opportunity to speak about the role of the mitochondria donor. Their comments highlighted some interesting and diverse perspectives.

The first participant to ask a donor-related question enquired whether the terminology surrounding the donation process is accurate:

> *"Is it fair to call healthy mitochondria "donated" if the majority of mitochondrial proteins are encoded by the nuclear genome?"*

An answer to this question was provided by a fellow audience member who agreed that *"the mitochondria are not really donated it is just the mitochondrial DNA"* since mitochondria are made up of about 1500 different proteins *"of which all but 13 are coming from the mother who is going to give birth to these embryos."*

The second audience member who raised the issue of donor status took specific objection to the type of reasoning seen above. This participant complained that *"The discussions we are hearing are about DNA, DNA, DNA!"* and warned that such a narrow focus amounted to one of the *"classic pitfalls of reductionist biology"* adding *"they are not just a mitochondria donor, they are donating the body of the embryo."*

A third audience member spoke out in support of the formation of an HFEA mitochondria donor register. They acknowledged that many children will not wish to find out information about the person who had donated mitochondrial DNA but felt that those who did wish to learn this information should have the option to do so.

Manchester

This issue did not feature in the Manchester debates apart from in passing. Participant A mentioned that donors should be protected and respected, while Josephine Quintavalle expressed the view that any children born following this procedure should have access to detailed information about how they were conceived.

f) Regulation and Choice: Who decides?

London

In relation to the question of 'who decides?' Mike Parker, who was sitting on the London panel in his capacity as an ethicist, suggested that consideration ought to be given to the interdependencies between choice, cost and justice. Patient-centredness and autonomy are morally important, he argued, but this cannot be separate from the *"ethics of who should be paying for this."* He suggested that if the technique was to be privately funded then its use could legitimately be seen as matter of individual choice in a rather limited sense. He did point out, however, that a solely private funding structure would create an unjust situation whereby a potentially valuable preventative tool was only available to wealthy, well-resourced individuals or those willing to go into debt.

Some members of the London audience, however, were sceptical about the suggestion that individual parents should be given the power to choose whether or not to use the techniques. They questioned the motivations behind using mitochondria replacement as opposed to other options including adoption and egg donation. For example, one participant asked the panel whether *"genetic relatedness"* should be considered a medical or social benefit. This point was picked up on by another audience member who identified himself as a biologist and argued that if you were to take a rigidly scientific risk-benefit analysis approach to the problem, according to which medical benefits are granted a greater degree of significance, then the answer was self-evident:

> *"The unknown risks* [to the child and future generations] *are not justified by a relatively minor* [social] *benefit* [genetic parenthood]."

It was Mike Parker who provided a counter-narrative to this. He pointed out that *"genetic relatedness matters to many people. It is not trivial for everyone*." Later in the debate he built on this point by arguing that *"medicine is about providing social benefits as well as physical benefits*." He argued that *"the question of whether such interventions should be available cannot be 'dodged' by the use of the label 'social'."*

Manchester

As had been the case in the small group discussions, the notion that individual families should have the right to make a choice about whether or not to take advantage of the techniques was very influential throughout the Manchester debate. Participant A persuasively argued that:

> *"What we are saying is that there is the potential to have a different choice, and I think that if you don't agree with it then you don't have to have it, nobody would force you… If you do, and these techniques do exist, well then I think it's unethical not to offer them. In my opinion, that is where there is a real ethical question."*

At one point Josephine Quintavalle challenged the notion that the ultimate decision should rest with prospective parents by suggesting that the desire for parents to be genetically related to their children "*at all costs"* was overshadowing the welfare of the child. This comment was followed by some expressions of disagreement from members the audience.

She went on to suggest

> *"If the idea is to have 'my child' but we want it healthy, I'm suggesting we look to cure it afterwards*."

This prompted a number of comments to the effect that developing preventative techniques and continuing to search for treatments are not mutually exclusive endeavours. Josephine Quintavalle maintained that it is worth posing the following question:

> *"Why sacrifice a perfectly healthy embryo….why not simply use that embryo without manipulation*?*"*

Dr Rahman pointed – to signs of agreement around the room – that for many of the patients that she sees genetic parenthood remains a very important issue, meaning that using a donor egg would be unacceptable.

Dr Pohlschmidt built on her fellow panellists point by explaining that for many women with mitochondrial disease one of the hardest things to reconcile themselves to is the decision not to have their 'own' child for fear of passing on the mutation, even though they are in fact fertile. She ventured that this scenario was quite different from that faced by women who accept egg donation because *"they have come to terms with the fact that they are infertile*."

The issue of *international* regulation was raised by Josephine Quintavalle. She pointed to the United Nations Educational, Scientific and Cultural Organisation's Universal Declaration on the Human Genome and Human Rights and referred to *"considerable concern worldwide"* about mitochondria replacement. One audience member dismissed these points: *"They're only laws, they're only words; they can be changed'*, adding *"we need to change in order to move forward."*

It was suggested by another audience member that it would helpful to hear the wording of the international legislation that allegedly prohibited mitochondria replacement. This was provided, and was followed by a point from the chair about the ambiguity of the wording in

such declarations, an observation which was repeated by an audience member who went on to explain:

> *"I also don't believe that because there is a diversity of international opinion that should change our opinions and what our progress with this is."*

g) Putting the issues in context

London

At the London meeting there was a desire to gauge the scale of potential uptake if mitochondria replacement techniques were to be made available. The question of whether the '1 in 5000' incidence statistic[7] represented too many people to treat was put to the panellists. Alison Maguire predicted that there would not be a huge flood of people coming forward because not everyone who has access to the technique will want to use it.

Following a further question from the audience member, Alison Maguire confirmed that many families do not find out that a mother is a carrier of the mutation until they have a child who is affected by the disease. Indeed, this is exactly the scenario that had confronted her. Alison added that a screening programme for all women of child bearing age would be a *"huge expense for a disease which is relatively rare"* and suggested it was therefore unlikely to take place. Certain sections of the audience found this difficult to accept and several follow up points were made in support of a wider screening programme: *"One affected person can highlight that many people are carrying the gene because you can just look at the maternal line."*

Alison Maguire responded to subsequent questions about treatment options by explaining that there were a number of projects looking for ways to treat mitochondrial disease, but that the complexity of the conditions posed significant obstacles. She concluded by saying that: *"treatment options are not forthcoming so prevention is the way forward."*

Manchester

Similar queries about the scale of the problem were raised in Manchester. Dr Rahman explained that the '1 in 5000' statistic had been derived from a number of separate epidemiological studies which had corroborated each other, and confirmed that this number related to people who were already aware that they had the disease.

An impassioned question about screening was put to the panellists:

> *"What have we got in place that is going to identify these young women that don't even know they've got the disease? How are we going to find these people? We have to find them otherwise we can't stop it."*

Whereas cost had been identified as the main prohibiting factor in London, Dr Rahman explained that a broad screening of the population was not an option because of sociological considerations:

> *"It is not felt to be ethical to screen for a disease for which we have no treatment."*

[7] As set out in the HFEA's open consultation website http://mitochondria.hfea.gov.uk/mitochondria/

This prompted a strong response from an audience member who had lost his son to the disease:

> *"But for these young women who become pregnant, unwittingly, there is another life that's ruined."*

Participant A spoke up at this point, explaining:

> *"I understand why you can't do wide screening but for me that is why these developments are truly so amazing."*

Appendix 1 – Discussion handouts

Participants were provided with one to two page information handouts for each of the five discussion areas.

Handout 1 - Implications for identity: DNA from three people

What is this?

Children born from these techniques will have inherited nuclear DNA from their parents and mitochondrial DNA from a donor. This is a first for medical science and some people may have concerns that it raises the question of whether it will impact on the future child's sense of identity.

Why is this potentially an issue?

It is our genes, together with environmental factors, that shape our physical characteristics and are therefore important to identity. Genes are long interlinked chains of our nuclear DNA. Mitochondrial DNA, which comprises a very small proportion of total DNA, is thought only to play a role in energy production and is not responsible for any personal characteristics or traits. So, on the one hand a mitochondria donor might be thought to be similar to a bone marrow or blood donor. Donors could be seen as contributing to the recipient's health and wellbeing while not influencing the recipient's sense of identity.

On the other hand, some people feel that although mitochondrial DNA comprises a very small portion of genes, this is still vital to our genetic makeup. After all, mitochondria can have a devastating effect on health if they do not function normally. Also, as mitochondria are passed down through generations they can be used to trace maternal ancestry. Some people therefore have concerns about the effect mitochondria replacement may have on a person's sense of self and what makes them who they are.

Questions for consideration:

- How do you feel about this issue? Why?
- What do you think are the most important points raised in relation to this issue?
- To what extent do these issues impact on your views on whether these new techniques should be used in treatment? Why?

Handout 2 - Regulation of mitochondria replacement

What is this?

Mitochondria replacement would only ever be legalized in the UK if it were deemed safe enough by expert consensus. The HFEA as the regulating body, would need to decide how to monitor and regulate use. They would only allow specialist clinics to offer these treatments if they had the relevant expertise and equipment to do so. They would also need to consider the following questions:

- When and how should patients be able to access mitochondria replacement?
- Who should decide when mitochondria replacement is used?

Why is this potentially an issue?

There are a number of options for how treatment is offered. For example, clinics and their patients could decide when mitochondria replacement is appropriate in individual cases.

Another alternative is that HFEA could 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.

Yet another option is that HFEA could 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.

Factors which may affect which mitochondria replacement technique (PNT or MST) is used include whether couples have an ethical preference for one technique over the other and whether one technique is shown to be safer or more efficient that the other.

Questions for consideration:

- How do you feel about this issue? Why?
- What do you think are the most important points raised in relation to this issue?
- Who do you think should decide whether and when patients can use mitochondria replacement techniques? Why?

To what extent does this issue impact on your views on whether these new techniques should be used in treatment? Why?

Handout 3 - Affecting future generations: Changing the germline

What is this?

Any changes to a person's mitochondria will be passed down to the next generation, and if the child is a daughter, to the one after that and so on. This is referred to as affecting the female germ line.

Germ line modifications have never been permitted on embryos before and this may raise important social and ethical questions.

Why is this potentially an issue?

Some people are concerned that modifying the germ line would affect the child's right to an 'open' future. This means that a decision is made, on a future child's behalf. In this case, the decision would be to ensure the future child and their future children are free from disease.

Many people think that a life free from disease is a more 'open' one than a life with mitochondrial disease. However, the decision to perform mitochondria replacement is an irreversible choice not just for the future child, but future generations too.

Because of this some people are concerned that mitochondria replacement is tampering with nature. They feel that germ line modification is a step too far. Others feel that, because we already intervene in other areas of reproduction and medicine (for example, in vitro fertilisation) it doesn't make sense to apply this argument to mitochondria replacement.

Questions for consideration:

- How do you feel about this issue? Why?
- What do you think are the most important points raised in relation to this issue?
- To what extent do you think that parents have the right to make a decision that will impact on their child's future like this? Why?

- To what extent does this issue impact on your views on whether these new techniques should be used in treatment? Why?

Handout 4 - Avoiding mitochondrial disease

What are current options for avoiding mitochondrial disease?

If a woman has mitochondrial disease, there is a risk that when she tries to conceive naturally the disease may be passed onto her child. This is because mitochondrial DNA is inherited from the mother. People in this situation have a number of options available to reduce the chance of this happening. However, there are advantages and disadvantages associated with each option:

Adoption: A woman, or couple, may choose to adopt a child rather than conceiving naturally. This will mean that they do not risk passing on mitochondrial disease to their child. However, the child will not be genetically related to either of the intended adoptive parents.

IVF with donor eggs: In vitro fertilisation (IVF) is a process in which an egg is surgically removed from a woman's ovaries and fertilised with her partner's sperm outside the body. The subsequent embryo is later placed in the woman's womb. People affected by mitochondrial disease may choose to have a child through IVF with eggs donated by a woman who does not have mitochondrial disease. However, the child will not be genetically related to the intended mother.

Testing embryos: An alternative to IVF with egg donation or to adoption is to create embryos using IVF and then test them to see if mitochondrial disease is present. Any embryos without the disease would then be transferred to the intended mother. This technique is called preimplantation genetic diagnosis (PGD). PGD gives people the opportunity to reduce the chance of having a child with mitochondrial disease. However, it cannot guarantee a child free from disease. This is because an egg can either contain mitochondria that are all unhealthy, or it can contain some healthy and some unhealthy mitochondria. When choosing an embryo using PGD, embryos with the lowest number of unhealthy mitochondria can be chosen, which reduces the chance of having an affected child. However, there is still a chance of the disease developing.

Testing of foetuses: Another option is to have a child naturally, and then to test the foetus during the pregnancy to find out whether the child will be born with a particular disease. This technique is called prenatal diagnosis (PND). If a foetus is diagnosed with mitochondrial disease, the prospective parents could decide to continue the pregnancy or could opt for a termination of the pregnancy. Parents could be offered IVF with PGD (pre-implantation genetic diagnosis) followed up by PND to confirm if the child will be born free of the disease. As with PGD, it cannot guarantee that the baby born will be unaffected. Even if a girl is born and appears healthy, she may herself carry a proportion of unhealthy mitochondria, which could lead to her children being affected by mitochondrial disease.

What are the new techniques for avoiding mitochondrial disease?

Scientists have developed two new methods that could help to preventing mothers from passing on mitochondrial disease to their children (and their children's children and so on). If approved, these techniques would take place within licensed clinics and may allow children to be born free from mitochondrial disease. These techniques would be preventing mitochondrial diseases caused by faults in mitochondrial DNA, but not those caused by faults

in nuclear DNA. Scientists are still working on these techniques to find out which will be the safest and most effective.

Pro-Nuclear Transfer (PNT): Immediately after fertilisation, an embryo has two pro-nuclei. These are the parts of the egg and sperm that hold the nuclear DNA. Pro-nuclear transfer (PNT) involves removing pro-nuclei from an embryo with unhealthy mitochondria immediately after fertilisation. The pro-nuclei, are then transferred into a donated embryo. This donor embryo contains healthy mitochondria, but has had its own pro-nuclei removed.

Maternal Spindle Transfer: A maternal spindle is a structure within a woman's egg that contains only the mother's half of a child's nuclear DNA. The father's half of the nuclear DNA comes from the sperm. Maternal spindle transfer (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 healthy donor egg with healthy mitochondria (from which the donor's spindle, and therefore the nuclear DNA, has been removed).

How are the new techniques different from the current options?

At the moment, modifying an embryo is allowed in scientific research, if that research has been deemed to advance knowledge and treatment into fertility or serious diseases. Embryos created for research are discarded before they reach 14 days old and are never transferred into a woman. If these techniques were to be made available for treatment, it would be the first time that modified embryos were used to make a child.

The proposed treatments are limited to mitochondrial DNA replacement and would not involve modifying the nuclear DNA.

Some people have concerns that modifying embryos for health reasons is the first step on a slippery slope towards designer babies. The concern is that, once modifying embryos to avoid mitochondrial disease is accepted, this will be extended to approving embryo modification for more minor conditions or for cosmetic traits such as height, hair and eye colour. Others however argue that is not the case, since these further steps would require new research, techniques and further changes to the law before they were possible.

Some people are not concerned at all about a slippery slope if this means that more genetic diseases can be avoided or treated before birth. They suggest that it is a slope worth sliding down. Others consider that slippery slope arguments are meaningless because almost all forms of technology can be used for good or bad and that we solve this through adopting social norms and regulations.

Questions for consideration:

- How do you feel about the current options available to avoid mitochondrial disease? What are their benefits? And drawbacks?
- How do you think the new techniques are different from those that are currently being used? How are they better? How are they worse?
- How do you feel about the fact that the new techniques involve the modification of embryos? Why?

Handout 5 - Status of the mitochondria donor

What is this?

If mitochondria replacement techniques become legal, law makers would have to decide how to classify the mitochondria donor. They would need to consider the status of the donor and what, if any, information about the donor (e.g., personal, medical or contact details) should be available to the future child.

Why is this potentially an issue?

Currently, people donate many different types of tissue for medical purposes. Each one of these donation processes has very specific regulations regarding the rights of the donor.

People who donate their sperm or eggs can only do so if they agree to be identifiable to any future child. A donor conceived child can also get medical and personal information about the donor and is able to contact them once the child reaches the age of 18. This is based on the idea that donor conceived children have a legitimate interest in the person or people who contributed to their genetic makeup through supplying half of their nuclear DNA.

On the other hand, people who wish to donate blood, bone marrow or other tissue do so anonymously. This is partly because donation of non-reproductive tissue is not seen as key to a person's sense of identity – although in bone marrow donation, some donor DNA is also transferred to the recipient.

People's views on how mitochondria contribute to a person's identity, or sense of identity, may affect what they think about the status of the donor. Some people may feel that the child should have the option of accessing as much information as they like about the donors. Others may feel there is no obligation on the donor to reveal their identity and that forcing donors to do so may put them off donating.

Questions for consideration:

- How do you feel about this issue? Why?
- What do you think are the most important points raised in relation to this issue?
- How should we think of the relationship between the child and the mitochondria donor? What kind of role or status should the donor have?
- To what extent does this issue impact on your views on whether these new techniques should be used in treatment? Why?

Appendix 2 – Agenda

Medical Frontiers: Debating mitochondria replacement

Time	Session
18.00 – 18.30	**Arrival and registration** **Tea, coffee and finger food available**
18.30 – 19.00	**Introductions from the Chair and HFEA/OPM** **Mitochondria replacement: Some facts** **Introductions from the panel** Having been introduced by the Chair, each panel member will outline some of the issues and views, in order to trigger discussion.
19.00 – 19.30	**Explore the key social and ethical issues** Group discussions, where each group will have the opportunity to discuss two of the following sets of issues: 1. Avoiding mitochondrial disease 2. Affecting future generations: Changing the germline 3. Implications for identity: DNA from three people 4. The status of the mitochondria donor 5. Regulation of mitochondria replacement
19.30 – 20.25	**Ask a question; debate the issues** The final session will take the form of a lively debate using a Question Time format. Panel members will field questions that emerge from the group discussions before opening up discussion to the floor.
20.25 – 20.30	**Thank-you and next steps from the Chair**