SECONDARY LEGISLATION SCRUTINY COMMITTEE
Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015
Written Evidence

Contents
Lord Walton of Detchant ........................................................................................................... 2
Dr Elizabeth Allan ..................................................................................................................... 4
Anscombe Bioethics Centre ...................................................................................................... 10
Bioscience Sector: the Academy of Medical Sciences, Genetic Alliance UK, the Lily Foundation, the Medical Research Council, Muscular Dystrophy Campaign, the Progress Educational Trust, the Royal Society and the Wellcome Trust ........................................................................................................ 12
British Medical Association .................................................................................................... 17
CARE ........................................................................................................................................ 18
The Christian Institute ............................................................................................................. 22
Christian Medical Fellowship ................................................................................................ 25
Professor Bobbie Farsides ...................................................................................................... 28
Professor Golombok ................................................................................................................ 30
James Lawford Davis .............................................................................................................. 31
Lily Foundation ....................................................................................................................... 33
MRC National Institute for Medical Research (confidential material removed) .................. 34
Edward Morrow, University of Sussex .................................................................................. 35
Muscular Dystrophy ................................................................................................................ 38
Professor Savulescu, University of Oxford ........................................................................... 40
Scottish Council on Human Bioethics .................................................................................. 43
Dr Trevor Stammer, St Mary's University .............................................................................. 56
Lord Walton of Detchant

I should immediately confirm that I have a special interest in this topic. The work which is under consideration, and which would, I believe, lead to a major development in preventative medicine if the regulations shortly to be considered by the House were to be approved, is being undertaken in the department of neurology and in the department of human genetics at the Centre for Life in Newcastle upon Tyne, and is being led by Professor Douglas Turnbull, currently Professor of Neurology in the University, who holds the Chair which I held more than 30 years ago.

I must say at once that I have been involved in an indirect sense, not in the research itself, but in consultation with my colleagues in Newcastle on this topic, for more than four years, since the possibility now envisaged was under early consideration. Since that process began, there has been extensive consultation with members of the public, and with a huge variety of scientific bodies and with others concerned with ethical issues in medicine, about which I have been kept informed, and I have no hesitation in saying that the research which has been conducted in Newcastle has in effect led the world, and offers the only hope of effective prevention of devastating mitochondrial disease yet to have emerged as a result of medical research.

I do not propose to go into great detail in this letter as I know that you have received many submissions, but I would like to make the point, first, that all of the human characteristics, including physical and mental constitution, behaviour, intelligence, and so many more, are effectively controlled by genes which are located in the nucleus of every human cell, of which approximately 23,000 have been identified. By contrast, the 37 genes which are located in the mitochondria, tiny structures, or organelles, which float freely in the cytoplasm of the cell, outside the nucleus, are concerned solely with converting food and its products into energy through the release, for example, of high-energy phosphate bonds into the cytoplasm; in other words, the mitochondria act in a sense as the engine-room of the cell, but do not convey or represent any other human characteristics such as those which are controlled by the 23,000 genes in the cell nucleus.

In the course of my clinical practice as a neurologist in Newcastle and later in Oxford over very many years, I have seen and diagnosed and attempted to support many patients suffering from mitochondrial disorders resulting from mutations in one or more of these 37 mitochondrial genes. The resultant diseases are in many respects devastating, and although they vary considerably in their severity, these mutations can lead, for example, to deafness, blindness, epilepsy, progressive dementia, and, perhaps at times most disturbing of all, progressive muscular paralysis resembling superficially some of the effects of the human muscular dystrophies. Apart from simple supportive measures, no form of treatment has yet been identified to modify the effects of these diseases, which invariably shorten life and in many respects are clinically devastating. Epidemiological studies have suggested that up to 6,000 individuals in the UK may suffer from mitochondrial disorders of varying severity.

One particularly troubling aspect is that, since for practical purposes there are virtually no mitochondria within the sperm, but they are situated within the cells of the ovum, hence these mutations are passed on by affected women to all of their children of either sex. Over the years I have had many discussions, often extremely painful, with women who have become fully aware of what the prospects are in relation to their offspring. I have found many of these consultations extremely depressing, and there is a universal view among the affected women who have been counselled, not least in the Newcastle centre but also elsewhere, that they
support with great enthusiasm any method which would be capable of enabling them to have unaffected children. I have often said that human suffering is not easily quantified in numerical terms.

I am aware that there have been a number of submissions opposing this technique, developed in Newcastle after extensive research, but in my sincere opinion as a Christian and a lifelong member of the Methodist Church, I do not believe that the opposition can be justified on religious grounds. I have seen the views expressed by Professor Snyder in the United States, who has said that the diseases are terrible, however the treatments are non-existent and the Newcastle technology so far is a tour de force. He believes, however, that more research and that more consultation should be undertaken before mitochondrial transfer by implantation of embryos created by this research should take place. Nor does he seem to be aware of the virtually universal support of this research, after extensive and careful consideration, expressed by distinguished scientists in the UK and by organisations such as the Royal Society, the Medical Research Council, the Wellcome Trust, the Association of Medical Research Charities and many more. This advice is in striking contrast to the fact that the Nuffield Council on Bioethics and the Human Fertilisation and Embryology Authority in the UK held extensive consultations in 2012 into the ethical social and scientific issues raised by mitochondrial donation techniques. This identified broad public support for the use of these techniques within a robust regulatory framework, and expert scientific review panels in April 2011, March 2013 and June 2014 have found no evidence to suggest that the techniques are unsafe for clinical use and have concluded that these methods should have the potential of producing great benefit for families of patients with mitochondrial disease. Embryos produced by the research in Newcastle have shown every characteristic of normal human embryos, but of course it has been necessary for them to be allowed to degenerate because, at the present time, it is not legally permissible for them to be implanted in the uterus of the women with these serious mutations, unless and until regulations to allow this procedure have been approved by Parliament.

I can only add my personal opinion that this brilliant research carries enormous hope to women with mitochondrial mutations likely to result in devastating diseases in their offspring, and I believe that the procedures which have been undertaken by the HFEA and the Nuffield Council on Bioethics, and other bodies, with outstanding support from a huge range of highly qualified scientific and ethical experts, indicate that this method is likely to be safe and effective. At the very least, society owes it to the many women concerned that the matter should be fully debated in Parliament.
Dr Elizabeth Allan

1. The regulations are inappropriate in view of changed circumstances since the enactment of the parent Act.

The regulations are intended to permit eggs and embryos created by cell nuclear transfer procedures (maternal spindle transfer (MST) and pronuclear transfer (PNT) respectively) to be used for implantation in a woman, if the purpose is to prevent transmission of serious mitochondrial disease.

These cell nuclear transfer procedures would originally have been banned under sections 3ZA(2) and (4) of the parent Act, the Human Fertilisation and Embryology Act, as amended ('HFE Act'), which state that eggs and embryos respectively, can not be licensed for implantation in a woman (i.e. could not be classified as ‘permitted’ eggs or embryos) if their nuclear or mitochondrial DNA had been ‘altered.’

(2) A permitted egg is one -
   (b) whose nuclear or mitochondrial DNA has not been altered.

(4) An embryo is a permitted embryo if -
   (b) no nuclear or mitochondrial DNA of any cell of the embryo has been altered.

Since MST and PNT are both nuclear transfer procedures, they alter nuclear and mitochondrial DNA in eggs and embryos. Eggs and embryos created by these procedures could therefore not be classified as ‘permitted’ for implantation in a woman under these sections of the HFE Act.

However, provision for a regulation-making power was made in section 3ZA(5) of the HFE Act which could overturn any restrictions in sections 3ZA(2) - (4) if it was to prevent the transmission of serious mitochondrial disease. This would permit children to be born whose nuclear and / or mitochondrial DNA had been altered.

However, although sections 3ZA(2) - (4) of the HFE Act prohibit any alteration in nuclear or mitochondrial DNA in gametes or embryos that are to be implanted, the Government has consistently and repeatedly altered the meaning of a key term in these sections for the last two years. They have done this in a series of Government and Ministerial statements and answers to Written Parliamentary Questions where they have tried to deny that MST and PNT are

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1 Annex I
2 The genetic modification would happen through the processes described in regulation 4 (for eggs) and regulation 7 (for embryos). The egg (‘egg A’ in regulation 4) or embryo (‘embryo A’ in regulation 7), that is to be used for implantation would have its nuclear DNA removed, but would retain its mitochondrial DNA. It would then have nuclear DNA from a second woman inserted in the case of ‘egg A’ and pronuclear DNA from another woman and a man in the case of ‘embryo A.’ This would produce the ‘permitted egg’ (‘egg P’) in regulation 3, and the ‘permitted embryo (‘embryo P’) in regulation 6.

The egg being used as the basis for implantation (‘egg A’) would therefore have a 100% change in its nuclear DNA, but would retain its own mitochondrial DNA. In the case of the embryo to be used as the basis for implantation (‘embryo A’), it would have a 50-100% change in its pronuclear DNA (depending on whether the sperm came from the same source), but would retain its own mitochondrial DNA. In both cases, there would probably be a small carryover of mitochondrial DNA from the nuclear transfer from ‘egg B’ and ‘embryo B,’ resulting in mitochondrial DNA from two sources. Therefore in both cases, both nuclear and mitochondrial DNA in the egg and embryo would be altered.
‘germline genetic modification,’ or even ‘genetic modification;’ repeatedly stating that these cell nuclear transfer procedures do not ‘alter’ nuclear or mitochondrial DNA:

“The proposed mitochondrial donation techniques only allow for unaltered nuclear DNA to be transferred to an egg or embryo that has unaltered healthy mitochondria. The key consideration is that these techniques only replace, rather than alter, a small number of unhealthy genes in the ‘battery pack’ of the cells with healthy ones.” (Government response to the Department of Health consultation on the draft Regulations (page 15) (22.7.2014))

“The key consideration is that these mitochondrial donation techniques only substitute, rather than alter, a very limited number of unhealthy genes in the ‘battery pack’ of the cells with healthy ones.” (Reply to Lord Alton, 6 Feb 2014: Column WA77 [HL4907])

“The proposed donation techniques will allow unaltered nuclear DNA to be transferred only to an egg or embryo that has unaltered healthy mitochondria.” (Parliamentary Under-Secretary of State for Health, Jane Ellison. Debate on “Mitochondrial Replacement (Public Safety)” Column 121, 1.9.2014)

“…the genes present in the mitochondrial and nuclear DNA used in these procedures will not be altered.” (Reply to Lord Alton, 22 Jan 2014: Column WA129 [HL4439])

“…these techniques do not involve altering the genes in the nuclear DNA” (Reply to Lord Alton, 29 Aug 2013: Column WA359 [HL2080])

“The genes present in the donated mitochondria will not be altered nor will the nuclear DNA of the child’s parents’ egg or embryo that will be used in these procedures.” (Replies to Lord Alton, 30 Oct 2013: Column WA259 [HL2755] and 12 Nov 2013: Column WA113-114 [HL3115])

The Government have been keen to say that nuclear transfer does not ‘alter’ nuclear or mitochondrial DNA in the eggs or embryos. However, this appears to have unintended legal consequences for both the HFE Act and the Mitochondrial regulations, since if the cell nuclear transfer procedures are no longer classified as ‘altering’ DNA, they would no longer be banned under sections 3ZA(2)- (4) of the HFE Act.

Eggs and embryos created by cell nuclear transfer could therefore potentially already be classified as ‘permitted’ eggs and embryos under sections 3ZA(2) and (4) of the HFE Act respectively; and Regulations under section 3ZA(5) would therefore no longer be needed to make provision for this.

Furthermore, creation of ‘permitted’ eggs and embryos by cell nuclear transfer techniques would not be limited to being for the purpose of preventing the transmission of serious mitochondrial disease, since sections 3ZA(2) and (4) do not have any such condition attached.

The Government therefore appear to have completely undermined the entire legal basis on which their own regulations have been made, in effect invalidating them. Their position that nuclear and mitochondrial DNA are not altered in eggs and embryos that have undergone MST and PNT, would render the draft regulations not only completely redundant, but also legally confusing and contradictory since they would conflict with existing legislation.
To return the legal situation to that which was the original intention of these sections of the HFE Act, it appears that the Government's understanding of the techniques must change in order for the Regulations to be possible as currently drafted. At the very least, this would seem to require the retraction of a number of Government and Ministerial statements and answers in response to Written Parliamentary Questions, and the issuing of public statements to the contrary, stating unequivocally that the cell nuclear transfer procedures maternal spindle transfer (MST) and pronuclear transfer (PNT) do, in fact, alter nuclear and mitochondrial DNA in eggs and embryos themselves, not just in the germline. This would retain cell nuclear transfer within the category of 'altering' nuclear or mitochondrial DNA in eggs and embryos.

Without this, it is difficult to see how the regulations could in any way be sensibly considered, since the Government would at the same time be fatally undermining the legal basis of the regulations and producing a legally confusing and contradictory situation. This would also raise questions about the procedural propriety of pursuing regulations which had been fundamentally misconstrued by the Government.

2. The regulations give rise to issues of public policy likely to be of interest to the House.

The regulations would sanction germline genetic modification through cell nuclear transfer procedures (maternal spindle transfer (MST) and pronuclear transfer (PNT)). This would permit the creation of children with DNA from three people in virtually every cell of the body.

This germline genetic modification through nuclear transfer is a biological fact, and exists irrespective of a recent ‘working definition’ of genetic modification that the Government has published for the purposes of denying that ‘genetic modification’ is taking place, (Indeed, this ‘working definition’ is crucially flawed in several ways.)

The genetic modification would happen through the nuclear transfer processes described in regulation 4 (for eggs) and regulation 7 (for embryos), as described above in footnote 2.

This gives rise to issues of public policy likely to be of interest to the House.

Dr. Elizabeth Allan
12 January 2015

4 See footnote 2 above.
5 “The working definition that we have adopted is that genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations. This will be kept under review.

On the basis of that working definition, the Government's view is that the proposed mitochondrial donation techniques do not constitute genetic modification.” (Government response to the Department of Health consultation on the draft Regulations (page 15) (22.7.2014))


6 For example, in addition to attempting to exclude cell nuclear transfer from the definition of genetic modification, this definition would also exclude altering individual sequences of mitochondrial DNA (as it deliberately excludes all mitochondrial DNA from the definition). It would also exclude the insertion of stably-maintained DNA that is independent of nuclear chromosomal DNA.

See also the entry for 3rd September 2014: http://tedmorrow.wordpress.com/category/general/
ANNEX I

HUMAN FERTILISATION AND EMBRYOLOGY ACT 1990 (AS AMENDED)

3 Prohibitions in connection with embryos

(2) No person shall place in a woman—

(a) an embryo other than a permitted embryo (as defined by section 3ZA), or

(b) any gametes other than permitted eggs or permitted sperm (as so defined)...

3ZA Permitted eggs, permitted sperm and permitted embryos

(1) This section has effect for the interpretation of section 3(2).

(2) A permitted egg is one -

(a) which has been produced by or extracted from the ovaries of a woman, and

(b) whose nuclear or mitochondrial DNA has not been altered.

(3) Permitted sperm are sperm -

(a) which have been produced by or extracted from the testes of a man, and

(b) whose nuclear or mitochondrial DNA has not been altered.

(4) An embryo is a permitted embryo if -

(a) it has been created by the fertilisation of a permitted egg by permitted sperm,

(b) no nuclear or mitochondrial DNA of any cell of the embryo has been altered, and

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

(5) Regulations may provide that -

(a) an egg can be a permitted egg, or

(b) an embryo can be a permitted embryo,

even though the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease.

(6) In this section -

(a) “woman” and “man” include respectively a girl and a boy (from birth), and

(b) “prescribed” means prescribed by regulations.”.
ANNEX II

Examples of the Government’s description of ‘altered’ or ‘unaltered’ nuclear or mitochondrial DNA in maternal spindle transfer and pronuclear transfer:

Government response to the Department of Health consultation on the draft Regulations (page 15) (22.7.2014):

“The proposed mitochondrial donation techniques only allow for unaltered nuclear DNA to be transferred to an egg or embryo that has unaltered healthy mitochondria. The key consideration is that these techniques only replace, rather than alter, a small number of unhealthy genes in the “battery pack” of the cells with healthy ones.”


Reply to Lord Alton, 6 Feb 2014 : Column WA77 [HL4907]

The Parliamentary Under-Secretary of State, Department of Health (Earl Howe): “The proposed mitochondrial donation techniques only allow for unaltered nuclear DNA to be transferred into an egg or embryo that has unaltered healthy mitochondria and the original nuclear DNA removed. The key consideration is that these mitochondrial donation techniques only substitute, rather than alter, a very limited number of unhealthy genes in the ‘battery pack’ of the cells with healthy ones.”

http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/140206w0001.htm#14020660000140

Parliamentary Under-Secretary of State for Health, Jane Ellison (Debate on ‘Mitochondrial Replacement (Public Safety)’ Column 121, 1.9.2014):

“The proposed donation techniques will allow unaltered nuclear DNA to be transferred only to an egg or embryo that has unaltered healthy mitochondria.”

http://www.publications.parliament.uk/pa/cm201415/cmhansrd/cm140901/debtext/140901-0003.htm#14090125000083

Reply to Lord Alton, 29 Aug 2013 : Column WA359 [HL2080]

The Parliamentary Under-Secretary of State, Department of Health (Earl Howe): “…[these techniques]… do not involve altering the genes in the nuclear DNA”

http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/130829w0002.htm#1308131000827

Reply to Lord Alton, 30 Oct 2013 : Column WA259 [HL2755]
The Parliamentary Under-Secretary of State, Department of Health (Earl Howe): “The genes present in the donated mitochondria will not be altered nor will the nuclear DNA of the child’s parents’ egg or embryo that will be used in these procedures.”

http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/131030w0001.htm#13103061000646

Reply to Lord Alton, 12 Nov 2013 : Column WA113-114 [HL3115]

The Parliamentary Under-Secretary of State, Department for Business, Innovation and Skills (Viscount Younger of Leckie) (Con): “The genes present in the donated mitochondria will not be altered nor will the nuclear DNA of the child’s parents’ egg or embryo that will be used in these new IVF procedures.”

http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/131112w0001.htm#13111264000221

Reply to Lord Alton, 22 Jan 2014 : Column WA129 [HL4439]

The Parliamentary Under-Secretary of State, Department of Health (Earl Howe): “…the genes present in the mitochondrial and nuclear DNA used in these procedures will not be altered.”

http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/140122w0001.htm#14012210000559
The Anscombe Bioethics Centre is very concerned about this legislation for a number of reasons, beginning with the physical risks posed by mitochondrial donation for the individual created and for his or her descendants. When assessing these risks, it must be remembered that the techniques proposed do not treat existing individuals affected by mitochondrial disease, but instead deliberately produce new individuals in highly novel ways carrying risks both to those conceived and to future generations. Transfer of nuclear material between gametes or embryos constitutes in fact germ-line genetic manipulation of a kind which engages international expressions of concern as found in, for example, Article 24 of the UNESCO Universal Declaration on the Human Genome and Human Rights.

The risks of mitochondrial donation both for the individual and for that individual’s descendants are very real, while the risk of an affected woman passing on a mitochondrial disorder to her child via natural conception though also real is largely avoidable, since the possibility always exists of her choosing not to conceive, and perhaps seeking to adopt a child instead. The risks and harms of mitochondrial donation would be incurred merely in the course of ensuring some form of genetic connection, albeit a very unusual connection, between the woman wanting a child and the child she wants to have.

Mitochondrial ‘donation’ (in reality, it is the nuclear material that is ‘donated’ or at least moved) offers no advantage of any kind in terms of safety over conventional egg donation, but on the contrary creates risks in the course of deleting material from the egg donor - or, in the case of pronuclear transfer, from the donor embryo who is destroyed together with the original embryo to create the final ‘fusion’ embryo. The Anscombe Centre is opposed to the conception of children using donor eggs for a variety of reasons concerning, among other things, parental responsibility and medical risks for the woman donating. However, we would stress that the transfer of nuclear material from and into donor eggs merely adds risks for children to existing risks for the egg donor, without any medical benefit for the child.

Emotional risks for the child created by mitochondrial donation, especially if, as the draft legislation envisages, the identity of the egg or embryo donor is kept hidden from the child, are also a matter for serious concern. Since the HFE Act was passed, there has been growing awareness of the interests of donor-conceived people in obtaining identifying information on their donor parent. The right of donor-conceived offspring to receive this information was confirmed by a court ruling of 2002 in response to the application of a donor-conceived adult, Joanna Rose. Such rights should not now be effectively eroded; on the contrary, such minimal rights of children to identifying information on those who brought them into being and contributed to their genetic makeup should be firmly upheld.

Since mitochondrial donors are in fact donating not just mitochondria but a whole ovum minus the nuclear material, it is very questionable whether, as the Bill claims, “mitochondrial donors are not related to any children who were, or might have been, born following treatment services using their donation and therefore no provision is made to allow access to information in connection with entering into a marriage, civil partnership or intimate physical relationship, nor to access information about other children who share the same donor.” The hard-won gains of donor-conceived individuals to identifying information on those who helped to form them should be extended to those created from donor eggs with subsequent nuclear
modification, if such techniques are in fact introduced (as we would argue they should not be). The attempt to erase, albeit only partially, the egg donor mother’s identity in the case of e.g. maternal spindle transfer may cause more identity problems for the child than conventional egg donation, not fewer. It should not be assumed in advance that the egg donor mother, who provides the bulk of the egg, minus the nuclear material, is not a ‘real’ mother, in contrast to the woman who provides the spindle or polar body (also a partial genetic mother, in our view). It should be for those conceived by these procedures to seek contact with the egg donor mother if they wish - or in the case of pronuclear transfer, with at least the genetic mother of the ‘donor’ embryo from whom they were partially formed.

We have an especially strong ethical objection to pronuclear transfer, as this procedure destroys two embryos each time it is carried out: the commissioning woman’s original embryo, and the donor embryo used to provide all the non-nuclear material in the formation of the final embryo. Neither the HFEA, nor any other body or individual, should have the role of deciding that an embryo deliberately created for the purpose of pronuclear transfer faces medical risks or challenges to its future life such as to make it suitable to have its pronuclei lethally harvested for the purpose of helping to create an entirely separate embryo. Human lives should not be used as mere building blocks for other human lives, but should be respected in their own right. A child so produced will owe his or her life to the deliberate destruction of two pre-existing embryos, leaving a permanent legacy in every one of that child’s cells. The psychological effect on the child is something we can only guess at, but is unlikely to be positive; such procedures are also likely to have a bad psychological effect on the women who contribute to the formation of embryos for the sole purpose of forming spare parts for the final child. Even if the egg donor is not the mother of the PNT embryo created, she is certainly the genetic mother of the embryo destroyed to create it (together with the commissioning woman’s original embryo). The egg donor is, in fact, no less closely related genetically to that destroyed embryo than any genetic mother is related to her genetic offspring (or than the commissioning woman is related to her own destroyed embryo).

In short, we would argue that neither pronuclear transfer nor any other form of mitochondrial donation is justified in view of the risks and harms these procedures pose, including to future generations. Such risks and harms are created in the course of germ-line manipulation which is not needed and is carried out simply because some form of genetic connection is desired by a woman wanting a child with the child she wants to have. This desire does not justify embryo destruction (which occurs in every instance of pronuclear transfer) nor does it justify genetically modifying those conceived in such a way as to cause them identity problems, nor does it justify altering the germline with potential harmful effects on generations to come.

Dr Helen Watt
Senior Research Fellow
Anscombe Bioethics Centre
6 January 2015
Bioscience Sector: the Academy of Medical Sciences, Genetic Alliance UK, the Lily Foundation, the Medical Research Council, Muscular Dystrophy Campaign, the Progress Educational Trust, the Royal Society and the Wellcome Trust

We are writing on behalf of the bioscience sector and patient groups to assist your committee in its consideration of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (Regulations), which we support. In particular we commend the detailed scrutiny and consultation process which has resulted in informed and clear regulations.

Mitochondrial disease is a devastating and debilitating condition. Many children born with the condition will not make it to adulthood. New IVF techniques (mitochondrial donation) could allow women who carry mitochondrial disease the reproductive option to choose to have their own genetically related children unaffected by these devastating disorders. We support mitochondrial donation as a reproductive choice to enable families to avoid having children with serious mitochondrial disease.

The relevant Regulation-making powers were included in the Human Fertilisation and Embryology Act 2008 (Act), enabling the Secretary of State to make regulations when appropriate, to allow the Human Fertilisation and Embryology Authority (HFEA) to licence the use of these ground breaking therapies in the clinic. This Act passed through Parliament after extensive debate in both the House of Lords and House of Commons, generating an unprecedented 80 hours of parliamentary time.

The relevant section of the Act was carefully scrutinised and was itself the result of debate where both Houses concluded by an overwhelming margin that Regulation-making powers in this area was appropriate.

The Regulations are the culmination of seven years of extensive scrutiny; there have been independent ethical reviews, three separate reviews of the scientific evidence on the technique’s safety by a specially convened independent panel of experts, and an extensive public consultation, independently validated, which has revealed broad public support.

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7 http://www.thelilyfoundation.org.uk/animation/
9 http://www.publications.parliament.uk/pa/cm200708/cmhansrd/cm081022/debtext/81022-0016.htm#08102255000176
10 http://www.publications.parliament.uk/pa/id200708/dhansrd/text/80204-0002.htm#08020422000094
11 A detailed timeline of this process is appended in Annex A
14 HFEA, Expert review of scientific methods to avoid mitochondrial disease 2012: http://www.hfea.gov.uk/9359.html
17 An overview of the key studies reviewed in these deliberations are appended in Annex B
It is an accepted fact in the clinical and research communities, and should be recognised by
the Committee, that it is never possible to answer every question on safety before new
procedures are used in people for the first time. However, if medicine is to progress,
clinicians must be permitted to use new techniques with informed consent of the patient
when they are ethical (including that the potential benefits outweigh the potential risks),
and when there is sufficient evidence of safety and effectiveness. An exemplary consultation
and review process has revealed that mitochondrial donation has reached this stage.

We therefore welcome the Regulations, and the detailed and informative explanatory
memorandum supporting them. As provided in the parent Act, these Regulations allow the
statutory regulator, the HFEA, to consider applications for licences permitting the use of
these techniques in treatment. The HFEA and its expert committees are highly regarded
internationally for their expertise in evaluating whether proposed techniques are sufficiently
safe and effective. This will include whether centres that apply for licences have the
necessary staff, expertise, skill and equipment to perform the proposed activity. The
Regulations, if adopted, simply allow this further review process to begin, and thus ensure
that regulatory oversight, itself under Parliamentary control, runs concurrently with scientific
progress. This enabling legislation would put the UK on the same footing as the situation in
other countries, including the US, where mitochondrial donation is not specifically illegal and
regulators are empowered to decide whether treatment should be allowed based on safety
and efficacy data.19

We recognise, as did the Minister in her evidence to the House of Commons Science and
Technology Select Committee,20 that some people will always object to the techniques on
principle, regardless of the scientific evidence about safety. It was never the intention of the
Act for Parliament only to permit the HFEA to consider applications after all possible safety
studies had been concluded and when the procedure was judged entirely safe. Rather the
intention of the Act was to enable the statutory regulator to consider applications when the
science and research had progressed to a point where therapeutic uses are possible and to
ensure that the HFEA was given the relevant parameters within which to carry out those
duties. This is identical to the role of the HFEA in many other areas of clinical practice.
Allegations about lack of safety will be matters for the HFEA in any licensing decision;
there is no evidence on safety that warrants delaying these Regulations.

19 http://www.independent.co.uk/news/science/benefits-of-threeparent-babies-will-likely-outweigh-the-risks-
experts-claim/
20 http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-
committee/news/141016-mit-ev/
Bioscience Sector – Written Evidence

Annex A

Timeline: debating mitochondrial donation regulations since 2000


2005 - The Science and Technology Committee publish the extensive report Human Reproductive Technologies and the Law, supporting further research in this area.

2005 – University of Newcastle obtain license to work with human oocytes.

2008 – Human Fertilisation and Embryology Act passed, allowing researchers to develop techniques to prevent transmission of maternally inherited mitochondrial disease.

April 2010 – Researchers at Newcastle University develop techniques to prevent diseased mitochondria being passed from mother to child.


July 2012 – HF EA runs series of public dialogue events across the UK.

November 2012 – HF EA runs two public discussion events in Manchester and London.

March 2013 – Publication of a letter in The Times supporting changes in legislation. Signed by: Sir John Sulston (Nobel Prize winner), Baroness Deech, Baroness Warnock, Lord Willis of Knaresborough, Lord Winston, Sir Tim Hunt (Nobel Prize winner), Sir John Savill (Chief Executive, MRC) and Sir John Tooke (President, Academy of Medical Sciences).

March 2013 – HF EA publishes report on public consultation and updated scientific review, agreeing advice to Government on ethics and science of mitochondrial donation. Expert panel concludes that the techniques have potential to be used, if safety and efficacy are refined. Consultation reports broad public support for the techniques.

June 2013 – Department of Health (DH) and HF EA state that draft regulations would be issued later in 2013, then taken to further public consultation.

March 2014 – Draft regulations for mitochondrial donation published by DH and public consultation launched for three months. House of Commons holds an adjournment debate, called by Jacob Rees-Mogg MP. Briefings held by DH in both Houses of Parliament.

April 2014 – Evaluation of HF EA public dialogue and consultation published, concluding the HF EA and Sciencewise collaboration to be a credible and efficacious exercise in public engagement and consultation.

June 2014 – HF EA releases third scientific review of safety and efficacy of mitochondrial donation. It finds no evidence to suggest either technique is unsafe and that both have potential to be used in a specific set of patients with serious mitochondrial disease.

July 2014 – DH publishes Government response to public consultation on draft regulations.

September 2014 – Commons backbench debate on mitochondrial donation, called by Fiona Bruce MP.

October 2014 – HF EA publishes addendum to the 2014 updated scientific review. Parliamentary Office of Science and Technology holds briefing on Preventing Mitochondrial Disease – debates about mitochondrial replacement.

Commons Science and Technology Select Committee holds evidence session on mitochondrial donation. Findings are shared in letter from Committee Chair Andrew Miller to minister Jane Ellison.

December 2014 – Government publishes regulations on allowing mitochondrial donation.
Mitochondrial donation: what is the research?

Mitochondrial donation techniques have been successfully performed in monkeys and mice, leading to the birth of healthy offspring.

Techniques have also been used on human eggs and fertilised human eggs, in both cases leading to the successful development of a bundle of cells, suggesting that they would develop as normal if implanted in the uterus.

Safety is and will always be of paramount importance and the techniques have received unprecedented scrutiny by the Human Fertilisation and Embryology Authority’s specially convened Expert Scientific Review panel. Through three separate reviews, the panel found no evidence to suggest that the techniques are unsafe for clinical use and concluded that both techniques have the potential to be used in patients with mitochondrial disease. Never before has a new reproductive technology been subjected to such thorough investigation before it has been approved.

1983 – Pronuclear transfer (PNT) performed in mice (without mitochondrial abnormalities). PNT-derived embryos developed normally, similar to development of unmanipulated embryos, and resulted in birth of normal offspring.¹

1997 – PNT again successfully performed in mice (lacking mitochondrial abnormalities), demonstrating efficiency and reproducibility of PNT.²

2005 – PNT successfully performed in mice carrying a mitochondrial DNA (mtDNA) abnormality, preventing transmission of the defect and resulting in the birth of offspring showing no evidence of disease.³

2005 – Maternal spindle transfer (MST) performed in a wide range of animals as controls in somatic cell nuclear transfer experiments, suggesting it is an efficient technique.⁴

2009 – MST successfully performed in mice and leads to the birth of pups with no growth abnormalities or epigenetic defects.⁵

2009 – MST successfully performed in non-human primates (rhesus macaques) to prevent transmission of mitochondrial disease and lead to the birth of four healthy offspring.⁶

2010 – PNT used in abnormally fertilised human embryos to prevent transmission of mtDNA disease, resulted in the development of blastocysts, which appeared as normal as controls.⁷

2013 – The four MST macaque offspring showed normal health after three years with no evidence of abnormalities.

2013 – MST successfully performed in a different subspecies of rhesus macaque with a different mtDNA sequence. No difference in nuclear–mitochondrial genome interactions was noted.⁸

2013 – MST performed in activated and normally fertilised human oocytes. Embryos produced from MST-derived normally fertilised oocytes went on to develop normally to the blastocyst stage and produced embryonic stem (ES) cell lines similar to controls, with a euploid karyotype (normal multiple of chromosomes), all of which contained only donor mtDNA.⁹

2014 – MST-derived rhesus macaques (born in 2009) continue to show no evidence of abnormalities five years later.¹⁰

On-going – Experiments are being pursued to evaluate the clinical use of these techniques. Progress is encouraging.
References


4. HFEA, April 2011 Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.


13. HFEA June 2014, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception

14. HFEA June 2014, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception
British Medical Association

The BMA supports the use of mitochondria replacement techniques for the avoidance of severe disease or disability and welcomes the introduction of these draft regulations. This issue has been the subject of intense debate and scrutiny over a number of years and we believe the time is now right to move a step closer to the use of the technique in clinical practice.

The amendment to the Human Fertilisation and Embryology Act in 2008, to include a regulation-making power to allow the use of this technique in clinical practice, followed a detailed consultation exercise and many hours of debate in both Houses of Parliament. Since then there has been an expert ethical review carried out by the Nuffield Council on Bioethics which concluded in 2012 that, if shown to be acceptably safe and effective, it would be ethical for families to use the techniques. In addition, the Human Fertilisation and Embryology Authority carried out a major public engagement exercise (which received a positive review from external evaluation) which found broad public support for the use of the technique to help those who want to use it to avoid these devastating conditions in their children.

As well as review of the ethical aspects of these techniques, there has been significant scrutiny of the science that underpins them. The HFEA appointed a panel of expert scientists which has carried out three independent reviews of the science. The latest review, reporting in June 2014, found no evidence to suggest that the techniques were unsafe and recommended some further work that should be undertaken before moving into clinical practice. The UK is in the privileged position of having an effective and trusted regulator which makes the decision about whether and when to allow new techniques to proceed. If the Regulations are passed by Parliament this does not mean that the work can go ahead; it gives the Human Fertilisation and Embryology Authority the power to approve the procedure as and when it deems it appropriate based on expert review and evidence. By passing the Regulations, Parliament would be giving the HFEA the tools it needs to carry out the important job it has been set up to do.

The BMA believes there is a moral imperative to pursue this work, without delay, for the benefit of those who would wish to use this option as their only chance to have a healthy, genetically related, child. The very high level of both scientific and ethical scrutiny to which these techniques have been subjected give us the confidence that as a society we are ready to move a step closer to seeing the use of the technique in clinical practice. Introducing the Regulations now will allow the HFEA to consider licensing these techniques as soon as sufficient evidence of safety is available. Waiting until all of the necessary evidence is available before beginning this process of passing Regulations will result in unnecessary delays in using the techniques to benefit patients.

Dr John Chisholm CBE Chair
Medical Ethics Committee
British Medical Association
9 January 2015
This submission has been put together mindful of the points of interest set out by the Committee in its submission guidance with particular reference to the following points:

“Politically or legally important or give rise to issues of public policy likely to be of interest to the House;
Inappropriate in view of changed circumstances since the enactment of the parent Act;”

The proposed regulations will be of special interest to the House because they are so controversial that Parliament is the only legislature to have been asked to sign off on such legislation anywhere in the world. The basis for the controversy primarily concerns two interdependent areas:

I. Public Safety

There are widespread safety concerns about the public safety proposals. In this regard it is worth being aware of the following:

i) The only study of pronuclear transfer in humans (the Zhang study) resulted in an abortion, a miscarriage and a still birth.\(^{21}\)

ii) The United States Food and Drug Administration (FDA) has looked at the same proposals and has decided that there is a need for more safety tests before proceeding. Professor Evan Snyder, who chairs the scientific panel advising the FDA on mitochondrial transfer has said that there is a need for more pre-clinical research in animal models.\(^{22}\)

iii) The HFEA has produced three safety reports – all of which crucially fail to engage with the Zhang study – in which it outlines an extensive list of pre-clinical safety tests that it recommends should be conducted prior to deciding to proceed. It is not clear whether or not these tests have been concluded. One would have thought they should have been concluded and written up in peer-reviewed journals and the results made available to concerned parliamentarians before Parliament is asked to decide whether or not to accept the regulations.\(^{23}\)

iv) A number of leading scientists have expressed their opposition in detail including Prof Stuart A. Newman, Professor of Cell Biology and Anatomy, New York Medical College;\(^{24}\) Prof Paul Knoepfler, who sent an open letter to parliamentarians;\(^{25}\) and Dr Ted Morrow, who has written widely about the dangers.\(^{26}\)

v) Over 40 scholars from different countries around the world wrote to The Times calling on the British Government to abandon its plans. They noted specifically that the changes proposed by the British Government would impact the germline

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\(^{22}\) [Scientist warns on new three-parent IVF treatments](http://www.independent.ie/life/family/mothers-babies/scientist-warns-on-new-threeparent-ivf-treatments-30749662.html)

\(^{23}\) The 2011 HFEA report can be accessed [here](http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html) The test proposals are set out pp. 20-22

The 2013 HFEA report can be accessed [here](http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html) The test proposals are set out pp. 19-22

The 2013 HFEA report can be accessed [here](http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html) The test proposals are set out pp. 30-32


CARE – Written Evidence

vi) Fifteen experts and scholars from different parts of the world wrote to The Guardian warning on the eugenic concerns associated with the proposals.  

2. Ethics

Pronuclear and Maternal Spindle Transfer both involve the engineering of an embryo with the purpose of creating a human being with certain properties. While the legislation proposed certainly does not allow for engineering to select for certain hair or eye colour, and the engineering in question is to address a real problem, namely seeking to prevent passing human mitochondrial disease from one generation to another, it still crosses the ethical line and amounts to the creation of a designer baby. Once humans are created to have certain properties a hugely important ethical line is crossed and one inevitably confronts the potential commodification of the properties with all that entails for how the resulting human beings are dealt with. Proponents of the technique would object to this, suggesting that the language of designer babies should only be applied where the designing is for trivial purposes like selecting for hair or eye colour, but two points must be made in response. First, just because designing a child without human mitochondrial disease is not trivial does not make it any less an act of design. Second, the key point is that while the legislation in question might be very tightly drafted and narrowly relate to mitochondrial disease, that would not change the fact that the line has been crossed and a precedent will have been formed. Five years down the line one could easily imagine someone else suggesting that designer children processes should be used in an additional context and then ten years later in still another context, etc, etc, ad infinitum.

The truth is that this legislation proposes forming a precedent that actually has major implications for what it means to be human and suggests that the United Kingdom should be the first country in the world to do so.

The Government has sought to limit the controversy associated with its regulations by deploying certain semantic formulations that do not stand up to scrutiny and which have indeed become considerably more vulnerable since the decision to introduce these regulations was announced on account of important new research which has come out in the intervening period which substantially changes the debate.

In the first instance the Government has been very keen to argue that the procedures in question do not create three parent children. They argue that the role of (what those talking in terms of three parent children would describe as) the second parent should instead be seen in the same way one regards an organ donor. This is based on the fact that the DNA donated by the ‘donor’ is mitochondrial DNA and not nuclear DNA and that, crucially, mitochondrial DNA is concerned with the provision of energy for the cell and not with defining the traits of the resulting child, which comes from the nuclear DNA. They argue that because the child will only have nuclear DNA from two parents they should really be considered to be a two child parent.  

27 http://www.thetimes.co.uk/tto/opinion/letters/article3717615.ece
CARE – Written Evidence

In the second instance, and for exactly the same reasons, the Government has been very clear that it would not be appropriate to define procedures that it wants to be made legal as genetic modification. They argue that this language should only be applied to the engineering of nuclear DNA.\textsuperscript{30}

There are, however, two major problems with both these positions. First, all the scientists who we have spoken with argue that according to the normal, straightforward, scientific use of the term, any modification of the DNA – be it mitochondrial or nuclear DNA – amounts to ‘genetic modification.’ The Government seeks to justify making a distinction on the basis that mitochondrial DNA simply provides cell energy rather than impacting the traits of the resulting person. This, however, is not used by scientists to introduce a distinction between engineering nuclear DNA, which is then called genetic modification, and engineering mitochondrial DNA which is then not called genetic modification. In terms of the simple use of language both are examples of genetic modification and thus the effort to develop a semantic formulation to avoid calling what these regulations propose ‘genetic modification’ would seem to be born of a political desire to circumvent the drawing of parallels between GM foods and GM babies.

Second, and even more importantly, since the Government began to use this argument, and crucially since the parent Act was passed, a number of pieces of research have been published demonstrating that mitochondrial DNA is not just concerned with energy provision in any event but that it also impacts the traits of the resulting child. This resulted in the New Scientist acknowledging in September 2014 that children created by this technique would have the traits of three parents and not just two. This makes it completely clear that the idea that the third parent should be viewed as an organ donor is completely unsustainable. The third parent not only plays a key parenting role in making the creation of a life possible – which completely differentiates it from an organ donor who assists an already existing life – but also plays a key parenting role impacting the traits of the resulting children. The argument that nuclear DNA defines traits and mitochondrial DNA is just about energy has been swept away by research that has been published in the last twelve months.\textsuperscript{31}

Compatibility with EU Law?
While this legislation does not seek to implement EU law important questions also arise concerning its compatibility with EU law.

Article 9 of the Clinical Trials Directive states: ‘No gene therapy trials may be carried out which result in modifications to the subject’s germ line genetic identity.’ (NB. This is now replicated in Article 90 of Regulation (EU) No 536/2014 of the European Parliament and of the Council of Europe, 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. This will not be operational, though, until 2016 and until then the current Directive remain in place.)

\textsuperscript{30} Ibid.
\textsuperscript{31} www.newscientist.com/article/mg22329871.600-threeparent-babies-its-more-messy-than-we-thought.html
The same point is made by Prof Stuart Newman http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html and Dr Ted Morrow lists 11 academic papers highlighting the impact of mitochondrial DNA on personality traits http://tedmorrow.wordpress.com/2014/10/30/influence-of-mitochondrial-dna-on-personality-traits-some-evidence/
Our understanding is that this would prevent clinical trials of pronuclear or maternal spindle transfer in the UK.

This provision has been implemented into UK law through the Medicines for Human Use (Clinical trials) Regulations 2004 and Article 19 (3) does deal with this matter.

Specifically it states: ‘19 (3) The licensing authority shall not authorise a clinical trial involving products for gene therapy if the use of those products in that trial would result in modifications to any subject’s germ line genetic identity.’

The only way around this would be to not have clinical trials, but given the level of public concern especially regarding safety (ComRes polling shows that public opposition significantly outweighs support\(^{32}\)) it seems inconceivable that this would be possible. Moreover the HFEA has already recommended a follow-up process that it is likely a court would deem to amount to a clinical trial.\(^{33}\)

The House may wish to seek an assurance that given public concern there will indeed be clinical trials and secure an explanation from the Government about how this will fit with the Clinical Trials Directive and the Medicines for Human Use (Clinical trials) Regulations 2004.

**Conclusion**

All the above points mean that the controversy attached to these regulations is such that they should be of special interest and concern to the House and that the specific bases for this controversy – both as they relate to matters of public safety and to ethics – should be drawn to the attention of the House. Moreover, the fact that it is now apparent that human mitochondrial DNA impacts traits and does not simply provide battery packs, leaving the definition of traits to nuclear DNA, should also be drawn to the attention of the House. This was not clear when the parent legislation was passed in 2008 and significantly impacts the ethics of the proposal as the New Scientist has now recognised. The fact that it also does not seem compatible with EU law, unless there is an intention to bypass clinical trials, is also deeply disturbing especially given the levels of public safety concern expressed in polling. ComRes polling demonstrates that support for the proposals fell from 35% in favour to 34% against in February 2014, to 18% in favour and 46% against in August 2014.\(^{34}\) Mindful of all this it seems very unfortunate that the legislation is being introduced in the form of unamendable secondary legislation that will only be subject to one debate. In addition to drawing the attention of the House to the above points, therefore, we would also suggest the Committee considers recommending that more time than usual should be allocated for the debate examining these regulations.

Dr Dan Boucher
Director of Parliamentary Affairs, CARE


The Christian Institute

1. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 ('the Regulations') would make the UK the only country in the world to allow ‘germline’ genetic modification of children, where the genetic changes are passed on to future generations. The Christian Institute opposes the Regulations, which would introduce the techniques in question – Maternal Spindle Transfer (MST) and Pro Nuclear Transfer (PNT).

2. It is claimed that the new techniques will help women with a rare type of illness called mitochondrial disease. TV reports feature sick children with such illnesses. But the techniques would not cure those children. Instead, scientists want to create new disease-free babies by using eggs supplied by a second woman. An embryo, formed from the genetic material of three parents, would be implanted via IVF.

3. The Human Fertilisation and Embryology Authority’s Expert Panel recommended long-term follow-up monitoring of children born from these procedures, yet the Government is ignoring this key public safety protection – citing legal “difficulties”. This ought to have prevented the publication of the Regulations, but the Department of Health has pressed ahead regardless.

The process behind bringing the Regulations to Parliament

4. The Regulations were tabled on the day the House rose for the Christmas recess, 17 December 2014. Consequently, many Peers and MPs will not have sufficient time to consider the Regulations and their implications before they are voted on. For such a significant change, which will result in the UK being the first country in the world to legislate for these procedures, there ought to be proper scrutiny of these Regulations.

5. The Government has rightly consulted on this issue (what it calls ‘mitochondrial donation’), but we cannot agree with the Health Minister’s statement that this has been “comprehensive and transparent”.

6. On 20 March 2013, a press statement from the HFEA announced it found “broad public support” for the two procedures consulted on. However, when asked in question 6 of the consultation whether the law should be changed to allow the procedures, over half of respondents (558 out of 1,055) said no. In the HFEA’s presentation of the results, small public meetings were given equal weighting to the public consultation despite being from a small, select sample.

7. The Government’s own consultation in 2014 again sought to minimise the public opposition to MST and PNT. Of the 1,857 responses to the consultation, 1,152 were opposed to the introduction of the new techniques and 700 were in support. This means that 62% of respondents were against the plans. Why has this been interpreted as overall support?

The UK setting a precedent

8. Techniques that modify the human germline are currently forbidden in the UK and around the world. This prohibition should remain in force. If germline modification in the form of MST and PNT were allowed, the UK would be in danger of becoming a bioethical rogue state.

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35 Mitochondrial Donation: Written Statement – HCWS132, 17 December 2014
9. The UK Government has not ratified the Council of Europe’s *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine*, but would do well to heed its contents. Article 13 states: “An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and *only if its aim is not to introduce any modification in the genome of any descendants*” (emphasis added). We believe the international consensus on this research has been ignored by our Government so that the UK appears “innovative”.

10. The Food and Drug Administration in the USA considered the issue in February last year, but concluded that there is not sufficient data to know if the techniques can be performed safely. This should serve as a salutary warning to our country. The Chairman of its special panel warned as recently as November 2014 that the techniques have not yet been shown to be safe.

**Defining genetic modification**

11. MST and PNT are forms of genetic modification. The genes in mitochondrial DNA pass from a woman’s egg into every cell of her offspring. Changing the genetic structure of an egg or embryo, as these techniques do, is undoubtedly genetic modification. However, the working definition of genetic modification the Government has adopted denies this basic observation.

12. The Department of Health’s definition of ‘germline modification’ specifically excludes the mitochondrial genome so as to reduce the controversy around these procedures. This incorrect definition has influenced the media debate and misrepresents the truth of the matter.

**Ongoing safety concerns**

13. The dangers relating to the techniques have been consistently dismissed and downplayed throughout the course of consultation on MST and PNT. There is no guarantee that these techniques are safe. Senior scientists have expressed concerns about the possibility of unhealthy mitochondrial carry-over, or the incompatibility between nuclear and mitochondrial DNA which might result. The genetic interactions within a single cell are complex and this area of science requires further research.

14. Adverse consequences arising from these techniques may not be reversible and will have far-reaching consequences since the procedures have implications far beyond the specific child involved. In order to downplay fears about the safety of the techniques, mitochondrial DNA has frequently been likened to a battery, doing nothing other than providing energy. This oft-used analogy has coloured the debate on mitochondrial replacement and has ignored emerging evidence – recently highlighted by the New Scientist journal – that mitochondrial DNA plays a more important role in forming a person than initially thought.

**This is not a cure for mitochondrial disease**

15. The debate has been framed as a cure for mitochondrial disease. But these techniques will do nothing to treat those who currently suffer from mitochondrial disorders – around 12,000 people in the UK. Instead, the proposals allow the manufacture of new children who will be at risk of unknown harms.

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36 *USA Today*, 26 February 2014
37 *The Independent*, 17 November 2014
16. Furthermore, mitochondrial disorders will continue to occur randomly within the population. We should be investigating treatments for those adults and children with mitochondrial disorders rather than opening up a new form of eugenics.

6 January 2015
Christian Medical Fellowship

On behalf of the Christian Medical Fellowship, the UK’s largest faith-based group of health professionals, I would like to take this opportunity to draw the Committee’s attention to a number of recent warnings about the lack of evidence of safety and efficacy of the techniques involved, and to new evidence that mitochondria play a more significant role in a person’s identity than has been previously thought.

There is a lack of data from species more closely related to humans that it would be wise to complete before proceeding to human clinical trials. What data there is from animals gives rise to further safety concerns. Several pre-clinical safety tests recommended by the HFEA have either been dismissed, or not concluded, published or peer reviewed.\(^{40}\)

In introducing provision into the Human Fertilisation and Embryology Act 1990 (as amended) for regulations to be passed that will allow techniques which could be used to prevent the transmission of serious mitochondrial disease for a few women, the Government gave assurance that the power to make these regulations would only be considered ‘once it was clear that the scientific procedures involved were effective and safe’.\(^{41}\)

By 2014 the HFEA stated that ‘no evidence was found to suggest that the techniques would be unsafe in humans’.\(^{42}\)

However this statement does not take full account of the mixed evidence currently available and neither does it take account of the lack of evidence for safety.

- Professor Evan Snyder, chair of the scientific panel advising the US Food and Drug Administration (FDA) on mitochondrial transfer, concluded in November 2014 that there are too many unresolved safety issues and that it is premature to proceed. Acting chairman of the FDA committee, Daniel Salomon has similarly said: ‘I think it is pretty ridiculous how little data there is to support any of this, and that worries me.’\(^{43}\)

- On the only occasion one of the proposed techniques (pronuclear transfer) was attempted in humans in China, it resulted in an abortion, a miscarriage and a stillbirth.\(^{44}\)

- Animal studies have yielded variable outcomes including some concerning results. When mitochondrial replacement has been carried out experimentally, it has been shown to alter the metabolism\(^{45}\) and cognitive ability\(^{46}\) of mice. In other species it results in male sterility,\(^{47}\) accelerated ageing\(^{48}\) and changes the expression of many hundreds of genes.\(^{49}\)

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\(^{40}\) For example, the HFEA has admitted that: ‘Current research using PNT in Macaques has yet to be shown to be successful’ however instead of waiting for evidence of safety and efficacy they have instead concluded that safety tests are no longer required to be carried out on non-human primates. Para 3.6.2. http://www.hfea.gov.uk/docs/Mito-Annex_VIII- science_review_update.pdf_.

\(^{41}\) http://www.hfea.gov.uk/6372.html


\(^{45}\) http://europepmc.org/abstract/MED/9546205

\(^{46}\) http://www.nature.com/ng/journal/v35/n1/full/ng1230.html
Christian Medical Fellowship – Written Evidence

- Even some who are closely in this research acknowledge that there may be significant incompatibilities, causing abnormalities: ‘The question of whether the manipulations associated with nuclear genome transplantation might induce epigenetic anomalies remains to be resolved’.50

- Dr Paul Knoepfler has strongly warned about the epigenetic harm caused by nuclear transfer,51 Reinhardt et al found evidence of mito-nuclear mismatch52 while Burgstaller et al conclude that: ‘The dynamics by which mitochondrial DNA (mtDNA) evolves within organisms are still poorly understood’ and they warn of: ‘potential complications for therapies in human populations’ from the preferential replication of even tiny amounts of carry over of mutated mtDNA.53

- Dr Paul Knoepfler also warns that: ‘The UK and the specific leaders making this decision, should they rush forward on this, could well find themselves on the wrong side of history on this one with horrible consequences.’54 Indeed: ‘there is an equal or arguably greater chance that it will tragically produce very ill or deceased babies.’55

Since the interactions between the mitochondrial genome and the nuclear genome are so poorly understood still, it is premature to proceed with human mitochondrial transfer, particularly in view of the fact that this would introduce unknown, irreversible and transmissible changes to the human genetic code down generations. It seems particularly ironic that trying to create genetically related children free of mitochondrial disease for a few women (10 or so at year56) will put their own daughters, and granddaughters, at risk and in need of embryo screening.57

Advocates of these techniques can tend to downplay the relevance of the mitochondria in the individual’s genetic make-up, yet we can all agree that there will be three adults with whom a baby shares a parental genetic connection, even apparently minor.

However Bayliss presents evidence that the contribution of the mtDNA is important in shaping a person’s narrative and determining who a person will be.58 The Committee will also no doubt be aware that the New Scientist recently revised its position on mitochondrial donation, suggesting the role of mtDNA may have been underestimated: ‘Recent research suggests that they play a key

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47 http://www.cell.com/current-biology/abstract/S0960-9822(12)01442-X?cc=y,
53 http://www.hfea.gov.uk/8178.html
54 http://www.cell.com/cell-reports/abstract/S2211-1247%2814%2900395-7?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2211124714003957%3Fshowall%3Dtrue
57 House of Lords Answers to Written Parliamentary Questions, Hansard. 6th May 2014.
58 As a result of these unknown long-term health and safety concerns, the HFEA recommends that: ‘Until knowledge has built up that says otherwise, the panel recommends that any female born following MST or PNT should be advised, when old enough, that she may herself be at risk of having a child with a significant level of mutant mtDNA, putting this child or (if a female) subsequent generations at risk of mitochondrial disease. Thus, we recommend that any female born following MST or PST is advised that, should she wish to have children of her own, that her oocytes or early embryos are analysed by PGD in order to select for embryos free of abnormal mtDNA’. http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf
role in some of the most important features of human life. This raises the ethically troubling prospect ... that children conceived in this way will inherit vital traits from three parents.’

A child has the right to identify and know who his/her three genetic parents are. Denying such knowledge may not be compliant with their human rights. This is already a right granted to children who are adopted so would create a situation where children resulting from three parent embryos techniques are being discriminated against.

Lastly, we note that over 60 countries specifically prohibit human germline engineering because of its profound social, ethical and unpredictable safety consequences for future generations. A statement by the Council of Europe warns that the creation of children with genetic material from more than two progenitor persons is incompatible with human dignity and international law.

We therefore strongly recommend that Government wait until these techniques have passed more safety tests, in order to ensure these techniques do not cause more harm than benefit, before legislation is passed.

January 2015

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59 Three-parent babies: It’s more messy than we thought, New Scientist, 18 September 2014 http://www.newscientist.com/article/mg22329871.600-threeparent-babies-its-more-messy-than-we-thought.html#.VDVfJWd0zcs

60 http://www.bionews.org.uk/page_352766.asp
Professor Bobbie Farsides

My name is Bobbie Farsides and I hold the post of Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School. I am writing to your committee's work in relation to the proposed regulations regarding mitochondrial donation, and in particular any doubts that might have been raised regarding a lack of attention to the ethical issues raised by the proposed technique.

For the past fifteen years I have conducted research into the views, experiences and practices of health care professionals and scientists operating in ethically contested fields of biomedicine. This has included work with assisted reproduction services, stem cell scientists and fetal medicine experts. I have also been involved in a significant amount of public policy work relating to these fields and to the donation of bodily materials and products for medical and scientific use more generally. Most recently I was on the working group which produced guidance on Cell based Advanced Therapies for the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO).

The first point I wish to make is that there is good social scientific evidence available to show that many people conducting cutting edge work in the biomedical sciences and medicine are alert to and concerned to address the ethical issues raised by the techniques they strive to develop, even before their work commences. My own work has shown that the human embryo is viewed as a 'moral work object' even by those whose work will inevitably result in its destruction, and I have come to believe that the first protection afforded to the public is often as a result of the growing moral sophistication of those who work in translational medical research. Whilst being acutely aware of the needs of their patient group, they are also aware of the moral spotlight upon their work and the potential for opposition/concern.

Secondly, where some individual teams or centres may not have taken on the ethical agenda as explicitly as others regulatory and professional bodies are committed to ensuring that the policy and guidance documents they produce are informed by, and clear in their approach to, ethical issues raised by the therapies in question. Ethicists are increasingly involved in developing the protocols and frameworks through which regulatory bodies and specialist committees address the ethical and legal issues relevant to a new or newly expanded procedure.

At the same time as this there is a growing commitment to public engagement and the enhancement of public understanding of science. The HFEA has to some degree led the way in consulting the public and relevant stakeholders, and bodies such as the Nuffield Council on Bioethics also seek to inform their expert reports by canvassing broader views on the subjects they tackle, including mitochondrial research. Furthermore, major funders such as the Wellcome Trust ensure that their grant holders become practiced in communicating their work and engaging with the public's response. Clearly there are inherent dangers (both methodological and philosophical) in relying too heavily on the data collected by exercises designed to capture the 'public morality', but they are helpful in allowing one to judge the 'heat' around a particular issue and how if at all the 'temperature' changes over time.

As a result of my interests and my experience of similar events I was asked to Chair one of the Public engagement evenings hosted by the HFEA during their consultation period regarding mitochondrial donation. The event took place in London and was well attended with several participants having travelled from outside the city. Discussion was lively and the atmosphere in the room was respectful of the people present who told personal stories of their families having been affected by mitochondrial diseases. There were dissenting voices in the room, but interestingly
these were not from members of a concerned public, but rather recognised spokespersons of pressure groups with a tradition of opposing advances in genetic medicine and/or the use and/or of destruction of human gametes and/or embryos.

Another striking aspect of the debate was the lack of scientific understanding on the part of some of those more vociferous in their opposition, including a member of the panel of invited speakers who persisted in making no distinction between the procedures under discussion and the highly emotive issue of cloning. My impression was that a clear account of the science, which has thankfully been made available through a range of publicly accessible resources, would go a long way towards reassuring the general public, even those who might start out with concerns about such issues as ‘having three parents’.

Another term that often comes into play in the face of radical change is the ‘slippery slope’ the idea being that either logically and/or empirically the step being taken (which may not itself be considered immoral) will mean that we have accepted moral principles which could apply equally to practices we would find immoral. Or to present the empirical version - taking this step would inevitably lead us on to practices which are morally unacceptable. I will admit to being no fan of slippery slope arguments, however, even if you give them space in this debate they can be rebutted.

For some people the first step onto the slope was already taken when human eggs and embryos became the subject of medical and scientific attention outside the context of ‘natural’ reproduction. But even these people should be reassured by the fact that a combination of law, professional guidance and scientific and medical culture in this country has ensured that we have not slid down any steep slopes, Rather change has been limited and gradual, and on this issue anticipated rather than unexpected. In practice, the regulatory mechanisms and rights of inspection have been used to full effect. As an American scientist who styled himself a ‘stem cell refugee’ told us within the context of our research, the regulatory framework in this country has allowed science to thrive and has allowed the scientists the space to work.

I believe that there has been a great deal of work done to highlight and then give people space to address the ethical issues raised by this procedure. In the process I think large sections of the public have been reassured and (with the help of some responsible science journalism) the public understanding has shifted away from an alarmist (and incorrect) vision of cloned individuals with three parents being created to order, to that of a rare and highly regulated medical procedure developed in response to particular family’s experience of serious and often fatal disease. In time I believe the story will become an important component of this country’s donation narrative, and as such we are well placed to meet the ethical challenges that poses due to the substantial amount of work already carried out by world leading teams and individuals concerned with the ethical interests of donors and their recipients.

In closing I should say that I shall have the privilege of addressing a meeting of the All-Party Parliamentary Group on Medical Research in Committee Room 6 of House of Commons on Tuesday 13th January on the subject of the proposed regulations. I hope that this meeting will be helpful to members of both Houses.

Bobbie Farsides
Professor of Clinical and Biomedical Ethics
Brighton and Sussex Medical School
University of Sussex
Mitochondrial DNA transfer will, for the first time, produce children with two genetic “mothers” in that these children will have nuclear genes from the mother who gives birth to and raises them (the social mother) and mitochondrial genes from a donor. This has raised concerns about the potentially negative consequences for children’s identity development and psychological well-being.

Although no children have yet been born under these circumstances, it is possible to speculate on the likely psychological outcomes for such children from the findings of research on children born through other assisted reproductive technologies that involve two “mothers”, the most closely comparable of which are egg donation (where children have a social mother and a genetic mother - the egg donor) and gestational surrogacy (where children have a social mother and a gestational mother - the surrogate). In the case of genetic surrogacy, the surrogate donates her egg in addition to hosting the pregnancy, i.e. she is the genetic and gestational mother of the child. An in-depth longitudinal study of the psychological development of egg donation and surrogacy children from age 1 to age 14, conducted at the University of Cambridge Centre for Family Research, has found these children to be well-adjusted with positive relationships with their parents. Thus the absence of a biological link to the social mother does not appear to have an adverse effect on parenting or child development. Further research on older children and adults born through gamete donation conducted by the Centre for Family Research has shown that some wish to search for, and make contact with, their donor. Their primary motivation is curiosity – a wish to understand more about themselves – and not the desire to form a parental relationship with the donor. Although this latter study focused largely on the offspring of sperm donors rather than egg donors, it seems likely that some people born through egg donation will also be interested in searching for their donor as they grow older (egg donation is a relatively new procedure compared with donor insemination and thus a large proportion these children have not yet reached adulthood).

These findings suggest that children born through mitochondrial DNA transfer are unlikely to be at risk for psychological problems as a result of their biological origins. However, they may wish to make contact with their donor. It is important to note that children born through egg donation or surrogacy wish to find out about the person who contributed half of their genetic make-up and/or gave birth to them. For children born through mitochondrial DNA transfer, less than 1% of genetic material is involved. Thus these children are even less likely to experience psychological difficulties resulting from their biological origins, or to be interested in their donor, than are children born from existing assisted reproductive procedures such as egg donation and surrogacy.

Professor Golombok,  
Director, Centre for Family Research,  
University of Cambridge
James Lawford Davies

I specialise in the law relating to reproductive and genetic technologies, human tissue and cells, and related research. In 2004–5 I acted for Newcastle Fertility Centre in relation to their application for a research licence from the Human Fertilisation and Embryology Authority ("HFEA") to carry out pronuclear transfer to prevent the transmission of mitochondrial disease.

I. Scrutiny

There have been important recent reviews of mitochondrial replacement techniques, including the review by the Nuffield Council on Bioethics, the scientific reviews by the HFEA, and their recent public consultation. However, careful scrutiny of mitochondrial donation dates back many years. For example, the Chief Medical Officer’s Expert Group Report, ‘Stem Cell Research: Medical Progress with Responsibility’ (2000, the ‘Donaldson Report’) considered and recognised the future potential use of the technique in treatment. It was then considered again by the House of Commons Science and Technology Committee in their extensive 2005 Report ‘Human Reproductive Technologies and the Law’, and the Committee also supported further research in this area.

Perhaps the most notable and detailed review of the research came later in 2005 when an Appeal Committee of the HFEA considered an appeal by Newcastle University against a decision by the HFEA Licence Committee to refuse a licence for research involving pronuclear transfer on the basis that the proposed research was not permitted by the legislation. Detailed submissions were prepared by both parties to the appeal, and after a full day hearing, the Appeal Committee was satisfied both that the research could be lawfully licensed, and also that it was both necessary and desirable.

In support of the University’s case, we obtained letters from leading scientists and researchers of the day who all expressed their endorsement for the proposed research. These included supportive submissions from, amongst others, the late Dame Anne McLaren, Lord Walton of Detchant, Professor Martin Bobrow, and Professor Peter Rigby. All of these submissions are noteworthy, and considered both the science and the merits of this research in detail. An in-depth review of their comments is beyond the scope of this document, but I should like to make one brief quotation from the Dame Anne McLaren’s letter. Dame Anne was, amongst many other things, a member of the Warnock Committee which designed the framework for the regulation of embryo research in the UK. After expressing her view that she saw no reason why the applicants should not be granted a research licence she stated as follows:

“I incidentally, my recollection of the Warnock committee, which met at a time when transgenic animals were being widely discussed and homologous recombination made gene therapy a plausible long-term goal, is that we all knew what was meant by the “creation of human beings with specific characteristics” [which the Committee proposed be prohibited], and it would never have occurred to us that “health” would be considered a specific characteristic.”
James Lawford Davies – Written Evidence

Whilst I accept that the reviews of the past are in no way binding on your Committee, it would be unfortunate if the very thorough and lengthy review process which has preceded this one—off evidence session were to be over--looked or under--estimated. I also accept that considerations in relation to treatment may be different to research, but I would stress that this particular research has always been proposed and reviewed in the knowledge that treatment and human application of the technology was the ultimate goal – a goal intended to avoid the transmission of mitochondrial disease.

2. Permitting Licences for Treatment

There appears to be much confusion surrounding the purpose and effect of the draft Regulations appended to the Department of Health’s ‘Mitochondrial Donation’ consultation paper of February 2014. For example, in the recent Parliamentary debate on this issue, there are numerous references to the regulations “permitting PNT and MST”, “permitting these procedures”, “the Government’s stated intention to allow the creation of three--parent embryos”, and “legislating to allow techniques”.

The draft Regulations do not permit PNT or MST, and do not allow these techniques to be used. The draft Regulations permit the HFEA to consider applications for licences permitting the use of these techniques in treatment.

To my mind, this is a very important distinction. If the draft Regulations become law, it does not follow that the HFEA will grant licences for the techniques to be used imminently, or indeed at all. By way of illustration, as described above, Newcastle University’s initial application for a licence to carry out the research was originally refused by the HFEA and only permitted after further detailed review – a process which took well over a year.

As with all licence applications, the HFEA will consider whether the proposed activity is safe, and whether the applicant has the necessary staff, expertise, skill and equipment to perform the proposed activity. It follows that even if the draft Regulations are passed, there will be a further tier of in---depth scrutiny by the HFEA and their external advisors before any licence is granted permitting the use of these techniques. The draft Regulations simply allow this further review process to begin.

It is not in anyone’s interests – least of all the HFEA or the researchers – to permit or proceed with an unsafe treatment.

James Lawford Davies
Lawford Davies Denoon Solicitors
12 January
Lily Foundation

The Lily Foundation Charity is committed to funding researching into Mitochondrial Disorders, raising awareness and supporting affected families.

The charity is run by myself and Liz who have both lost children to this disease, so we know first-hand the devastating impact it can have, not only on the affected child but also on the family left behind after the child dies.

We regularly speak to families who are going through the same pain as we did, and the conversation about the risk to subsequent children arises frequently. The thought of bringing another child into the world who will loose skills, suffer pain that cannot be managed, and steadily deteriorate until their little bodies cannot go on any more is often just too much for many families to endure.

These families have had to resign themselves to the fact that they will not be able to have their own child despite their obvious longing to complete their family after suffering such trauma. That is until now.

All we would ask, is that you remember is that it is us, the families that will ultimately make the decision as to whether or not we choose to use these techniques if available. There will be no pressure, it will be an informed decision supported by professionals, it will be our choice, and each family will decide if it is right for them, but for those families who carry the disease and desperately do want another child this technique is a lifeline.

For families like us, the consideration of risk is very different from those who object from the side---lines with no real understanding of this disease. Unaffected opponents talk about safety issues and ethical dilemma’s as a matter of course, however when you have lost a child and you compare a ‘potential unknown risk of the child developing a problem in later life’ with the very real risk that your child will be born with a condition that will take their life in childhood, then there is no comparison. This is a risk that many of our families would jump at the chance to take, as actually it is not a risk at all, it is hope.

As a charity and patient group we have absolute confidence in the expert scientific panel who have extensively scrutinised these techniques far beyond any other novel medical procedure to date, and after watching our children endure the unimaginable, we are now being offered real hope that we can have a healthy baby free from mitochondrial disease.

We urge you, please do not delay considering these regulations, as we know many families who could benefit from these techniques. No perceived theoretical safety risk could be worse than the disease itself. Please don’t deny our families the opportunity to move forward with their lives. They have been through enough already.

Allison Maguire
The Lily Foundation
Research, Education & Family Support
12 January 2015
I also understand that you have received a number of submissions that highlight experiments requested by the HFEA Panel of scientific experts in their Reports on the science and safety of techniques to avoid transmission of mitochondrial disease, but which the correspondents suggest have not yet been completed. Although I do not know the details of these submissions, I am writing to give my own views on the state of the science.

I have served on the HFEA Panel since its inception. Although we have not been formally active since we published our addendum to the Third Report in October 2014 (which would require a formal request from DH, via the HFEA), I have kept up to date with relevant published data and with at least some of the unpublished work that is proceeding, particularly in the labs of Mary Herbert and Doug Turnbull in Newcastle, UK and with that of Shoukrat Mitalipov in Oregon, USA.

First, I should stress that the conclusions of our Third Report were based on extensive review of not just the published literature, but also on unpublished data from, and interviews with, all the main protagonists. This included not just the labs developing the mitochondrial donation techniques, but also groups who have expressed reservations based on theory or some (in our view largely inappropriate) animal models. Much of the as yet unpublished data had to remain confidential for fear of compromising the ability of the groups to publish their work, but the Panel reviewed this as thoroughly as we could, and used this to inform our conclusions. This unpublished work contributed to our overall conclusion that there was no evidence to suggest that the methods were unsafe and that they were likely to be effective, certainly more so than the currently available option of preimplantation genetic diagnosis (PGD).

Those opposing the adoption of the Regulations will not have seen these unpublished data.

As mentioned above, I have also recently been updated on the recent progress of work in both Newcastle and Oregon. These have gone a long way to addressing the few remaining experiments, highlighted in our Third Report, that our Panel recommended to be completed before the methods should be applied clinically. (N.B. As I am sure you are aware, this is a judgment that would need to be made by the Regulator (the HFEA) and is distinct from the adoption of the Regulations by Parliament, which has to precede this.)

I would be the first person to highlight any problems associated with the safety or efficacy of the Mitochondrial Donation methods, indeed the Panel deliberately focused its attention on issues that had been raised as a concern. However, I have heard nothing during the period since our last Report that changes my view that the methods are not unsafe, moreover the direction of travel remains very encouraging.

Professor Robin Lovell Badge, FRS, FMedSci
12 January 2015
1. The HFEA expert panel has not adequately assessed all of the evidence presented to it.

The HFEA convened a panel of experts to examine evidence for the safety and efficacy of MR on three occasions (2011, 2013 and 2014). My colleagues and I submitted evidence to the panel after the second review based on a paper we published in Science (Reinhardt et al., 2013). This paper reviewed data from 25 studies on 6 species where the effects of MR have been experimentally examined. In their response, we were assured that the panel would “of course give careful consideration to the points you raise”. Although our paper was cited in the third review (Human Fertilisation and Embryology Authority, 2013), only 2 studies conducted in fruitflies and mice were discussed and critiqued for spurious reasons. None of the other studies were discussed.

2. A recent meta-analysis of 61 studies carried out in 29 species has been published, showing clear effects of mitochondrial replacement.

This meta-analysis expands on Reinhardt et al, taking a similar approach to that used by bodies such as the Cochrane Collaboration to conduct systematic reviews of evidence. It provides an indication of the overall effect that one might expect should mitochondrial replacement be carried out in a future experiment. The study (Dobler et al., 2014) found a statistically significant moderate effect overall, and therefore indicates that MR in humans would also result in significant and moderate harmful effect.

3. Genetic variation in mitochondrial DNA does influence an individual’s personality.

There are a number of published studies that indicate genetic variation in the mitochondrial DNA influences an individual’s personality (defined as between individual consistency in behaviour). This includes evidence from humans (Skuder et al., 1995; Kato et al., 2004; Shao et al., 2008; Kishida et al., 2009) as well as model organisms (Tanaka et al., 2008; Gimsa et al., 2009; Yu et al., 2009; Batorynski et al., 2011, 2014; Løvlie et al., 2014; Šíchová et al., 2014). As such it is incorrect to assume that mitochondrial replacement will not influence an individual’s identity. None of these data were assessed by the Nuffield Council on Bioethics nor the HFEA expert panels.


There are several studies that have investigated how the variation in the nuclear genome influences the outcome of an individual having a particular mutation in the mitochondrial genome (Hao et al., 1999; Johnson et al., 2001; Bykhovskaya et al., 2004; Hudson et al., 2005; Deng et al., 2006; Ballana et al., 2007; Davidson et al., 2009; Potluri et al., 2009). Similarly, there are several studies that have shown the reciprocal effect i.e. how variation in the mitochondrial genome influences the outcome of an individual having a particular mutation in the nuclear genome (Bonaiti et al., 2010; Kim, A et al., 2010; Strauss et al., 2013; Gershoni et al., 2014; Vartiainen et al., 2014). None of these studies were identified by the HFEA expert panels, despite many being published well before the reviews of evidence were carried out.

Together these studies provide compelling evidence that mitonuclear interactions are relevant to human biology, that they influence a range of important traits (including characteristics one would usually think of as belonging to part of an individual’s identity), and that as such mitochondrial replacement has not yet been shown to be safe for application in a clinical setting.

Edward Morrow
Royal Society Senior Research Fellow
University of Sussex
References


Edward Morrow, University of Sussex – Written Evidence


Muscular Dystrophy

Summary
The Muscular Dystrophy Campaign strongly supports the draft Regulations as we believe they provide an effective regulatory and ethical framework within which research can be undertaken to develop a safe technique to help a relatively small number of women with specific mitochondrial disorders to have a baby free of mitochondrial disease.

We are greatly encouraged by the public support shown during several consultation exercises for the next steps to be taken to develop a treatment using pioneering research techniques. Indeed, the public recognises the potential of the techniques to prevent the inheritance of devastating mitochondrial diseases, giving women whose lives are overshadowed by these conditions the opportunity to bear unaffected children.

The need for regulatory change
Under current regulations researchers can investigate the technique using eggs and embryos donated to research but are only allowed to keep the embryos alive long enough to test whether the technique has worked. Initial testing of the new techniques in the laboratory has been successful; however, for the technique to be tested further and moved toward clinical trials, a change to the regulations is required.

Following an extensive public consultation, the Human Fertilisation and Embryology Authority found that “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”.

What are the views of women with mitochondrial disease?
“I wholeheartedly support the development of this technique. For me, offering such a treatment to women if it is shown to be safe, effective and if it is fully regulated is an ethical imperative. It’s not just about women with mitochondrial disease being able to bear their own children - I would happily consider adopting or fostering a child. It is about having reproductive choice, and above all it is about preventing the transference of mitochondrial disease wherever possible. For some families, this technique may have the potential to halt the suffering that these brutal diseases have inflicted across generations.” Rachel Kean

“Over the years I have been seen by many doctors and specialists at Great Ormond Street Hospital for Children, Guy’s Hospital, and others for tests and consultations, and am still seeing specialists. How mitochondrial myopathy affects my life now is that I rely on my wheelchair and other people for support, I cannot stand up without support. I have difficulty in speaking clearly enough for people to understand me, so I have a Lightwriter machine which vocalises what I type into it, I have a tremor and find it difficult to write, and have other involuntary muscular spasms, which give a tendancy to lean to my left side.

Overall, I have poor muscle development so am not very strong and need help in everything I do, I also am prone to catching colds and coughs and have to take antibiotics on a regular basis over winter. I also take medication three times a day, and a laxative to aid my digestive system.” Elizabeth Howard

Mitochondrial donation and the next stage in research
For many years, the Muscular Dystrophy Campaign has funded research led by Professor Doug Turnbull at Newcastle University and this has led to the development of new IVF-based techniques with the potential to prevent the transmission of mitochondrial disease from affected women to their future children. The proposed techniques would fertilise the egg of a woman with mitochondrial disease with her partner’s sperm and transfer the nuclear genetic material of the
fertilised egg to a donor egg with healthy mitochondria that has had its own nuclear DNA removed.

**Background**

**What are mitochondria?**

They are microscopic energy-producing structures inside cells. They are sometimes referred to as the 'powerhouse' or 'batteries' of the cell. Since muscle cells require a large amount of energy to function, they tend to contain more mitochondria than other cells.

**What is mitochondrial DNA?**

More than 99% of a cell's DNA exists in the 46 chromosomes of the nucleus, half of which are inherited from the mother and half from the father. The DNA in the nucleus contains more than 20,000 genes. The mitochondria have a very small amount of DNA, including 37 genes. Mitochondrial DNA is inherited from the mother only.

**What is mitochondrial disease?**

Mitochondrial diseases are a group of conditions which affect the body's ability to power its cells. They may lead to sight loss, hearing loss, speech loss, severe mobility issues, cognitive difficulties and stroke-like episodes. The prognosis for each individual is almost impossible to predict.

It is estimated that 6,000 people in the UK have a mitochondrial disease. Of these about 3,500 have a mitochondrial myopathy which, in the most severe cases, can cause debilitating and life threatening muscle weakness and the Muscular Dystrophy Campaign supports these individuals.

January 2015
Professor Savulescu, University of Oxford

I am writing to support the passing of legislation permitting mitochondrial transfer to treat mitochondrial disease. I will briefly outline the ethical issues involved and why ethical considerations speak strongly in favour of this procedure.

From an ethical perspective, mitochondrial transfer is most accurately described as a form of transplantation, or micro-organ transplantation.

The human body is made up of microscopic building blocks called cells. There are around 100 trillion of them in the human body. There are around 200 different kinds of cells and they make up the tissues (like muscle) and organs (like heart, liver, lung) of the body.

Every cell has a two main parts: the nucleus and the cytoplasm (like the egg yolk and white of a fried egg). The nucleus contains the DNA or instructions/plan for the cell. It determines how the cell functions and what it will be. The cytoplasm is the workshop where the instructions are carried out. It contains tiny organelles which do this work. One of these is the mitochondria. These provide the energy for the cell. They are sometimes call energy packs. One theory is that they were originally bacteria that the cell captured to work for it, millions of years ago.

In mitochondrial disease, these energy packs don’t work properly. In extreme cases, infants die in the first year because no cell can work without energy.

Mitochondrial transfer is essentially the transplantation of healthy mitochondria to people with diseased mitochondria, just as we might transplant one kidney from a healthy person to another with kidney failure. But this transplantation is at the microscopic scale: organelle transplantation.

Mitochondrial transfer essentially replaces the whole workshop of the cell at the very earliest stage of human development. The only way to do it at present is to take the egg from a healthy woman and remove its entire nuclear DNA. This leaves all the healthy organelles of that cell, including healthy mitochondria. Then the nuclear DNA, which contains all the instructions for life, is transferred from the sick woman's egg. This combination is like a total organelle transplant. But the child will be genetically the child of the nuclear donor, except without mitochondrial disease.

All the ethically important characteristics of the child will be derived from the nuclear donor (the woman with the mitochondrial disease) - organ structure and function, personality, intellectual and emotional characteristics, appearance, etc.

Just as nothing of importance changes about a person when he receives a heart transplant, nothing of moral importance changes when a cell receives a mitochondrial transplant. These are processes which differ merely in scale.
The mitochondria carry tiny amounts of their own DNA, which follows the mother’s line but these code only for the energy metabolism of the cell. They serve no other important or morally relevant function.

There are many kinds of foreign DNA in our bodies. Our cells contain DNA from viruses. There are 10 times as many bacteria in our gut (which have DNA) than there are cells in our bodies. It is DNA in the nucleus of our cells that has the important influence over who we are and how we develop. This is NOT affected by mitochondrial transfer.

Mitochondrial transfer is sometimes misleadingly described as 3 person IVF. While IVF is necessary to transplant the organelles, this is more accurately described as transplantation. Three people are not having a child together with a mix of characteristics, any more than a person with a heart transplant becomes mixed with the donor in any important way.

Importantly, by doing this transplant at the very early stage, the disease is cured. The children of the offspring of this procedure will themselves be free of mitochondrial disease. It would be eradicated forever in this family.

There is no sound ethical basis to oppose this therapy. Opposition is based on misunderstanding, misrepresentation or personal values that should not influence public policy. It would be immoral to consign thousands to death when we have a cost effective cure. It would be to be responsible for their deaths. The only ethical option is to legislate to support this form of transplantation. People often have difficulty with medical innovation and technology. Organ transplantation and brain death were controversial when first introduced. It is the same with mitochondrial transfer. But it is equally life saving.

Transplantation has been one of the great success stories of medicine. Mitochondrial transfer is another step down that road.

Certain forms of transplantation would raise very significant new ethical issues. Brain transplantation or nuclear transplantation (cloning) do raise very serious ethical issues. Liver, heart and lung transplantation do not. Mitochondrial transfer is like liver or heart transplantation - it merely replaces damaged tools within the body.

Life is like a painting. There is the painter, who creates the art. And then there is the paint brush, canvass and paint. These are important and necessary, but they are the instruments. Nobody should object if Da Vinci changed a paint brush. These instruments of the painting are like the organs of the body, including the organelles such as mitochondria. If they are damaged, we should replace them.

There has been an extraordinarily scrupulous and exemplary seven year process of creating responsible legislation. There have been independent ethical reviews, three separate independent expert reviews of all the scientific evidence on the technique's safety, and most
Professor Savulescu, University of Oxford – Written Evidence

importantly a widespread public consultation which has revealed broad support. Each day we delay, potentially another baby dies. It is time to pass this legislation.

Professor Julian Savulescu MB, BS,
BMedSci, PhD Uehiro Chair in Practical Ethics
Director, Oxford Uehiro Centre for Practical Ethics
Director, Institute for Science and Ethics, Oxford Martin School
University of Oxford
9 January 2015
Scottish Council on Human Bioethics

The Scottish Council on Human Bioethics (SCHB) is an independent, non-partisan, non-religious registered Scottish charity composed of doctors, lawyers, biomedical scientists, ethicists and other professionals from disciplines associated with medical ethics. The principles to which the Scottish Council on Human Bioethics subscribe are set out in the United Nations Universal Declaration of Human Rights which was adopted and proclaimed by the UN General Assembly resolution 217A (III) on the 10th of December 1948.

Executive Summary:

1. The SCHB is of the opinion that the law should not be changed to allow Maternal Spindle Transfer (MST) and Pro-Nuclear Transfer (PNT) to take place for Scotland under the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. This is because, the proposal is:

   - A matter which may be devolved to the Scottish Parliament in the very near future
   - Misleading the general public through the use of the term ‘mitochondrial donation’
   - Contrary to international legal instruments
   - Unclear with respect to consequences
   - Genetic engineering which alters the gene line irrevocably
   - A precedent that will eventually and inevitably lead to the further engineering of prospective babies
   - Misleads parents to believe that they are having a child ‘of their own’ when in reality they may have to share parenthood with another woman (the egg donor)
   - Undermines the manner in which children born from these procedures may understand their sense of identity since they may not accept that they only have two parents

2. Moreover, the possibility of promoting MST and PNT in order for parents to believe that they can have ‘children of their own’ while addressing mitochondrial disorders should not be envisaged until the two following questions have been satisfactorily addressed:

   - The wish most couples express for a child ‘of their own’, and
   - The important bonds that exist between the biological parents and the child.

3. If it remains unclear why parents want to have a child of their own, then it remains unclear why the considerable risks related to MST and PNT should even be contemplated when other procedures already exist which enable couples to have a healthy child.

4. Finally, the SCHB notes that new alternatives to both MST and PNT are already being pursued by scientists in the treatment of mitochondrial disorders which can be considered

5. **Note:** The SCHB has asked UNESCO’s International Bioethics Committee (ICB) for an opinion on MST and PNT. In this regard, because of its international responsibilities, it would be appropriate for the UK Department of Health to support the development of an ICB report on the procedures. It would also be inconsiderate of the UK Department of Health to contemplate legalising MST and PNT before the IBC’s report on the subject has been published.

**Definitions:**

6. Though the expression ‘Mitochondrial Donation’ is used in the **2008 Human Fertilisation and Embryology Act**, the SCHB believes that the UK Department of Health’s characterisation of MST and PNT as ‘mitochondrial donation’ is scientifically deeply misleading and reflects a manipulation and misunderstanding of what is really being suggested. It represents a lack of professional discernment in the UK Department of Health as to its role in the context of a democracy in helping the general public understand what the procedures actually mean from a biological perspective.

7. The SCHB would like to question why the UK Department of Health is continuing to use the ambiguous term of ‘mitochondrial donation’ when this has already been shown to potentially mislead the general public.\footnote{Calum MacKellar, Questions relating to ‘mitochondrial replacement’, BioNews, 741, 10 February 2014, http://www.bionews.org.uk/page_395064.asp} This can have very serious repercussions and undermine the democratic process.

8. Certainly the more detailed biological description of both these procedures provided by the Human Fertilisation and Embryology Authority (HFEA) as part of its public consultation made it abundantly clear that it is the chromosomes that are transferred during both procedures, and not the actual mitochondria.\footnote{See: HFEA, New techniques to prevent mitochondrial disease, http://mitochondria.hfea.gov.uk/mitochondria/what-is mitochondrial-disease/new-techniques-to-prevent mitochondrial-disease/ (Accessed on 27 January 2014)

9. Moreover, it is noted that it is not just new mitochondria that are being used in a defective unfertilised or fertilised eggs but a whole new unfertilised or fertilised egg emptied of its maternal spindle or pronuclei, respectively. Mitochondria only form a small part of these new eggs.\footnote{Mitochondria only constitute 15 to 35 per cent of a cell’s total mass. See: Mitochondria, Wellcome NEWS, Spring 2012, p. 24.}
10. The mitochondria are certainly not taken out of one egg and safely transplanted into another egg, from which all or most of the latter’s mitochondria have already been removed. It is, therefore, not so much a process of ‘mitochondrial donation’ or ‘mitochondrial transfer’ but of ‘chromosomal transplantation’.

11. The UK Department of Health mentions in its consultation that:

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

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

12. Again, the SCHB believes, that this is an inappropriate distortion of the facts since there is no question of ‘saving lives’ through the procedures. Instead, it is only certain lives that are brought into existence through MST and PNT. This reflects an unacceptable lack of discernment and even misinformation on behalf of the Chief Medical Officer.

**Devolution of Human Embryology to Scotland under the Smith Commission**

13. In the light of the referendum vote on the 18th of September 2014 and the commitment expressed to strengthen the powers of the Scottish Parliament within the UK, the Smith Commission\(^65\) has indicated with respect to Health and Social Affairs that:

“61. The parties are strongly of the view to recommend the devolution of abortion and regard it as an anomalous health reservation. They agree that further serious consideration should be given to its devolution and a process should be established immediately to consider the matter further.

62. The devolution of xenotransplantation; embryology, surrogacy and genetics; medicines, medical supplies and poisons; and welfare foods (i.e. matters reserved under Sections J2 to J5 of Head J – Health and Medicines, Schedule 5 to the Scotland Act 1998) should be the subject of further discussions between the UK and Scottish Governments. Those discussions are without prejudice to whether or not devolution takes place and in what form.”

14. Because of the above, the Scottish Council on Human Bioethics would like to ask the UK Parliament to not enact the **Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015** for Scotland.

It would be appropriate for the Westminster Parliament to put all new legislation on hold concerning these subject matters for Scotland until it has been established which elements will be devolved to the Scottish Parliament. In the UK, it is only natural that the complex nature of devolved responsibilities in this range of policy areas should be delayed for Scotland in consideration of the full enactment of new legislation.

Human Procreation

15. Traditional human procreation does not take place out of thin air. It takes place through the participation of the man and the woman as whole persons. More specifically, this participation takes place through the means of reproductive cells (sperm and egg cells). In this regard, it is important to consider how these reproductive cells can be understood in the context of reproduction. This is not an easy matter but, generally, each reproductive cell may be considered as a kind of representative of each of the partners in the procreative process. As such, each sperm cell becomes a representative of the whole man and each egg cell becomes a representative of the whole woman.

16. Of course, sperm and egg cells have no moral value of their own but when they come together to form an embryo, their representative wholeness cannot, in any way, be dismissed as unimportant. On the contrary, it is fundamental since it is the reproductive cells that are the means for procreating another specific ‘whole’ living child.

17. This also means that if the sperm and egg cells were significantly modified in a technical manner, such as with MST, questions can be asked whether they would still represent the wholeness of the partners from whom they originated. Would they not be seen, instead, as being foreign in the same way as if the reproductive cells of a foreign man or woman (i.e. from outside the couple) were used? The procreative process may then be taking place with reproductive cells that no longer represent the partners and could be seen as an intrusion into the exclusive relationship of the couple.

Kinship and Personal Identity

18. It is noteworthy that as soon as persons become aware of their existence and are not affected by any serious mental disorders, they usually ask themselves questions about who they are. Of course, the answer to such questions may continually be changing and the quest for identity may never really reach a final conclusion.

19. But one of the most important aspects of this identity is related to a person’s understanding of his or her origins of existence. For example, individuals may want to identify who caused them to exist (and their ancestors) as well as their biological, social and cultural origins in seeking to recognise, understand and make sense of who they really are.

20. When parents, children or other relatives, who have been separated for some reason, eventually seek to re-connect with each other, their reasons for doing so are often difficult to articulate. They frequently struggle themselves to understand what they are actually
looking for though they do recognise that it is something which, to them, is very important. In some cases, of course, they would like to know if they are at risk of having a genetic or other biological disorder but many studies indicate that they are also doing this out of ‘curiosity’ which may reflect a deeper reason such as a search for identity, to know more about themselves or ‘emotional significance’.

It is indeed recognised that people, who do not have any genealogical roots, may often experience a deep sense of genealogical void or bewilderment; of being cut off from the causes and reasons for their existence which helps them build their identity.

21. As a result, individuals usually regard these ancestors and family relatives as being a single community who are ‘cemented’ together. For example, children realise that their existence originated from the personal existences of their ancestors and that their own existence is inherently tied to these previous existences. Without these parents or ancestors they would not exist. As a result they begin to understand that a long chain of ancestors resulted in their existence. It is as if one large communion between the child and his or her ancestors was present, in a kind of single block, who are all the cause of each other’s existences down the ages (the cause may be genetic, gametal such as an emptied egg or something else). People appreciate that because they actually exist because of all their forefathers they owe their existence to them in some way. There is a sense of being dependent on, and even belonging to, these earlier existences. That all these past existences are seen, in some way, as part of the ‘whole’ existence of the child. The child knows that he or she only exists because of his or her ancestors and the prior continuum of descent.

22. In some form, all these existences come into a kind of communion in which there are deep relationships of unconditional acceptance but also responsibility. And this communion does not only exist between parents and their child but with grandparents, siblings, cousins and other family members.

Parents want children of their own

23. The desire by parents to have children ‘of their own’, or at least as much as possible ‘of their own’, is the driving force behind the interest in procedures such as MST and PNT.

24. In addressing the issues raised by the regulation of MST and PNT, it is very important to examine the deep bonds that exist between parents and their offspring. For example, many parents, as the responsible partners in the creation of life, know intuitively that they belong to the child and that the child, in receiving life, belongs to them, i.e., there exists a sort of mutual belonging.

The deep sense of loss or incompleteness felt by parents who are unable to be directly responsible for the creation of life in their child is one of the underlying reasons why many seek assisted reproduction rather than adoption. In other words, the fact that prospective parents even consider, let alone undergo, expensive procedures for artificial reproduction indicates the importance they attach to the biology of creation. Such parents are aware, even if subconsciously, that the lack of biological connection may prevent them from feeling a sense of belonging with the child or the child with them.
25. One of the most fundamental questions which arises from the use of MST and PNT is the fact that at least three individuals are participating in the creation of human life. From this perspective, and although chromosomal DNA is extremely important in the creation of a being, it is impossible to just reduce the concept of parenthood to the persons who contributed to this chromosomal DNA. This is because without an enucleated egg or fertilised egg from another couple, no new life would ever have existed. From an ethical perspective, chromosomes by themselves have no real value as such. They only become ethically meaningful if they are transferred into an enucleated fertilised or unfertilised egg and left to develop. In this regard, all those participating in the process of bringing a life into existence may be considered, in some form and to varying degrees, as the ‘real’ creators of the creature. They may then also experience some or all the corresponding aspects of parenthood bonds and mutual belonging which arise between creators and their creatures.

26. In the case of MST or PNT, it is not only what is being used that is important (and whether DNA, cytoplasm or any other material is considered) but the amount of individual participation in the creative process, be it at a biological or even manipulatory level. A participation which could then also give rise to creator-creature (parent-child) bonds.

27. In this regard, the UK government is arguing that any child resulting from MST or PNT would not be interested in knowing the identity of his or her egg donor. This is because it is just her emptied egg, and not her chromosomes, that is being used to generate the future child. Thus, in contrast to the donation of whole eggs, the government does not want children born from these two new procedures to be able to identify their egg donors.66,67

28. This is, however, very unfortunate and seriously misunderstands the concept of causal parenthood which may be seen as very important to the resulting child who may want to know which individuals were the actual cause of his or her existence.

29. Probably the best example of causal parenthood in which biological parenthood, including genetic parenthood, was seen as being less important than other considerations was reflected in the famous Californian Buzzanca case which took place in 1997. The case arose when an infertile couple, Luanne and John Buzzanca, contracted three separate adults, a sperm donor, an egg donor and a surrogate woman, to help them bring their child into existence through IVF. As a result, a baby girl was subsequently born in 1995. But before the birth took place, and after the Buzzancas signed a contract with the surrogate, John Buzzanca decided to leave his wife and filed for divorce. After a lengthy legal battle over who should pay child-support for the little girl, judges eventually decided that both John and Luanne were to be considered the legal parents even though they did not have any biological, including chromosomal, connections to her. This was because the baby girl would never have been born had not Luanne and John both agreed to have a donated egg fertilised


67 UK Department of Health, Mitochondrial Donation: government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, 22 July 2014, p. 30.
with donate sperm implanted into a surrogate mother. Thus, the court found that the child’s very existence was every bit as much their responsibility as if things had been done the traditional way. This decision acknowledges that it was the persons who were the primary cause for the child’s existence who had parental priority over any other individuals who had caused the child to come into being.

30. This, of course, does not mean that any of the other persons who had caused Luanne and John’s daughter to exist cannot be considered as some kind of parent, such as a genetic or gestational parent. It just means that when any person is partly responsible for the very existence of a child, through any means, then this is sufficient to qualify this person as a causal parent. As such, the daughter of Luanne and John Buzzanca actually has five causal parents whom she may possibly want to identify and with whom she may even want to begin relationships.

Similarly any child born from MST or PNT may also want to identify his or her egg donor (even if her egg’s chromosomes had been removed) since he or she would be aware that without this woman’s emptied egg he or she would not exist.

31. Another example is the hypothetical experiment where two identical twin women are being treated at the same IVF clinic and there is some mix up with their eggs. Assuming, for the sake of the hypothetical experiment, that the women’s eggs were exactly the same from a genetic perspective, there would be no genetic test to tell from which woman the eggs originated. If a son, for example, was born from one of these eggs, could it not be assumed that, when he grows up, he may want to know which twin’s egg was fertilised to bring him into existence? This would happen even though both women produced identical eggs from a genetic perspective. It would surely be important for the child (and the mother) to know which of the eggs was actually used. This means that it is not only the chromosomes or what is found in the genes that matters but also the fact that a certain person brought into existence a certain child through cause and effect. In other words, that a certain life brought into existence another life.

32. This is important since it also reflects the manner in which, historically, individuals have understood who their ancestors or offspring were in matters, for example, of the inheritance of a crown. At that time, no one knew of the existence of chromosomes nor did anyone understand the manner in which biological heritage functioned but they did comprehend that a certain life brought into existence another life.

Again, it was never so much chromosomes or genes that mattered in a historical context but the fact that a certain person brought into existence another person through cause and effect.

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68 Another example is if an adoptive child seeking out his biological father discovers that there is a match for paternity with a certain man but then discovers that this man is not his father but the twin brother of his biological father. The discovery that this man is, in fact, his uncle will be a matter of great significance even though the genetic heritage of both twin brothers is the same. What the child in search of his biological identity is seeking is not merely genetic information of a certain kind but also the truth about the manner of his conception, information about the relationship between his biological father and mother, his kin, siblings, grand-parents, and a great deal more. Jacqueline A. Laing, Artificial Reproduction, Blood Relatedness, and Human Identity, The Monist, Vol. 89, No. 4, (p 548-566). p. 551-552.
33. With MST and PNT the same understanding would exist. In other words, parenthood cannot just be reduced to chromosomes. Instead it is all those who are the cause, including from a biological perspective, of the existence of a child (including the egg donor) who can be considered as causal parents.

**Kinship in Relation to MST and PNT**

34. With natural reproduction, the 'real' creators and the chromosome providers are the two same persons. However, with a number of new fertility procedures, such as with MST and PNT, the involvement of the causal creators becomes very complex and may vary quite considerably. Thus, a real risk exists that the future child may be confused as to the manner in which he or she understands who his or her causal (creator) parents really are. This may be important for him or her to establish a healthy sense of identity.

35. The UK Department of Health mentions in its consultation that:

“1.24 The dominant DNA (the nuclear DNA) in any child born from these new techniques would be that of the mother and the man providing the sperm (usually the father). Although it would be the case that DNA from three people (the mother, the man providing the sperm and the egg donor) would be present in the child, only a tiny percentage of the child’s DNA would come from the egg donor. Most importantly, the residual DNA from the donor would only be mitochondrial DNA so would not affect the resulting child’s personal characteristics and traits. This is because mitochondrial DNA only contains genes that are essential for normal mitochondrial function; personal characteristics and traits are derived from the nuclear material.

1.25 This was reflected in the HFEA’s report of its public dialogue, in which most contributors rejected the “three parent IVF” idea for these reasons. The Nuffield Council on Bioethics report similarly said that “mitochondrial donation does not indicate, either biologically or legally, any notion of the child having either a third parent or a second mother”.

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

36. In response, the SCHB notes that the HFEA and Nuffield Council on Bioethics were mistaken to suggest that “mitochondrial donation does not indicate, either biologically or legally, any notion of the child having either a third parent or a second mother”. They misunderstand the very concept of kinship which cannot be reduced to the personal biological characteristics and traits of a person but must also include the manner in which a child constructs his or her personal identity. An appropriate appreciation of the meaning of kinship, and how this strongly influences the manner in which a person understands his or her identity, is reflected in the above discussion.
37. Part of the identity of a person is based on knowing his or her origins including who was responsible for bringing him or her into existence (i.e. the parents). This cannot be reduced to the origins of the chromosomes but must also take into account all those who were the original cause of a person’s life and existence.

38. From a sociological perspective, MST and PNT are being proposed because couples want children of their own. But that is precisely not how the resulting children may see it. The children born from these procedures may not accept that they only have two parents. Instead they may want to know and have parental relationships with all the 3 or 4 persons who brought them biologically into existence. The SCHB has a lot of sympathy and compassion for persons affected by mitochondrial disorders since they are experiencing a lot of very real suffering. It believes, however, that they are being misguided about the ability of MST and PNT to give them children ‘of their own’ and this is extremely unfortunate and concerning.

39. It may also be the case that parents who use MST and PNT may be bringing a child into the world for their own sakes without fully considering the eventual wishes of the future child. That is, the child may want to know and/or have a relationship with all his or her biological parents. Though the social or chromosomal parents may concede to tell their child the truth when they are older, they would then have to understand that the child may wish to see and know his or her gametal parent(s) (the donor(s) of the eggs or the fertilised eggs) and express a sort of affection which he or she may already experience.

40. A broad societal discussion concerning the relationship between ‘being a creator’ and parenthood while trying to understand these parent-child bonds is, therefore, necessary when the creation of human life by novel means is contemplated. After all, it is because these creator-creature bonds are seen as extremely important by many couples that they are seeking fertility treatment and making sure that they have a child ‘of their own’.

41. Thus, the HFEA should provide in response to a request from a person born from MST and PNT identifying information for all the individuals responsible for bringing him or her into existence. This includes all the egg donors as well as the man who participated in creating the healthy embryo in PNT. This is because the person born from MST and PNT may consider all these 3 or 4 persons as his or her biological parents and he or she may want to know, or even have a relationship with, them in order to develop a healthy psychological identity.

42. Moreover, framing the concept of ‘genetic modification’ so that a comparison is made to organ donation, as was done by the UK Department of Health, is false and misleading. This is because with organ donation a life is already in existence whereas in the case of chromosomal transplantation between unfertilised or fertilised eggs, the very creation of life is being considered which is completely different from a philosophical and ontological perspective.
MST and PNT Contravenes International Law

43. The SCHB notes that the techniques on offer are not about treating people who are ill but about shaping future children and generations. It is also of the opinion that there are serious social and ethical implications to changing the germ line in the way proposed by MST and PNT.

44. Because parents would be intervening, with intent, into the genome (i.e. the complete set of genes, including chromosomal and mitochondrial genes) of their prospective children in MST and PNT, the procedures could be considered as germline interventions. This means that genetic modifications may be passed on to a child and all subsequent descendants. It would be the first time such intentional genetic modifications of descendants is considered and would open the door to further genetic alterations of human beings with unforeseeable consequences. Thus, for the UK to go it alone, without consulting its international partners, and allow both these procedures would create a very serious precedent.

45. The SCHB notes that any intervention seeking to modify the human genome of a person before he or she is created is contrary to international law, including the three following legal instruments:

(A) The United Nations Education, Scientific and Cultural Organization (UNESCO) - Universal Declaration on the Human Genome and Human Rights (Adopted on 11 November 1997) indicates that:

Article 24: That ‘germ-line interventions’ could be considered as a practice that would be ‘contrary to human dignity’.

In this regard, the UNESCO’s International Bioethics Committee explained in 2003 that “Germ-line interventions aim at the correction of a specific genetic abnormality in the germ cells or early embryo or at the introduction of genes that may confer to the embryo additional traits like increased resistance to certain diseases.”

(B) Council of Europe (47 Countries) - Convention for the Protection of Human Rights and Dignity of the Human Being with Regard To The Application of Biology and Medicine (ETS – No. 164, Entered into force on 1 December 1999) indicates that:

Article 13 – Interventions on the human genome

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An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

In this regard, the **Explanatory Report** for Article 13 mentions that:

91. Interventions seeking to introduce any modification in the genome of any descendants are prohibited. Consequently, in particular genetic modifications of spermatozoa or ova for fertilisation are not allowed. Medical research aiming to introduce genetic modifications in spermatozoa or ova which are not for procreation is only permissible if carried out in vitro with the approval of the appropriate ethical or regulatory body.

92. On the other hand the article does not rule out interventions for a somatic purpose which might have unwanted side-effects on the germ cell line. Such may be the case, for example, for certain treatments of cancer by radiotherapy or chemotherapy, which may affect the reproductive system of the person undergoing the treatment.”

**C) The EU (28 Countries) Directive on clinical trials (2001/20/EC)**

This states in Article 9(6) that:

“No gene therapy trials may be carried out which result in modifications to the subject’s germ line genetic identity.”

46. Bearing in mind the UNESCO, Council of Europe and European Union Statements it would be very important to define the international implications for the UK to unilaterally pursue germline genetic engineering. For any female offspring conceived using such techniques in the UK, questions may arise relating to the necessary limits placed on her reproductive freedoms should she choose to eventually live in other countries in order to prevent germline alterations being transmitted beyond national borders.

47. Furthermore, for the UK Department of Health to consider allowing MST and PNT without undertaking any clinical safety investigations so that it does not come under the definition of a clinical trial (and therefore not regulated by the EU Clinical Trials Directive) would very likely be seen as irresponsible and even reckless by the general public.

48. The UK Department of Health mentions in its consultation that:

1.30 It is important to note that the UK Parliament has expressly provided for the possibility of regulations enabling mitochondrial donation and that it is our view that this power is compatible with the European Convention of Human Rights.”

49. In this regard, the SCHB disagrees that MST and PNT is compatible with the **European Convention on Human Rights**. Indeed, should a case be brought to the European Court of Human Rights (ECHR) related to MST and PNT, it is inevitable that the judges of the ECHR will base their decision on Article 13 of the **European Convention for the Protection of**
MST and PNT Represent Eugenic Practices

50. Both MST and PND could be considered as different forms of eugenic practices since the genome of future children are being intentionally modified through the procedures. Eugenic procedures are generally defined as strategies or decisions aimed at affecting, in a manner which is considered to be positive, the genetic heritage of a child, a community or humanity in general. As such they would contravene Article 3 of the Charter of Fundamental Rights of the European Union (Proclaimed in Nice on 7 December 2000) which indicates that “In the fields of medicine and biology ... the prohibition of eugenic practices, in particular those aiming at the selection of persons” must be respected.

51. When a eugenic choice between bringing into existence a disabled or non-disabled person is being considered, it is impossible to separate these persons from their physical characteristics. Any choice in this regard which then becomes public will be seen as very significant by the disabled community since it would suggest that they should also not exist. Even once they are born, the very identity of persons and the manner in which they understand themselves as individuals cannot be dissociated from their physical characteristics.

In summary, there is a real danger of discrimination to suggest that disabilities, which cannot be separated from persons, should not be brought into existence. This is because the disorder’s existence cannot be dissociated from a person’s existence. Instead, it is all persons with or without a disability who should be able to be brought into existence without favouritism, discrimination or bias. In other words, saying that a disorder should not exist, should never mean that a person with such a disorder should not be brought into existence.

52. In this respect, the SCHB is of the opinion that making sure that only certain persons are brought into existence in a eugenic manner significantly undermines the very basis of human equality and human dignity.

MST and PNT Involves the Destruction of Embryos

53. The SCHB notes that a significant ethical question would arise if human embryos are destroyed during this procedure.

54. In this regard, the UK Human Fertilisation and Embryology Act 2008 defines an embryo in Article 1: (1) (b) as: “an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo.”

55. For MST and PNT to be accepted for clinical use, it is unavoidable that many human embryos will be created solely for research purposes that will, eventually, be destroyed. This creates a serious ethical problem since the Council of Europe’s Convention for the
Protection of Human Rights and Dignity of the Human Being with Regard To The Application of Biology and Medicine\textsuperscript{70} indicates that:

\textit{Article 18: The creation of human embryos for research purposes is prohibited.}

56. In this regard, the Explanatory Report for Article 18 mentions that:

\textit{“116. The article does not take a stand on the admissibility of the principle of research on in vitro embryos. However, paragraph 2 of the Article prohibits the creation of human embryos with the aim to carry out research on them.”}

57. At present, out of the 47 countries of the Council of Europe only \textbf{two member states} (the United Kingdom and Belgium) have publicly indicated that they have no intention, at present, of signing or ratifying this convention. This is because, amongst other things, it would prohibit the creation of human embryos for research through cloning or other procedures (which the UK has already legalised) so that experiments can take place on them for up to 14 days after their creation.

58. Furthermore, if PNT were to be accepted as a form of routine treatment and because UK law defines an embryo as \textit{“an egg that is in the process of fertilisation”}, the procedure would require that at least two embryos are destroyed, each time, to reconstruct a third embryo with new healthy mitochondria. This would be seen as deeply offensive and unacceptable to the millions of people in the UK who believe that personal life begins at the moment of creation of the embryo.

\textbf{Further Risks with MST and PNT}

59. It should also be noted that assisted reproduction is not risk-free for the woman giving the eggs since egg retrieval procedures may risk ovarian hyperstimulation syndrome following aggressive hormonal treatments.

\textsuperscript{70} This is a legally binding document when ratified by a country. So far, 29 Member States have ratified this Convention with another 5 signing their intention to ratify. The UK has not signed or ratified this Convention.
As a medically qualified bioethicist, I am writing to express my grave reservations about the haste with which the Government is seeking to permit mitochondrial donation trials in human subjects. Whilst there are numerous factors that cause me concern, I will restrict my comments to just three points of particular importance.

a) The procedure(s) will require large numbers of donor eggs. The procedures are very similar to cloning techniques which are highly inefficient in animal work. Dolly the sheep eventually resulted from the use of 400 extracted sheep eggs which had dwindled to 267 after enucleation failures. The pressures on women to obtain the necessary quantities of donor eggs required has hardly been mentioned in the debate but has already led to research scandals known across the world.71

b) The rest of the world has reached a clear consensus that the techniques are not safe at the present state of our knowledge about mitochondrial and nuclear DNA interactions. Even in the UK, the prospect is being couched by its advocates in terms of “not being unsafe” which I find unnerving rather than reassuring. The New Scientist in September 2014 concluded that those in favour of proceeding “may have seriously underestimated the influence that mitochondria have”.72 Only a few weeks ago Profs Stuart Newman from New York Medical College73 and Evan Synder, Chair of the FDA warned of the dangers of premature human trials.74

c) These techniques can do nothing to help those born with mitochondrial disease and it is likely that research on mDNA transfer will divert money from research into cures for those not detected before birth. Furthermore it is estimated that this technique will detect a minority of cases, leaving several hundred people being born each year with mitochondrial disorders who will still need treatment, care and support.

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5 January 2015

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72 New Scientist 2014 Three-parent babies: it’s more messy than we thought
http://www.newscientist.com/article/mg22329871.600-threeparent-babies-its-more-messy-than-we-thought.html#VKWRU3sroQt