# Science and Technology Committee

## Mitochondrial Donation

## Consultation response from the Christian Medical Fellowship
## October 2014

The Christian Medical Fellowship (CMF) was founded in 1949 and is an interdenominational organisation with over 4,500 British doctor members in all branches of medicine, and around 800 medical student members. We are the UK's largest faith-based group of health professionals. A registered charity, we are linked to about 80 similar bodies in other countries throughout the world.

## Executive Summary

1. The arguments most commonly put forward to justify the use of mitochondrial donation for humans are variants on the following two questions posed in a recent BioNews article by Prof Frances Flinter[1]:

***Is it ethical to try and prevent the development of a treatment that might enable the birth of a healthy baby for a couple for whom there are no other options?***

***Is it ethical to avoid trying a treatment that could also avoid further tragedy in future generations?***

Our submission challenges the presuppositions behind two questions, which are central to the justification of mitochondrial donation.

### 2. Are there 'no other options' for prospective parents?

Many women who want a healthy, *genetically related* child, can use pre-implantation genetic diagnosis. Adoption or IVF with the use of a donor's egg are other available alternatives. In these cases, a child would not be fully genetically related but also would not be put at grave risk by an experimental, irreversible procedure. Furthermore, promising alternatives to both maternal spindle transfer (MST) and pronuclear transfer (PNT) are already being pursued by scientists in the treatment of mitochondrial disorders, that do not involve changing the germline (references below).

### 3. Will mitochondrial donation techniques 'enable the birth of a healthy baby'?

Evidence presented to the HFEA since 2011 suggests that the application of this technology will be more unpredictable, complex, risky and limited (to certain combinations of haplogroups) than is being claimed by the HFEA. Evidence to the FDA suggests the same. Even those who are involved closely in this research acknowledge that there may be significant incompatibilities, causing major abnormalities. Hence the HFEA recommendation to screen embryos of any females who might be born *following* MST or PNT.

[1] Professor Frances Flinter, BioNews 29 September, 2014.
http://www.bionews.org.uk/page_455952.asp

## 4. Will the use of mitochondrial donation 'avoid further tragedy in future generations'?

The results from mice and invertebrates suggest that many deleterious effects would not be revealed until adulthood. Again, this is evidenced by the warning that if a woman has a daughter born using these new techniques, her own daughter will have to use embryo screening to avoid the risk of passing on mitochondrial disorders, because there is such a risk her daughter will have abnormal mitochondria!

5. We are concerned that those promoting mitochondrial donation are ignoring the risks to the health of women alive now. Nuffield has noted that '*many more egg donors will need to be found…A shortage of egg donors is an acknowledged problem'*. Egg donation is ethically troubling and risky to women's health, and for this research, is of no benefit to them.

## 6. Are these techniques a 'treatment' for mitochondrial disorders?

Jeffrey Kahn of Johns Hopkins University admits that this is not about saving or treating lives: '*We're not treating humans. We're creating humans.'* Mitochondrial disease will continue to appear randomly at birth within the population. Indeed, very few women (about ten per year in the UK) would be candidates for even considering these techniques prior to pregnancy.

## 7. Is it ethical to 'try a treatment' (ie. experiment) on humans?

It is argued – often justifiably - that no research is 100% guaranteed to be safe, hence the need for human clinical trials. However these techniques are different to any others permitted before because they change the germline and impact future generations in ways we do not know and cannot predict. Serious safety issues associated with mitochondrial donation have been identified, and it seems ironic that trying to create genetically related children free of mitochondrial disease for a few women will put their own daughters, and granddaughters, at risk.

Acting chairman of the FDA committee, Daniel Salomon: '*I think it is pretty ridiculous how little data there is to support any of this, and that worries me.*

## 8. Are there other ethical and practical concerns with using new mitochondrial donation techniques?

Mitochondrial transfer is genetic modification and this modification is handed down the generations. It cannot be compared with a blood transfusion or a transplant.

All three genetic parents would play some role in the child's biological and genetic heritage, therefore the question is how much should that be recognised? Have politicians, the media and the proponents of this research seriously underestimated the influence that mitochondria have? The severity of the disease itself reflects the importance of the mitochondria for humans. Children conceived in this way will inherit some vital traits from three parents and need to be informed of that.

# Response from Christian Medical Fellowship

## Are there 'no other options' for prospective parents?

9. Procedures already exist that enable couples to have a healthy child of their own. The desire by parents to have children *genetically related* to them, and of course free of mitochondrial diseases, is the justification for the interest in the novel techniques, maternal spindle transfer (MST) and pronuclear transfer (PNT).

10. However for women who want (note, 'want' not 'need') to have a healthy child, *genetically related* to both parents, pre-implantation genetic diagnosis (PGD) is an alternative for many (albeit with some ethical concerns). Indeed, PGD is recommended by the HFEA for any females who might be born *following* MST or PNT, because of the risk that they will have a child of their own with mutant mtDNA.[2]

11. Adoption or IVF with the use of a donor's egg are also available alternatives. In these cases, the child would not be genetically related to respectively both or one of its parents but neither would the child or his/her children be put at grave risk by an experimental, irreversible procedure.

12. Moreover, alternatives to both MST and PNT are already being pursued by scientists in the treatment of mitochondrial disorders, that do not involve changing the germline. These are already making useful progress, and as one article concludes: *'This opens up new avenues to understand and develop therapies for mitochondrial diseases'*.[3]

13. We question whether the **risks to the child** created using these experimental mitochondrial donation techniques can ever be justified by the desire for him/her to be genetically related to both parents, when alternative options can be considered for prospective parents.

## Will these techniques 'enable the birth of a healthy baby'?

14. The HFEA review of the safety of these techniques, in June 2014, concluded that it is safe enough to create one baby from three parents. Assuming, that is, one considers the reviewers' double negative wording to say as much: '*The evidence [the panel] has seen does not suggest that these techniques are unsafe*.'[4]

15. However if the double negatives are removed then we are left with the words: 'The evidence [the panel] has seen does suggest that these techniques are safe.' So why do the HFEA not say this directly? The clear implication is that there may be evidence that panel has not seen, which further research might uncover, that would point to the opposite conclusion.

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[2] http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

[3] Anonymous, Correcting human mitochondrial mutations, 13 March 2012, e! Science News, http://esciencenews.com/articles/2012/03/13/correcting.human.mitochondrial.mutations,

[4] Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

16. Presumably the HFEA panel is aware that there remain too many safety concerns and unknown risks to justify a green light to creating reconstituted human embryos in order to avoid passing on debilitating and life-threatening mitochondrial disorders. But at the same time they cannot bring themselves to say 'no' to it.

17. In fact, evidence presented to the HFEA since 2011 suggests that the application of this technology and modification of the mammalian egg may well be more unpredictable, complex, risky and limited (to certain combinations of haplogroups) than is now being claimed by the HFEA.

18. For example, nuclear-mitochondrial compatibility is essential for nuclear transfer. Several scientific journal articles have highlighted concern that disrupting the 'fine-tuned' relationship between the nuclear and mitochondrial gene complexes will adversely affect health of the offspring.[5]

19. The HFEA have been provided with evidence that nuclear-mitochondrial interactions are disrupted following nuclear transfer, leading to 'unhealthy' mitochondria and compromised cell function.[6]

20. The macaque study by Tachibana et al had provided critical justification for the HFEA to recommend to the UK Government that the PNT procedure should be safe for human trials to proceed and that regulations should be introduced to permit their use to create new humans.[7] Although the HFEA has since admitted that: 'Current *research using PNT in Macaques has yet to be shown to be successful*' they have instead concluded that safety tests are no longer required to be carried out on non-human primates.[8]

21. Even those who are involved closely in this research acknowledge that there may be significant incompatibilities, causing abnormalities: 'In *addition to the risk of aneuploidy and other effects of the technical procedures, concern has been raised about the implications of possible incompatibilities between the nuclear genotype of the parents and the donor mitochondrial genomes. The potential biological significance of this stems from the fact that the majority of proteins involved in mitochondrial metabolism are encoded by the nuclear*

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[5] For example, Klaus Reinhardt, Damian K. Dowling, Edward H. Morrow. Mitochondrial Replacement, Evolution, and the Clinic. *Science.* 20 September 2013: Vol. 341 no. 6152 pp. 1345-1346. '...studies *in humans have only tracked health through to the blastocyst stage and in macaques to three years of age. The results from mice and invertebrates suggest that many deleterious effects of MR would not be revealed until adulthood.'* The same researchers note that studies on other organisms have found that mitochondrial replacement does indeed have a big (adverse) effect on genetic expression, but this has received little profile. See also http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

[6] Eg.. See St. John, J. C., R. E. Lloyd, et al. The consequences of nuclear transfer for mammalian foetal development and offspring survival. A mitochondrial DNA perspective. *Reproduction* 2004: 127(6): 631- 41. St. John, J. C., R. E. Lloyd, et al. The potential risks of abnormal transmission of mtDNA through assisted reproductive technologies. *Reprod Biomed Online* 2004 Jan; 8(1): 34-44).

[7] HFEA, Mitochondria public consultation 2012. Tachibana et al. (2013) *Nature* Vol. 493 issue 7434, p. 627-631.

[8] Para 3.6.2. http://www.hfea.gov.uk/docs/Mito-Annex_VIII- science_review_update.pdf_

*genome.'* 'The *question of whether the manipulations associated with nuclear genome transplantation might induce epigenetic anomalies remains to be resolved'.*[9]

22. PNT has been so unsuccessful with monkeys (causing *increased* abnormalities) that the HFEA suggests that monkeys are not a good model for humans and instead mice, or humans themselves, should be used for trials.

23. Adverse experiences with germ line modification and somatic gene transfer should serve as a warning for the enormous risks that would await mitochondrial gene replacement in humans.[10]

## Will the use of mitochondrial donation 'avoid further tragedy in future generations'?

24. The results from mice and invertebrates also suggest that many deleterious effects would not be revealed until adulthood. Thus the HFEA warns that if a woman has a daughter born using these new techniques, her daughter will have to use embryo screening to avoid the risk of passing on mitochondrial disorders, because there is such a risk her daughter will have abnormal mitochondria![11]

25. In other words, a mother can choose to use this technique instead of embryo screening but her daughter will have to use screening. 'Reproductive choice' only works for some. And why is this technique safe for the mother but not her daughter?

26. Those promoting mitochondrial donation appear to be ignoring the risks to women alive now. Very few have warned of the dangers to another – larger – group of women who will risk their health for this research, by providing their eggs.

27. Yet the Nuffield Council on Bioethics has warned that: ***'One of the major barriers mentioned by scientists*** *when assessing the potential for cell reconstruction techniques to become treatments is the fact that* ***many more egg donors will need*** *to be found to undertake the research required in order for the safety and efficacy of PNT and MST to be established, and if therapies are to be provided in future.* ***A shortage of egg donors is an acknowledged problem*** *in respect of donation for reproduction,* ***and it is not yet clear whether egg donors would be more likely to come forward in sufficient numbers to take part in mitochondrial donation for research or treatment use.'*** (my emphasis).[12]

28. Egg donation has significant health and ethical implications, including the health risk to the donor from powerful hormonal treatments, injections, invasive surgery, [13] and it is not for her own benefit.

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[9] Craven, Murdoch, Herbert, Turnbull et al, Mitochondrial DNA disease: new options for prevention. Hum Mol Genet. Oct 15 2011; 20(R2): R168–R174. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179382/

[10] Bredenoord, A., Braude, P. Ethics of mitochondrial gene replacement: from bench to bedside. *Br. Med. J.*. 2011;342:87-89. Also http://www.ncbi.nlm.nih.gov/pmc/articles/PMC543871/ A further example was the death of a healthy teenager in a clinical trial for gene therapy in 1999.

[11] http://www.hfea.gov.uk/docs/Mito-Annex_VIII- science_review_update.pdf

[12] http://www.nuffieldbioethics.org/sites/default/files/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf

[13] http://www.nlm.nih.gov/medlineplus/ency/article/007294.htm

29. In preliminary trials the Oregon team driving much of this new mitochondrial research used 106 eggs from seven women; one woman donated 28 eggs, indicating possible ovarian hyperstimulation syndrome (OHSS) which can be dangerous or even fatal.[14]

30. The two techniques used for mitochondrial diseases should be less wasteful of eggs than cloning techniques. However, 'fewer' still means many eggs. Every single embryo generated by the two techniques (spindle transfer and pronuclear transfer) ultimately needs at least two eggs, and probably more as the procedure is, first, unlikely to be 100% efficient and, second, at least half the embryos may be defective, if the published results are anything to go by.[15] So even more 'material' may be required in order to create an embryo considered suitable for transfer to a womb.

31. The team in the UK driving this new research, the Newcastle Fertility Centre, have not recently published information about the total number of eggs and embryos they have used in particular research projects. However a study at the Newcastle Fertility Centre, reported in *Human Fertility,* found that more than 20 eggs were collected from at least one in seven patients, 14.5% of these women were admitted to hospital and nearly all reported symptoms consistent with OHSS.[16]

In other words, between 1999 and 2003 a total of 49 women were admitted to hospital. Life-threatening complications occurred in two women.

32. Worryingly, there seem to be no definitive data on the number of women hospitalised for OHSS after egg donation, as a Parliamentary response reveals.[17] We know from an HFEA report[18] that just under half of 864 reported clinical incidents between 2010-2012 were due to OHSS. And: '*Each year approximately 60 instances of severe OHSS and 150 cases of moderate OHSS are reported to the HFEA*.'

## Are these techniques a 'treatment' for mitochondrial disorders?

33. None of the proposed techniques represents an actual cure for mitochondrial disease, which will continue to appear randomly at birth within the population. The techniques will not treat or save lives. These techniques can only be applied to families after they have been identified as being at risk of conceiving a baby with mitochondrial disease and will be used experimentally to create *new* lives - for women who want their child to be genetically related to them.

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[14] http://www.geneticsandsociety.org/downloads/Donna Dickenson Commercialization of Human Eggs in MT Replacement Research.pdf

[15] Tachibana et al. (2013) *Nature* Vol. 493 issue 7434, p. 627-631 found that 52% of embryos created through spindle transfer had chromosomal abnormalities – four times as many as control embryos. Craven et al. (2010) *Nature* Vol. 465, issue 7294: p. 82-85 reports that *'After transfer of two pronuclei, 8.3% of abnormally fertilized embryos developed to the blastocyst stage…This is approximately 50% of the blastocyst rate for unmanipulated abnormally fertilized embryos…'*

[16] http://www.publications.parliament.uk/pa/ld200708/ldhansrd/text/80110w0002.htm#08011053000119

[17] http://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2014-07-02/203642/

[18] http://www.hfea.gov.uk/docs/Adverse_incidents_in_fertility_clinics_2010-2012_-_lessons_to_learn.pdf

34. This is an important difference. Jeffrey Kahn of Johns Hopkins University correctly acknowledges that these techniques are not treatments for mitochondrial disorders but are experimental methods of creating new lives free of the disorders: '**We're *not treating humans. We're creating humans.*'**[19]

35. Very few women would be candidates for even considering these techniques. Only about 15% of mitochondrial diseases are even caused by mitochondrial DNA. So these techniques would not help 85% of the women with mitochondrial diseases. Moreover, mothers can pass on disorders without being clinically affected themselves. Most cases are not diagnosed until after birth as many are sporadic and/or miss a generation because of variable penetrance.

36. Government claims that about ten lives per year in the UK may be saved are based on estimates by the Wellcome Foundation that have not been verified. Earl Howe, Health Minister, said recently that: *'Numbers are based on advice from the Wellcome Centre for Mitochondrial Research at Newcastle University...based on the numbers of patients already undergoing some form of reproductive assistance each year in the form of either pre-implantation genetic diagnosis or prenatal testing...The* ***Department of Health has no written calculations that can be placed in the House of Lords library.***[20]

37. In other words, these techniques will not be of any benefit to most children or parents and children will still be born with mitochondrial disorders.

## Is it ethical to 'try a treatment' (ie. experiment) on humans?

38. It is argued – often justifiably - that no research is 100% guaranteed to be safe, hence the need for human clinical trials. However these techniques are different to any others ever permitted before, and would be prohibited in most other countries in the world, because they would change the germline and impact future generations in ways we do not know and cannot predict. Germline genetic engineering is a rubicon that should not be crossed.

39. The HFEA understand this concern, so suggest putting in place follow-up studies of children born using these new techniques. However this would not be legally required and follow-up studies are notoriously difficult to carry out over the long-term, especially if descendants also need follow up. Families cannot be contained in a lab, or in one place, like animals. There has been no follow up of the few children in the US born from similar techniques in 1996-7 (which were subsequently banned), nor evidence of how many were aborted or suffered abnormalities.[21]

40. This led acting chairman of the FDA committee, Daniel Salomon to say: '*I think it is pretty ridiculous how little data there is to support any of this, and that worries me.*'[22]

41. As we have noted in detail above (paragraphs 17-24), there are serious safety issues associated with mitochondrial donation and modification of the mammalian egg, which have been identified in animal studies, including decreased survival, inhibited growth, behavioural

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[19] http://www.sciencemag.org/content/343/6173/827.full
[20] House of Lords Answers to Written Parliamentary Questions, Hansard. 6th May 2014.
[21] http://www.nytimes.com/2014/06/29/magazine/the-brave-new-world-of-three-parent-ivf.html?_r=1
[22] http://www.nytimes.com/2014/06/29/magazine/the-brave-new-world-of-three-parent-ivf.html?_r=1

and fertility problems. This technique has also been tried in humans, resulting in an abortion and two stillbirths.[23]

42. It seems ironic that the primary rationale for permitting these techniques is to allow some women to have genetically related children free of mitochondrial disease. And yet there is a high likelihood that children created using these new experimental techniques will be put at **greater risk themselves,** and any abnormalities and problems will be **generationally transmissible,** and thus affect even more children.

## Are there other ethical and practical concerns with using these new techniques?

### Is it genetic engineering?

43. '*The Government has decided to adopt a working definition for the purpose of taking forward these regulations. 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.'*[24]

44. However back in 2013 the Government took a different line: '*…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 be a form of germline modification or germline gene therapy, as respectively recognised by the HFEA and the Nuffield Council on Bioethics.'*[25] There appears to be a deliberate lack of transparency here.

45. Lord Robert Winston says: '*Of course mitochondrial transfer is genetic modification and this modification is handed down the generations. It is totally wrong to compare it with a blood transfusion or a transplant and an honest statement might be more sensible and encourage public trust*.'[26]

46. The proposed techniques are unequivocally germline genetic modification as they would take place in the laboratory during IVF, and therefore be passed on to future generations with unknown consequences.

## The role of the donated mitochondria or 'third parent'

47. Advocates of these techniques downplay the relevance of the mitochondria in the individual's genetic make-up, yet we can agree that there will be three adults with whom a baby shares a parental genetic connection, and there will be identifiable genetic material from a second female parent which will be passed down the female generations.

48. Organ donors do not enable a person to come into existence but instead enable an existing person to stay alive. By contrast, with mitochondrial donation three parents create a *new* child by MST or PNT. They would all be biological parents, albeit playing different roles.

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[23] Fertility and Sterility Vol. 80, Suppl. 3, September 2003 s56 abstract.

[24] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf

[25] Earl Howe, 18 December 2013, Hansard http://www.publications.parliament.uk/pa/ld201314/ldhansrd/text/131218w0001.htm

[26] http://www.independent.co.uk/news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-babies-in-its-regulation-of-new-ivf-technique-9631807.html

49. So all three parents play some role in the child's biological and genetic heritage, therefore the question here is how much should that be recognised?

50. Others have argued that the contribution of the mtDNA is important in shaping a person's narrative and determining who a person will be.[27] A child has the right to know about the existence and identity of all of their genetic parents, as well as how they came into being. Therefore a person must be informed if they were born (created) using mitochondrial donation techniques

51. The New Scientist recently revised its position on the ethics of mitochondrial donation suggesting the role of mtDNA may have been underestimated. *'Recent research suggests that they play a key 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*.' [28]

## Conclusion

52. While we do not agree in principle with the use of these techniques, for both ethical and practical reasons, as a minimum we strongly recommend that Government wait until these techniques have passed all necessary safety tests before they are permitted to be used on humans.

53. We suggest that funding would be more effectively invested into researching treatments for the many who are already living with mtDNA disorders, and for those who will continue to be born with such disorders.

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[27] Baylis F. The ethics of creating children with three genetic parents. *Reproductive BioMedicine Online* 2013;26:531-534.

[28] *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