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Dear David,

Thank you for your email of 7 February 2015 enclosing a letter from Professor Paul Knoepfler of the University of California about mitochondrial donation.

I do appreciate you finding the time to attend the Roundtable Briefing on 4 February. I think it was important to explore issues of concern and I do recognise that some areas of dispute remain. I should say that the reporting and headline-making by *The Independent* in their representations of Professor Knoepfler's comments were overly simplistic and sensationalist. Reporting in general of the mitochondrial donation regulations and the Government's intentions has tended towards the unsophisticated.

I will address the points in Professor Knoepfler's letter in turn.

Risk of mitochondrial donation

One of the aspects of the scientific reviews which were studied in detail by the Expert Panel convened by the Human Fertilisation and Embryology Authority (HFEA) was the risk to health of these techniques.

The view of the Expert Panel was that experiments involving Pro-nuclear Transfer (PNT) and Maternal Spindle Transfer (MST) in animals (mice, macaques, and some other animals) have not given any cause for concern.

The experiments that have revealed problems associated with similar technology, are when two widely separated strains of mice have been involved (essentially subspecies) and specifically when the mice have two

substantially different types of mitochondria (heteroplasmy). In these cases the differences in the mitochondria are much more substantial than occurs in humans. And where only one type of mitochondria is present (homoplasmy), irrespective of the origin of the nuclear DNA, the animals do not show any defect.

Thus, whilst there is some evidence of problems associated with similar technology in inbred strains, where any normal variation in nuclear genes is missing, it was the Expert Panel's view that this was not relevant to the human situation. Humans are outbred species and there is good evidence from population studies that the nuclear and mitochondrial genes will not co-evolve unless there are reproductive barriers, which are again not evident in humans.

As far as increased risk of cancer is concerned, no evidence was given to, or found by the Expert Panel to suggest that any of the mitochondrial donation methods would lead to an increased frequency of mutations or epigenetic alterations therefore there is no reason to suspect any increased risk of cancer. No increased incidence of tumours after PNT or MST compared to controls has been noted in any of the evidence brought before the Expert Panel.

Cytoplasmic transfer to treat infertility

The use of cytoplasmic transfer to treat infertility is totally different to using PNT or MST to prevent transmission of serious mitochondrial DNA disease. The incidence of having miscarriages and children born with chromosomal and developmental disorders increases significantly in older women (and to some extent in older men), due to a much higher frequency of chromosomal abnormalities in the eggs (and sperm). Moreover, some of these women may have been infertile because their eggs had an even higher frequency of chromosomal abnormalities (in the late 1990s it would have been difficult to tell). It is therefore not surprising that some of the children born after cytoplasmic injection had such problems. The heteroplasmy observed is not surprising given that this is an expected outcome of introducing cytoplasm from one egg into another.

Not only are the PNT and MST techniques different from cytoplasmic transfer, women who carry mitochondrial DNA mutations have normal fertility and there is no evidence they have chromosomal abnormalities. In contrast, infertile women who are trying a completely untried technique are likely to be at high risk of chromosomal abnormalities. The technique was rightly stopped in the US.

The purpose of MST and PNT is also different from that of cytoplasmic transfer, and the two mitochondrial donation techniques are arguably less

invasive. The proposed Regulations in the UK are very clear - the methods of mitochondrial donation would not be permitted for treating infertility; they would be used only to prevent serious mitochondrial disease.

Further research needed

The use of non-human primate experiments was deemed by the Expert Panel, in its 2013 and 2014 reports, to no longer be necessary given the differences between non-human primate and human eggs / early embryos. Performing such unnecessary animal experiments would indeed be unethical given that non-human primates were not considered a good model for the human in this context.

There is and will be continued study to produce additional data regarding safety and efficacy. If the regulations are passed and an application is made for authorisation to offer mitochondrial donation in treatment, the HFEA will consider all this evidence (and other issues relating to management of patients, donors, and children) at that time on a case-by-case basis.

FDA

The situation as regards the regulation of IVF in the UK is very different to the US. The passing of the regulations in the UK would not in itself allow treatment to take place. The HFEA would have to consider each application from affected women and approve any application from a service to provide the treatment.

As a statutory independent regulator, it is for the HFEA to determine its own procedures for assessing applications for a licence to carry out a treatment service regulated by the Human Fertilisation and Embryology Act 1990, as amended (1990 Act). Applications for authorisation to provide mitochondrial donation treatment are no exception to this rule but, clearly, the HFEA will not provide authorisation if it does not consider it safe to do so.

The requirement in the Regulations for the HFEA to assess each application for mitochondrial donation on a case-by-case basis will include consideration of the evidence of safety and effectiveness.

As Professor Knoepfler will be aware, a special committee of the FDA was asked to assess benefits and risks, and to make recommendations regarding the design of possible clinical studies for Maternal Spindle Transfer (MST). A variety of evidence and opinion was heard over 1.5 days, some of which emphasised benefit and some of which emphasised risk. In considering this evidence (there was no report published) and from their own internal review, the FDA then asked the US Institute of Medicine to produce a consensus report on relevant ethical and social policy issues. This latter committee is currently considering the issues and has as yet made no recommendations, and work on the report is still ongoing.

Chair of the original Committee, Professor Evan Snyder, and two members, Carlos Moraeas (an expert on mitochondria), and John Gerhardt, recently signed a letter to the Guardian in support of the UK Regulations from a number of esteemed international scientists.

I hope this is helpful. Please do feel free to share this reply with Professor Knoepfler.

Yours sincerely.

PROFESSOR DAME SALLY C DAVIES
CHIEF MEDICAL OFFICER
CHIEF SCIENTIFIC ADVISER

EARL HOWE