



## Science and Technology Committee

Oral evidence: [Mitochondrial Donation](#), HC 730

Wednesday 22 October 2014

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Written evidence from witnesses:

- [Wellcome Trust](#)
- [Medical Research Council](#)
- [Human Fertilisation and Embryology Authority](#)
- [Muscular Dystrophy Campaign](#)

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Members present: Mr Andrew Miller (Chair); Jim Dowd; Mr David Heath; Stephen Metcalfe; Stephen Mosley; Graham Stringer; David Tredinnick

Questions 1-66

Witnesses: **Professor Doug Turnbull**, Director, Wellcome Trust Centre for Mitochondrial Research, **Professor Peter Braude**, King's College London, **Professor Robin Lovell-Badge**, MRC National Institute for Medical Research, and **Dr Edward Morrow**, Senior Research Fellow, University of Sussex, gave evidence.

**Q1 Chair:** I welcome the witnesses to this morning's session, which we are going to do in three parts. First, we will listen to you, then the regulator and then the Minister. We are going to reflect on what we hear and then decide what to do next. We are looking forward to hearing from you. May I formally ask the four of you to introduce yourselves very briefly?

**Professor Turnbull:** I am Professor Doug Turnbull. I am the national clinical lead for the NHS highly specialised service for mitochondrial disorders. I am also director of the Wellcome Trust Centre for Mitochondrial Research and the MRC centre for ageing and vitality, which involves an awful lot of mitochondrial research around ageing.

**Professor Lovell-Badge:** I am Robin Lovell-Badge. I am a geneticist, embryologist and stem cell biologist working at the MRC's National Institute for Medical Research, where I run a lab. I am also a member of the HFEA panel looking at the science and efficacy of these methods.

**Professor Braude:** I am Peter Braude. I recently retired as head of obstetrics and gynaecology at King's College London. I am a clinical scientist. I have a PhD in molecular embryology, and I am also a gynaecologist. I also sit on the HFEA panel.

**Dr Morrow:** I am Dr Edward Morrow. I am a researcher at the University of Sussex. My background is in evolutionary biology, and my specialist interest is sexual conflict.

**Q2 Chair:** To set the scene, Professor Turnbull, it would be helpful if you could explain a little about mitochondria and mitochondrial disease. Who may benefit from new techniques? What are the current options available for women with mitochondrial DNA mutations?

**Professor Turnbull:** In the simplest terms, mitochondria are like the powerhouses of ourselves; they are important in generating energy for all cells, and if those mitochondria—that powerhouse—are damaged they lead to a group of mitochondrial diseases. The unique thing about mitochondria is that they are the only bit of the cell that contains their own genes. Apart from the nucleus, which contains the chromosomes we get from our mother and father, mitochondria contain their own DNA. We get all the mitochondrial DNA from our mothers. The group of diseases we are talking about are genetic abnormalities of that mitochondrial DNA—the DNA that is passed down from mother to child.

These diseases affect about one in 5,000 of the population. They have a range of severity. In the most severe that I have ever looked after, patients died within the first 24 to 48 hours of life. Often, these diseases present in childhood and adolescence and are relentlessly progressive. We can do a lot to help with, say, the epilepsy or diabetes these patients develop, but there is no cure for mitochondrial disease; they are progressive disorders which affect about one in 5,000 of the population.

A lot of time and effort in our centre and others around the world is to try to find new treatments for mitochondrial disease, but in essence what we are talking about today is a way to try to prevent it. It is important to realise that the nuclear DNA comes from the mother and the father, and all the mitochondria come from the mother, so they are separate. If you are thinking about a cell, there is a bit there and the mitochondria are in the rest of the cell—that is where the nucleus is; the rest of the cell is here. What we are proposing to do in this technique is move the nuclear DNA from an egg, or early embryo, from a woman who carries defective mitochondria and defective mitochondrial DNA into an egg which has healthy mitochondria. You get the characteristics of both parents but the mitochondria and the mitochondrial DNA from another woman.

What do we offer now? If any woman who carries one of these mutations comes to our clinical service we provide them with fairly extensive genetic counselling. Clearly, part of that genetic counselling is that she is likely to pass this on to her child. A number of options are available. People might choose not to have children, they might choose to adopt or they might choose to get an egg donation. They might choose to say, “I’ve listened to all this. I want to have my own baby and I’m going to take the chance.”

Currently, we offer something called pre-implantation genetic diagnosis. This is a technique used for many different genetic diseases. A woman undergoes IVF and you collect several embryos and test which of them is likely to be most severely affected, and you hope to be able to offer the woman the opportunity to put the least severely affected embryos back. That is not always the case, because sometimes the embryos we want to put back are not particularly healthy and are unlikely to result in a pregnancy, and sometimes there are no healthy embryos. It is for that group of women, where PGD, for example,

would not be effective, that we feel that this sort of approach, to try to prevent the transmission of these diseases, would be really important.

**Chair:** In terms of the basic definition that Professor Turnbull gave, do any of you disagree? We can agree that that is a good starting point on which to build our discussion. Thank you very much.

**Q3 Graham Stringer:** The Human Fertilisation and Embryology Authority has done three scientific reviews, yet articles are still being written in scientific journals worrying about the safety concerns. Can you explain how the assessments have been done, and tell us a bit about how you assess those safety concerns?

**Professor Lovell-Badge:** For each of the reports we have done the HFEA has called for evidence. Generally, they put things up on their websites. Also, letters went out to a variety of experts around the world who it was felt might be able to contribute something to this. We would always get quite a significant number of responses, not all to do with the science. Of course, we were focused on the science, not the ethics. The panel would meet several times to go through all the written evidence we received. Meanwhile, the panel would also be trawling the literature, trying to find any relevant research that had been done. We would discuss that evidence. We would call in, or speak to on teleconferences or video conferences, various individual scientists we felt had something particularly important to contribute to the debate.

Whenever there was a question where there was some controversy, we made a particular point to address those issues at our meetings and by speaking to the relevant people. I think we were pretty thorough. Occasionally, as you said, some papers have been published which questioned some of our conclusions. We have always gone back and looked in detail at the reasons why and at the evidence within those articles. We have always come to the conclusion that, while some of the concerns being raised are scientifically interesting, we did not feel they were significant enough to cause us to change our conclusions that there is nothing unsafe about these methods.

**Q4 Graham Stringer:** Nobody can ever know everything; there are always unknowns in any scientific endeavour. How do you balance the risks of going down the path of mitochondrial replacement against the risks to the potential baby?

**Professor Braude:** That is a very legitimate and important question, but what we have to look at is theoretical or assumed risk based on evidence we can find and the inevitability of the alternative. That is terribly important. As Douglas was saying, every woman who has mitochondrial abnormalities will pass them on to their children. It is inevitable. The degree they will be affected by it is slightly different, but they will get the bad genes. How that will affect their children and their children's children is not easily calculable, but we have to balance that inevitability against the small risk. That is the crucial thing.

We can think of many cases like that; we could go back to other reproductive issues. For example, if we go back to 1990—many Members may remember the debates at the time—Robert Winston and Alan Handyside came up with the new technique of pre-implantation genetic diagnosis. At that stage they had some information from mice, but no primate

work. They had a little bit of information from human embryos in vitro, and a little bit of information that suggested that if you had frozen human embryos one or two of the cells might be killed in the process of freezing, but if you replaced those embryos you still got healthy children.

On the basis of that, they thought it would be not unreasonable to try this technology, looking at what the alternative was. The alternative was genetically damaged children, because that is what they were trying to avoid. It comes to a point where you say this is probably not unsafe or at least is safe enough to do the next important bit, which is the clinical experiment: “Let us do that and monitor it very carefully and see what happens.” That is what we have tried to do: look at the evidence to see whether there is anything that says to us fundamentally that this is not safe. We have not been able to find that. There have been some theoretical concerns, and we have tried to find ways of getting around those, but at the end of the day we have had to report that it is not unsafe.

In the next stage, it would be up to the regulator to say, “Is there enough information?” We have suggested a couple of other experiments that need to be done. Some we think are essential, critical—whatever you prefer—but those are already being done by the researchers, because they themselves apply their own standards and say, “We must do these experiments.” There are others that we think would probably contribute to our knowledge about mitochondria, but they are not essential from the point of view of having to have that information before somebody thinks about doing a clinical trial.

**Q5 Graham Stringer:** I am not sure it is possible to answer this question, but I ask it because of the public interest in the issue—there is public debate. As you say, it is inevitable that the child will have mitochondrial disease. Is it possible with mitochondrial replacement that the condition of the child would be worse than it would have been had they just taken the mother’s mitochondria?

**Professor Braude:** There have been some concerns about the mitochondria carryover; in other words, when you do this technology and move a nucleus you may be taking with it some of the bad mitochondria, for want of a better word. If you look at all the information coming from the Newcastle group, the American group and so on, the number is probably around 2%, which is very low considering that currently when we do PDG, as Professor Turnbull said, you are looking for the lowest amount of mitochondrial abnormality in the embryos in order to pick the lowest one to transfer. That could be 20% or 25%, so we already allow a technique that is much, much higher than any carryover. In fact, these technologies are developing such that there are more and more coming round the corner that may make this much lower. The answer is that, theoretically, it is possible but really unlikely compared with the advantages.

**Professor Lovell-Badge:** Apart from that potential carryover, which we think is at such a low level that it is unlikely to affect any child born directly from the method, there is a slight risk, looking at some animal experiments, that if the child born is female her offspring could potentially be at risk. We have expressed that concern in our reports, but we do not think it is a concern for the individual herself because the levels are so low.

In terms of introducing any other problem by doing mitochondrial replacement, our panel felt that some concerns, which Dr Morrow has raised for example, are really below the

radar. They are not going to occur at a frequency that we think would be relevant, or if they do, you would probably never ever know. We can talk more about these concerns. They are theoretical concerns that come from animal experiments where you fix the nuclear genome, such that the nucleus is the same in all your animals, whereas we know that humans are not inbred; they are outbred, so there is such a lot of variation in people anyway that you will never see any issue of the sort that Dr Morrow has suggested.

**Q6 Stephen Mosley:** Dr Morrow and also Dr Newman have submitted evidence about haplogroup mismatching. We are MPs, so in really simple terms can you explain your concerns regarding the interactions between mitochondrial and nuclear DNA?

*Dr Morrow:* In really simple terms, as Professor Turnbull explained, there are two genomes in every cell: the nuclear genome and the mitochondrial genome. They need to work well together. There are genes from both that interact with one another to make the cell work and make metabolism function properly. The evolutionary theory is that because of the pattern of mitochondrial inheritance—it is inherited maternally—there is an opportunity for one copy of the nuclear genome and the mitochondrial genome to be passed on together. It is called technically co-transmission. That selection operating on co-transmitted genomes—two partners that need to work together—means that there is a fine tuning of that partnership. If you take out one partner and put in a new one, you could end up with what we call mismatching, and the function of the cell may be affected.

**Q7 Stephen Mosley:** Are your concerns great enough that you think they invalidate the whole process, or is it simply a risk that prospective parents should be aware of?

*Dr Morrow:* That is a very good point. I think it is a risk that parents should be made aware of.

**Q8 Stephen Mosley:** But you do not think it invalidates the entire process.

*Dr Morrow:* I do not think it is for me to say that. An assessment of the evidence—for example, by the HFEA—needs to decide that. My assessment is that actually they have underplayed it or that they are not taking those risks seriously.

**Q9 Stephen Mosley:** I will move on to Professors Turnbull and Lovell-Badge. Why did the expert panel not recommend haplogroup matching more strongly in their report?

*Professor Lovell-Badge:* We did. We recommended it as a distinct possibility that should be looked at. It is not that we disagree with the theory and the evidence from animal models, particularly the drosophila models Dr Morrow has worked on, but that evidence has come from cases where animals have been widely separated for many years, so they have had a chance to co-evolve those interactions between mitochondrial DNA and nuclear DNA. Essentially, you have taken inbred lines, so you have made the nuclear genetic material constant, and introduced different mitochondria. That is the most extreme test of these theories.

In the human population, interbreeding is very common among different ethnicities, and problems to do with mitochondrial disease are not noticed. That variation in the nuclear genetic background means that there are thousands of genes involved, if they are in the nucleus, encoding something to do with mitochondrial function. The variability in all the different genes in natural populations is so enormous that the chance of making a correlation, having done mitochondrial replacement, with any specific incompatibility, is almost incomprehensible. You would never do it.

I think the concern in Dr Morrow's argument is really a statistical one. If you look really hard at thousands and thousands of cases, eventually you might possibly see something, but we are talking about patients where you can predict with pretty much 100% certainty that they will suffer, so it is very different.

**Professor Turnbull:** I have a couple of points. Our nuclear and mitochondrial genes are getting mismatched all the time; by about six generations approximately 40% or 50% of people have that link anyhow in normal populations. It is simply happening all the time to all of us who are not breeding with our cousins. It happens, and it is well described.

What Dr Morrow talks about is a hypothesis and a theory. It is very important to say that other evolutionary biologists do not agree. Adam Eyre-Walker, professor of biology and evolution in the same department as Dr Morrow, has a different view on this and does not think there is a risk. We are talking about something that is a theoretical risk—one part of a new evolutionary theory—versus a certainty of these diseases being transmitted. Evolutionary biologists themselves cannot agree which is the right way forward. It is very important that we listen to the arguments of Dr Morrow and others, but it is also important to give the Committee a view that there is discussion about this. It is not the view of evolutionary biologists, because two people in the same department have different views, whereas there is no disagreement that these diseases will be passed on to children.

**Dr Morrow:** I have three points to make. First, the submission I made to the Committee, which was a paper we published in *Science* and was also submitted to the HFEA, describes a set of studies from various species where evidence of mismatching has been shown. The HFEA received that. Professor Lovell-Badge is focusing on one particular study using inbred flies. What he is saying about that one particular study is correct, but there are other studies not using an inbred nuclear background that show the same effect.

The paper I submitted to the Committee is a verbal survey of some of the literature. A meta-analysis—a rigorous statistical analysis—of 61 studies, looking at 29 species with 500 estimates of the effect of changing the cyto-nuclear genetic background, found an effect. That statistical analysis suggests with 95% confidence that if you did MR in another species, in another organism, you would find an effect.

I recently identified seven empirical studies, which unfortunately I have not submitted to the Committee but there is a list of the references on my blog, showing evidence of mitonuclear mismatching in a range of traits that are relevant to humans: cardiomyopathy, type 2 diabetes, mitochondrial functioning and hearing loss. These are mitochondrial diseases, and their presence in an individual is due to a mutation in one genome being expressed dependent on the genetic background it is expressed with.

**Professor Braude:** If I may reply to Mr Mosley, first, we keep talking about the HFEA having said this and that. The panel is not the HFEA; it is a bunch of independent scientists asked by the HFEA to examine this condition and report to the HFEA and then to the DH. We have no reason to take a particular line; we are all independent scientists with no affiliations to make this happen one way or another.

Secondly, Mr Mosley said we did not pay it enough attention. There are three pages in a separate box in the report specifically dealing with mitochondrial interactions. We spent an inordinate amount of time on it—too much as far as I was concerned; we spent a long time on it—and wrote about it. At the end of it, the panel recommended that consideration is given to mitochondrial, mtDNA, haplogroup matching with selected donors, bearing in mind the practicality of doing it. It all depends where you get your donors from. It is all very well to say, “We want type A donors,” or whatever it happens to be, but what happens if they are not there? Do you say, therefore, “You will suffer with your disease because we cannot find the right donor,” or do you say, “We’ll take the theoretical risk and go ahead without haplotype matching”? That would be up to the clinics that actually practise this, but we have drawn it to attention, and I think Dr Morrow has said in public that if we did haplotype-match this goes away.

**Dr Morrow:** Haplotype matching may reduce the risk, so you have a more closely related mitochondrial genome that you are swapping in; but it may not work, because we know that it needs only one change, one single nucleotide in the mitochondrial genome, for an effect. Haplogroups—haplotypes—vary in many different loci. There are lots of differences. It is more closely related, but it is not identical.

**Professor Lovell-Badge:** I have looked at some of the papers that I think Dr Morrow was referring to. There was a recent one where I thought the title suggested that it would give some evidence. They had done some work to look at which gene encoded in the nucleus makes for a mitochondrial protein involved in oxidative phosphorylation types of energy. They worked out that it probably interacted with the mitochondrial encoded protein. They looked at variants and found some biochemical difference in vitro between those, but when they did some studies in vivo those differences seemed to disappear. Then they did a genetic analysis looking at type 2 diabetes. They did a study in a population of Ashkenazi Jews, which is a relatively less outbred population, if you like. They found a very weak association between this nuclear gene and the mitochondrial gene, suggesting that particular haplotypes of mitochondria were beneficial. So you could turn it round the other way and say that in some cases it might be better to choose a different haplotype because that would be even better.

The more we know about these interactions the better, but generally you are not going to be able to predict. In our report we felt it was safer to say you should match, if you can. We think it is going to be really hard to go ahead and test how important mitochondrial nuclear interactions are. Dr Morrow suggested when he gave evidence to us that maybe more experiments should be done using macaques. That in itself is not a very sensible suggestion because, if he is right and these things co-evolve, the critical mitonuclear interactions that occur in macaques are going to be very different from those occurring in humans. The only species you can do the work on is humans. We just feel that you are not going to get anywhere doing this.

**Q10 Mr Heath:** As a layman, it seems to me that with the almost infinite variation in nuclear DNA you will have those mismatches occurring very regularly without this technique being involved at all. If you have haplotype matching, you have a greater likelihood of matching than you would in the general population, because of that infinite variation, and whether you have the particular genetic material in nuclear DNA, or the expression of the gene there, is almost random. You are saying that even with haplotype matching there is a negative effect. I would suggest to you that, logically, there ought to be a positive effect—unless I am completely misunderstanding it, which is quite likely.

**Dr Morrow:** Mitochondrial diseases exist. One explanation for them is mutations in the mitochondrial genome. Another explanation is mutations in the nuclear genome. A third explanation is that they are caused by an interaction between those two genomes. In humans the possibility of mismatching may be manifest as mitochondrial disease.

**Q11 Mr Heath:** I think we had better not pursue that. We are undermining the entire purpose of what we are talking about.

**Professor Turnbull:** I run a national diagnostics service. The patients we look after have a pathogenic mutation in a mitochondrial gene or a nuclear gene. The biggest mismatch arises where you look at a nuclear genome in somebody who comes from a European haplogroup and somebody who is predominantly from Africa. We do not see an increase in mitochondrial diseases in that cohort. It is a theoretical risk, but I do not think it is a practical one.

**Mr Heath:** As someone whose heredity is from the Somerset levels, I think I am pretty safe.

**Q12 David Tredinnick:** Professor Braude, you said earlier that you thought there had been too much research on some aspects of this work.

**Professor Braude:** Not too much research. We spent a lot of time. The accusation against the panel is that we did not consider it. Our counter is that we spent a huge amount of time on it.

**Q13 David Tredinnick:** Can you estimate how much more research is needed before we will be ready for the first in-man, or if you prefer, in-person, trials in the UK? What will we need to know?

**Professor Turnbull:** The evidence that has been presented to the scientific panel has shown clearly that this technique is feasible. There is very little carryover, and it would prevent disease. The research currently being carried out is to try to ensure the safety of this technique, making sure that any embryos generated by it look and behave normally. That work is currently at least being reported in human embryos—it is in the process of being reported in human embryos. We are really talking about safety and efficacy. The HFEA scientific panel has already seen some of those crucial bits of information; others would be presented to a licensing authority. We are going to come to licensing later. What would those people want to see if we applied for a licence?



**Professor Lovell-Badge:** We suggested a couple of things that we felt were important to do or to finish off. There are different techniques. The spindle transfer technique has been pioneered in the US. Most of the evidence we requested is already published. We were a little worried about efficacy. It seemed to be a little inefficient. The data we have seen from the Newcastle group suggest that the other method—the nuclear transfer method—is probably more efficient, but the analysis we have seen has not gone as far as the analysis on the other technique, so we cannot say which is going to be best.

**Q14 David Tredinnick:** On that point, although maternal spindle transfer was successfully tested in macaques, it was then decided not to pursue non-human primate testing for other techniques. Can you elaborate a bit on that decision?

**Professor Lovell-Badge:** There are several reasons. We changed our minds. In our very first report we suggested that experiments on PNT in macaques would be useful, but we heard in evidence from Mitalipov's group in the States that they had tried to do PNT with macaques and failed. Experiments fail all the time for all sorts of reasons, but that meant that, if you were going to force someone to do those experiments, you would be starting off by saying, "We have no idea how to do it in macaques because it did not work using standard methods." You are going to have to use an awful lot of monkeys to do the work. There comes a point where it becomes unethical to propose doing experiments on non-human primates anyway.

We felt that the reason why it had probably failed when people tried to do this was that there are differences between the very early embryology of different mammalian species, including macaques and humans, and that was becoming evident from other little bits of information we were getting about the efficiencies of different methods—specific aspects of timing and how things work. We felt that in the end it becomes pointless doing an experiment on an animal model which is not good enough. There is no point doing experiments if macaques are not going to give you the exact answer you need to get from human embryos. In the case we knew, from all the work done in Newcastle, pro-nuclear transfer could be done efficiently with human embryos, so there came a point when there was no reason to justify it.

**Q15 Mr Heath:** Going back to what you said about the relative efficacy of the maternal spindle transfer and pro-nuclear, the position at the moment is that both are considered to be potentially viable techniques and there is no clear preference for one or the other. Is that right? If both prove to be satisfactory and we get to the next stage, I suppose there is a potential ethical difference between the two—some commentators would point to the differences. Do you think it would be justifiable therefore to use either technique and for there to be a degree of patient preference?

**Professor Turnbull:** As with everything, there should be patient preference. Throughout, patients are very involved in the whole process; we discuss everything. If a patient had a preference for one technique over another, that would be really important, so it is entirely appropriate. Just as we would be discussing the risks, they would be welcome to look at all the evidence before they made a crucial decision.

**Professor Braude:** There is one other possibility. Of course, you have to look not only at the technique, and the success of the technique in achieving what you are trying to do, but at the likelihood of pregnancy. If you are talking about the one using unfertilised eggs, which it does, and the other using fertilised eggs, which it does, it may be that you land up with more eggs normally fertilised in the PNT technique, because you fertilise them in an absolutely normal way rather than having to mess about with the spindle. You may land up with more embryos of suitable quality, either to be replaced or frozen for later use. It may turn out that efficiency is slightly better—it is just theoretical, but you can see why— independent of any ethical concerns about fertilised versus non-fertilised embryos.

**Professor Turnbull:** Of course, we would provide that information to women. They would have open access to all the information.

**Q16 Chair:** Taking us forward and assuming we are dealing with real patients, science is rarely about certainty. I do not think I have heard anything that implies that Professor Turnbull thinks Dr Morrow is a crank. He is a legitimate scientist. Do you think it would be proper in counselling patients about the pros and cons of techniques that you are developing to include in that counselling process an understanding of everything, including people's reservations, like those of Dr Morrow?

**Professor Turnbull:** Absolutely. The counselling for this will be complex. We already do complex counselling for women who are coming forward for PGT. I think it is a patient's right to have all that information presented to them in a format which they can understand, and that they have a chance to look at it and come back to discuss it. Often there are forums where mothers will talk among themselves as well.

**Q17 Chair:** Not in terms of the statistical gobbledegook that some processes use, but simple, basic information.

**Professor Turnbull:** Absolutely. As with anything, it is incumbent upon us—we are giving advice to patients on mitochondrial disease which is pretty complicated anyhow—to put it into an easily understood format.

**Q18 Jim Dowd:** That sounds all well and good and enlightened. Is it not the case though that the vast majority of patients, regardless of what condition they are experiencing, will be guided by what their clinician, doctor or medical adviser tells them? They will say ultimately, "What do you think is best?" You can give them all the information, but if they do not have a basic understanding and grasp of what you admit is a very complicated issue, how on earth can they make an informed decision in the sense of the information guiding their decision, rather than saying, "I've got all this information. I can't make sense of any of it. What do you think we should do?"

**Professor Turnbull:** My experience of this in reproductive choice—because we provide women with exactly the same information—is that women make entirely different choices. Some women will go for PGT; some will not have children; and some will have egg donation. It is remarkable. In this particular area, I think people really want to take charge. They see how important this decision is to their family and they invest a lot of time.

Women who are making these choices will have been our patients for years, so they have had lots of time to discuss this and think about it; they will have had lots of time to discuss it within their families. In reproductive choice, I have never had a patient say, “Doctor, what do you think?” With PGT where we say there is a level of risk, and we say, “There’s a big risk,” I have had patients say, “It’s my choice. I want to say which embryo goes back.” I agree with that; it is entirely their choice.

**Professor Braude:** I have one comment, because it is probably difficult for Professor Turnbull because he does the technique. One of the recommendations that came out of the report of the Nuffield Council on Bioethics was that when these techniques are offered, if they are to be offered, they should be offered, first, as part of clinical trials, so a very clear protocol is set up, including counselling, and, secondly, they need to be in specialist centres. You can see from all the discussion today just how complex mitochondrial inheritance it is. For the average geneticist, it is not easy to deal with, certainly not the average PGT centre and so on. There are not lots and lots of patients, so it will land up with people who really understand it and have considerable experience of counselling the kind of options Professor Turnbull is talking about. I do not think there is anybody saying, “Doctor, what do you think I should do?” These are very knowledgeable patients.

**Q19 Jim Dowd:** Professor Turnbull, you just said that this will not affect large numbers of people. Can I examine that for a moment? There have been recent estimates of the number of potential patients who would benefit from this, varying from 10 to 80, so I accept that we are not talking about large numbers. How do you think we can estimate more accurately the numbers of women who might benefit, compared with estimates made so far?

**Professor Turnbull:** I submitted a confidential paper, which is under review, that gives a number. That is based upon epidemiological evidence from the north-east of England and the known fertility rate. We know that there will be this number of women with mitochondrial DNA mutations who are likely to be getting pregnant every year.

**Q20 Jim Dowd:** How do you identify them?

**Professor Turnbull:** A lot of them are patients we are seeing in our clinic already—we know their families—or they are referrals. They tend to be families where we already have a great deal of family history and everything else. Among the number of women we have given, people will make different choices. I think the number of between 10 and 80 is not unreasonable. We simply do not know. We think some women will take the choice, because clearly there are some who are sitting there saying, “Please let us know,” but we do not know. It is not an unreasonable number. It is not going to be large numbers; a significant number of women will come forward. If this was available now, I think those are the sorts of numbers.

**Q21 Jim Dowd:** If we are to avoid serious mitochondrial diseases, what form would they take? What would we be alleviating?

**Professor Turnbull:** Most of these diseases affect predominantly the energy-requiring tissues, so a lot of it is related to progressive neurological, muscle and heart problems and

very bad diabetes. They tend to be multi-organ conditions. Many of my patients will have several different tissues involved, so they will be the sorts of progressive diseases that usually come on in childhood or adolescence.

**Q22 Stephen Metcalfe:** I would like to touch on the issue of follow-up. Varying views have been expressed about whether long-term follow-up should be compulsory as part of the treatment, whether it should be advised, or whether there should be a centrally-held register. What are your individual views on follow-up and its importance? Why is it so important that there be some form of follow-up?

**Professor Turnbull:** Follow-up would be important. It is very difficult to make it compulsory, but we would like that people were followed up; it is really important. We already have a system where we follow up patients through the national service, so it would be relatively simple to put forward a process that could follow up the patients. I would like to follow them up for as long as we possibly can. We have to learn, and the only way we are going to know is to learn about what actually happens during follow-up, so I am very keen. I hope we can. It should be part of the process that we put in place. I think it can be put in process relatively simply because we have a national service and we are already following up. Our centre already follows up about 650 patients with mitochondrial disease. We are not talking about vast numbers, and we would be delighted to have the opportunity.

**Q23 Jim Dowd:** Would that follow-up be generational as well?

**Professor Turnbull:** I hope it would be generational. Whether or not that is practically possible I just do not know. We already follow up the children from PGT; we are looking at them, and we would want to continue to follow up. It is inherently in the patient's and the doctor's interests.

**Professor Lovell-Badge:** I agree. In the reports that our panel produced we recommended that there should be a follow-up. We think that the probable risk to children born from these techniques themselves having disease is very low, but we feel they should be monitored and checked just in case there is some skewing of the carryover abnormal mitochondria to a particular tissue, which is theoretically possible. We felt it was particularly important to follow up any women born from this technique, because one of the hopes is that this method will eliminate the abnormal mitochondria from the family in subsequent generations as well. That is particularly important information.

**Professor Braude:** It is going to need some consent. It is all very well parents making the decision to follow up their children, but those children will become adults and they themselves are going to have to make decisions. Some of the follow-up might need to be invasive; you might need to know the degree of heteroplasmy—the mixture of good and bad mitochondria—in muscle, or perhaps in skin tissue. Indeed, with females who decided to have their own families, in some cases you might need to test their eggs to find out whether they were still carrying it. It is not non-invasive. Earlier you asked the question: is it safe? This is how you are going to find out whether it is safe, because you are going to follow up. You look at the biopsy and say, “Look, we’ve found no degree of high

heteroplasmy. It looks fine; carryover is minimal.” Slowly, you build up a picture which says, “Yes, the evidence was right,” or “It was wrong, and we need to stop and rethink.”

*Dr Morrow:* Precisely.

**Q24 Stephen Metcalfe:** Would anyone make it a condition of receiving treatment?

*Professor Turnbull:* I am not sure about the ethics of that. It is very difficult. As far as I am aware, we cannot compel anybody to come to our clinic. We just can’t do it. What would happen if somebody said, “I’m going to do it,” and then decided not to come? We are not going to get a policeman to go round. It is the practicalities of doing these sorts of things. It is in the patient’s best interests, but we know that that is not the only factor for people.

*Professor Braude:* When intracytoplasmic sperm injection was initiated in Brussels, which is when you take a single sperm and inject it into an egg when men have very few sperm, I will not say they tried to make it a condition, but they encouraged patients to have amniocentesis to test the chromosomes of the foetus, and the vast majority of patients took it up.

**Q25 Chair:** We are trying to get together some definitions. In terms of the working definition used by the Government, I have just been looking at some contradictory information. The Government use the phrase: “The working definition 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 replacement techniques do not constitute genetic modification. There have been criticisms of that view. What are your views?

*Professor Lovell-Badge:* My view is that you could call it germline modification—the HFEA used “germline therapy modification.” You are not changing specific DNA sequences, which is generally how I as an experimental biologist would talk about genetic manipulation or modification. You are swapping an intact mitochondrial DNA genome which, as we have already discussed, happens anyway through natural reproduction. It is not as if you are engineering a specific piece of sequence. I could put it in a number of ways. The men in this room choose for our children the mitochondrial DNA type they are going to have by choosing our partners with whom we are going to have children. Women do not have the same choice normally, but mitochondrial replacement is essentially allowing them that choice to avoid having mutant mitochondria, and have normal mitochondria. I do not see it as a form of genetic modification.

*Dr Morrow:* If it is germline modification, how can it not be genetic?

*Professor Lovell-Badge:* It is. We have not hidden from the fact that it is germline modification; we have always said that.

*Professor Braude:* What we said is that it is a germline therapy; in other words, we know this is going to affect subsequent generations. What is really important to appreciate is that this is not the first time this has happened in assisted reproduction; it happens all the time.

I go back to the issue of men with very small, poor or absent sperm in their ejaculate, due perhaps to a chromosome or genetic abnormality that they carry. They can avoid this by having an intracytoplasmic sperm injection. You can get maybe one or two sperm from the testicle and inject it into an egg, and they can have a child. If that child is a boy, it will carry the same genetic abnormality as the father, so this is germline therapy; it is what we have been doing for years. Nobody has queried that, because there is a positive benefit at the end of the day and it is a consequence of what you are trying to do. Here the same thing is happening. You are not modifying the actual genome of the mother and father; you are simply moving it into another bag. It is not modified; it is moved. Is it germline therapy? Yes, it is, with a very positive outcome, which is to avoid the kind of diseases that the children inevitably have if you do not do it.

**Chair:** That is a helpful point on which to end. Gentlemen, thank you for your contributions. We are now moving on to the second panel. If there is anything further you wish to contribute or to comment on, we would welcome it.

### **Examination of Witnesses**

Witnesses: **Peter Thompson**, Chief Executive, Human Fertilisation and Embryology Authority, **Robert Meadowcroft**, Chief Executive, Muscular Dystrophy Campaign, and **Professor Jonathan Montgomery**, Chair, Nuffield Council on Bioethics, and Professor of Health Care Law, University College London, gave evidence.

**Q26 Chair:** Gentlemen, welcome to the session. I think all three of you have been sitting listening. Would you be kind enough to introduce yourselves?

**Peter Thompson:** My name is Peter Thompson, chief executive of the Human Fertilisation and Embryology Authority.

**Professor Montgomery:** I am Jonathan Montgomery, chair of the Nuffield Council on Bioethics. My professional background is as an academic lawyer. I work at University College London.

**Robert Meadowcroft:** I am Robert Meadowcroft, chief executive of the Muscular Dystrophy Campaign.

**Q27 Chair:** I have a very straightforward question. Can you give some detail on what regulatory approach may be proposed for the use of mitochondrial donation technologies?

**Peter Thompson:** The HFEA is clearly the regulator. On the basis of the draft regulations the Department of Health consulted on in the summer, if Parliament passed them, we would be the licensing authority for these treatments. Those regulations would require us to make an assessment, on a case-by-case basis, as to whether or not a particular treatment should take place. We would be required to do that against certain criteria, notably whether the patient had a mitochondrial abnormality in their mitochondrial DNA, and whether or not there was a significant risk that a child born might suffer from a serious medical condition. We would also be required to make an assessment as to the competence of the clinic to do it.

To start with the last point, at present if you want to offer IVF in this country you need to do so under licence from us. We put on clinics a whole series of requirements, which include things like their facilities, staff competence, the guidance they issue and so on. A small number of those clinics offer PGD, which you heard about during the previous session. That is a much more complicated set of processes. Accordingly, to have a licence to do that we put different sorts of requirements on clinics—rather more onerous ones: their skillset is much higher, their equipment is much more sophisticated and so on.

If Parliament decided to make mitochondrial donation lawful, we would be seeking further sorts of criteria, because as you heard this morning, this is quite complicated biology and very few clinics will, certainly early on, be competent to offer it. What we would also need to do—because this is not set out in the regulations—is effectively design an application process. How would a clinic wanting a licence from us actually apply? What sort of evidence would they need to submit? We would need to work out how we would assess that evidence, but, as part of that, we would clearly be considering issues of safety and efficacy at whatever point in time we were asked to make that decision.

**Q28 Chair:** That would be case by case.

*Peter Thompson:* At the moment, my understanding is that the Government are intent on doing it on a case-by-case basis. We have sketched out a little bit of that in some of the evidence we sent to your Clerk, but there is a trickiness; until Parliament clearly signals that it wants to change the law, I do not think it is appropriate for us to have a consultation, or some sort of public debate, about exactly what an application process would look like. I hope that is a helpful indication.

**Q29 Chair:** Mr Meadowcroft, someone like you would have a view about what ought to be there.

*Robert Meadowcroft:* Regulation is very important. From the patient's point of view, there has to be a degree of protection as well—an assurance that the process is rigorous and the clinics are well organised and following ethical standards. There is a need for that regulation. One has to accept that, when faced with devastating illnesses and the thought of children being born with severe conditions, there is a degree of vulnerability among patients. Therefore, to have confidence that there is a regulated service, which we hope will become available, will deter people from seeking unregulated and potentially riskier services, clearly not in this country. In the age of the internet, there are possibilities for people to seek solutions they would be better off not seeking. I think there is also a need for public confidence. We are looking to take the next step with these techniques to help those families, so there needs to be public confidence that there is a rigorous process and rigorous regulation. I see it as all part of that.

**Q30 David Tredinnick:** How do you think patients will be assessed for their eligibility to utilise these techniques? What will the criteria be?

*Peter Thompson:* There are criteria clearly set out in the Act, and they are the two I referred to earlier. There is a big role—we will need to talk to the clinics involved—for the

particular package of evidence that comes with each application. If I look at how we currently do something related to PGD, pre-implantation tissue typing, which is still done on a case-by-case basis, there is usually a detailed letter from the treating clinician setting out the particular details of the case and why they feel this is the most appropriate treatment. In the regulation of PGD and pre-implantation tissue typing, there are already models we can successfully use as a basis for thinking about how we go about regulating mitochondrial donation.

**Q31 David Tredinnick:** Is it correct that generally new technologies are more lightly regulated as their use becomes more commonplace? Regulation can become less onerous. Might that apply in this instance later on?

*Peter Thompson:* It might. When we first started to license PGD, it was done on a case-by-case basis. Some years ago we moved to a condition-by-condition basis. Instead of approving every case, we approved every new condition. Over time, the range of conditions that can be tested has increased enormously as testing technology has developed. We have a number of clinics across the country that are licensed to do PGD. When one of them makes an application to do a new condition, if we grant that condition as sufficiently serious to warrant PGD, any of those clinics can offer that condition as part of a suite of conditions. That has developed over time. It is quite possible over time, should Parliament decide to pass this, that that may be the better view. Robert Meadowcroft has already hinted at it. I think there is a sense early on that with new and novel techniques a particularly rigorous form of regulatory oversight is probably appropriate.

*Professor Montgomery:* From an ethical perspective, it depends whether the questions are new ones or old ones. If the issue is about the seriousness of the risk prevented—from the particular condition—it makes sense to resolve that once carefully and not reopen it every time but keep it under review. If the issues are uncertain and developing, you would want to keep close scrutiny. I am not sure whether light or rigorous regulation is quite the right model; it is about questions which remain very uncertain and questions which seem to be getting some clarity. It makes sense not to have a bureaucratic hurdle that asks a question every time to which we already know the answer, but in the areas where we do not know the answer we should be able to keep looking closely.

*Robert Meadowcroft:* I would agree with that. I think that a case-by-case basis initially is the way to go forward on this. Patients will be cautious but not over-cautious. If there is evidence that this technique will help them and their families, they will be keen to explore it further and discuss it with their consultant, and measure the benefits and potential risks very carefully, but when evidence emerges that this is shown to be safe, all being well, I think there will be less concern on the risk side but more concern about the appropriateness for them and their family of the choices they will be looking at.

**Q32 Stephen Metcalfe:** That reassurance will be created by a wider and wider evidence base that things are performing as they should be. One way of doing that would be through long-term follow-up. How would you envisage the regulatory framework around follow-up working?



**Peter Thompson:** I think the issue here has already been touched on in the first session. I do not think that ethically one can compel follow-up. What we can do, however, is make it a condition of a licence for a mitochondrial donation centre that they should be required to have all the processes in place to ensure follow-up, and that part of the guidance they ought to give patients is what are the benefits of follow-up. It has already been touched on that it is not possible to compel a patient to sign up to follow-up, but we can certainly put a framework around a clinic about that and inspect against it. If a clinic that was licensed to do mitochondria could show us no evidence that they had processes in place to encourage follow-up, that might be a serious regulatory matter.

**Professor Montgomery:** I think we should distinguish levels of coercion in terms of encouraging follow-up. It is an area where we need to bear in mind that the parents using this technology are not the only people whose interests are at stake. It is perfectly reasonable, as we do in relation to other assisted conception techniques, to make sure we record enough information that makes it possible to track back, should it turn out that children born have some issues that may possibly be related to the technologies. We need to have the mechanisms in place to be able to track that back. I think it is reasonable for us to say to parents using these technologies that a certain level of recording is mandatory.

It is also reasonable to have conversations with prospective parents using these techniques about the expectations of the system to try to learn to give better care in the future. We know from the provision of intra-genetics services and other areas of donation in terms of assisted conception that it is possible to establish what seem to be good things to do without making them mandatory. We would expect, from Nuffield in this context, the expectation to be raised that it is important to learn more about this, and we hope that people who use it would also be engaged in follow-up. I do not think we would expect it to go as far as there being a mandatory requirement to undergo tests, or anything of that sort.

**Robert Meadowcroft:** It would be extremely difficult to require a mandatory requirement, particularly for children yet to be born. Their parents may well be committed to taking part in the follow-up and may see the benefits and importance of that, and younger children would clearly be brought by their parents to the clinic. In a sense, there would be that kind of encouragement, but, beyond that, children would take their own decisions if they are healthy and not in touch with the medical services. If they had difficulties, for whatever reason, they would be back in touch, and I am sure that the clinic, the centre, would wish to follow them. From our point of view, the difficulty for most people with rare muscle conditions is getting to see a specialist. They are desperate to go. These are very rare conditions and, therefore, they are keen to see the specialist and I do not think that would change, but if the children, through this technique, do not have the condition they would be in a different place, although I am sure the parents would be keen to bring them through.

**Q33 Stephen Metcalfe:** As with all things, there is a cost involved. Who do you think should be carrying the cost of operating this long-term follow-up? Is long-term follow-up a significant cost, or can it just be absorbed in the functioning of the clinics?

**Peter Thompson:** Doug has already mentioned the national federation in which he is involved. I do not know about their resource position. From the HFEA's position, all assisted reproduction treatments are reported to us as part of a statutory register, so to that

extent these treatments—we have already touched on the fact there will not be many of them—can simply form part of that register, which we would mark up in a particular way. That element, of at least holding some kind of national information at HFEA level, I do not anticipate being of any significant financial concern. We have an infrastructure that is already doing this for 60,000 IVF cycles a year, and a few are not going to make any difference.

**Q34 Stephen Metcalfe:** Presumably, the same answer would apply to the confidentiality of data; it is the same process.

*Peter Thompson:* Yes, it is already governed by the HFEA Act, which puts confidentiality requirements on the data we hold. They are at least as severe—if that is the right word—or possibly more so, for confidentiality as for any other medical data, so all that infrastructure is already in place.

*Professor Montgomery:* From the Nuffield report one can add two elements. One is that, given the uncertainties we heard talked about earlier, we would expect all this work to take place within carefully structured and designed trials so that it could be learned from. That implies that the obligations for seeing through that follow-up need to sit with the people leading those trials, and need to be costed as part of the funding of those trials.

We also recommended that these techniques should be not just within the context of clinical trials but also in specialist centres. That relates to the informed consent questions we heard about earlier. You need people to be able to support decision making, and that implies that the funding for this should be wrapped into providing a high-quality service.

**Q35 Chair:** Will the existence of that data lead to insurance problems in the future? Have you made any assessment of that?

*Peter Thompson:* I have not.

**Q36 Chair:** We have a lawyer in front of us. You must have thought about it.

*Professor Montgomery:* Perhaps I could answer as former chair of the Human Genetics Commission. The answer lies in the moratorium that has been agreed about the use of genetic information in the insurance industry. We currently have a system that has held up pretty well and ensures there is quite a long-term process whereby any changes need to be negotiated with a decent lead-in time. I have not been in that role since 2012, so I cannot tell you about the current state of play in the negotiations on continuation of the moratorium, but I do not think this raises a new set of issues. It is rather less pressing than the issues that would be available were widespread molecular genetic testing to become available. I think it would be under that umbrella.

**Q37 Jim Dowd:** I want to look briefly at the status of the mitochondrial donor. I know you are all aware of the consultation and the Government's response to this issue. Do you broadly agree with the position of the donor that the Government have outlined in the draft regulations?

**Peter Thompson:** The short answer is yes. There are two positions on this. Mitochondrial donation is unique. Should it be treated like gamete donation where, since 2005, the donation is known, or should it be treated more like tissue donation? For a whole series of reasons, the HFEA's position is that it should be non-identifiable, in other words treated more like tissue donation.

**Q38 Jim Dowd:** The Government took the view that it was somewhere in between, but more towards the tissue end of that particular spectrum, did they not?

**Professor Montgomery:** We need to recognise that there is quite a lot of nuance in the status question. We are very clear that, if the question is around parental responsibility and upbringing, we do not see mitochondrial donation as being in the same category as other attributions of parenthood, and not even in the same category as egg donation.

If you are asking questions about identification to the child, one of the issues to do with mitochondrial donation is that it is not unique just to the donor, in the same way as an egg donation is. Therefore, it did not seem appropriate to think of it in the same way as an egg donation—linking someone to a unique genetic parent—so we would also be supportive of that decision.

**Robert Meadowcroft:** We see it in exactly the same way. We do not see this as being in any way a third parent, or a second mother, but comparable with tissue donation.

**Q39 Jim Dowd:** I was going to ask what access should children born following these techniques have to information identifying the donor, but I think you have just covered that point, Professor Montgomery. Do you think there should be a voluntary database for information and contacts arising from this? If so, who should compile, police and monitor it?

**Professor Montgomery:** Nuffield did go as far as to say that that definitely should happen and we would be supportive of that. When we did our analysis of whether there were links between children who might be born from these techniques and their origins, we identified how complicated people's sense of their identity and their parenthood was. While at the moment, on our analysis, we do not see a sense that the link mitochondria would produce is thought to be equivalent to a parental link, there is obviously the possibility that people might feel that for themselves in the future. As we have learned in relation to other assisted conception techniques, it would feel wrong to rule out the possibility that affected communities could establish something of that sort. I do not think we thought it should be a regulatory requirement, but we could see why people might want to do that, and therefore would not want to obstruct it.

**Peter Thompson:** I do not need to go into detail, but our position is broadly the same.

**Q40 Jim Dowd:** Who will be responsible for instituting it?

**Peter Thompson:** If you look at tissue donation, my understanding is that there are already local voluntary arrangements for doing that. I am sure that, if there was felt to be a need, those sorts of things could be developed within the wider system. We certainly did not think it would be appropriate for a stand-alone national register.

**Professor Montgomery:** You would expect this to grow out of the people who use services. You would expect it to be linked to the specialist centres doing it, and driven by the patients using the services, not by providers.

**Robert Meadowcroft:** I was going to make the same point. I think that in 2013 the HFEA in their advice to Government made the point that the specialist clinics should keep these records and have them available on an opt-in voluntary basis.

**Q41 Stephen Mosley:** If Parliament passes these regulations, we will be the first country in the world to allow the introduction of these techniques. You talked about regulation and how you look at the family, the clinic and so on. How will it work when it comes to overseas patients? If we are the only country doing this, you can see a situation where parents from other parts of the world will want to come here to take advantage of the technique.

**Peter Thompson:** We license only treatment that takes place in the UK. If somebody comes here and is treated at a licensed centre, effectively the processes are the same. The questions about deciding what kind of evidence you might use in order to decide whether or not it is appropriate to do treatment are the same. It is for the clinic themselves to decide whether or not they treat UK or overseas patients, but if the treatment is to take place in this country, they will have to go through the same regulatory steps as a home-based patient would.

**Professor Montgomery:** There is a layer of complexity created by international movements. Although we are probably likely, if we approve this, to be the first country with legislation on it, we are not the only national ethics committee discussing the issues and techniques. I am aware of that from meeting the German and French national ethics committees a couple of weeks ago.

The Nuffield report flagged up a couple of significant issues. One relates to the legal status of any children who might be born. There is certainly a theoretical possibility that we might be treating people whose legal status in the country they return to is uncertain. This would be nothing like as widespread a problem as we already see internationally in relation to surrogate motherhood, where many countries have to grapple with the challenge created by the attempt to have good regulatory systems in their own jurisdictions, and citizens avoiding those or finding a cheaper way of doing it by going abroad. They then bring back their children and the legal systems have to work out how to accommodate that. They are mostly resolved worldwide by a combination of two main ways of dealing with it. One is around the woman giving birth counting as the mother, which is the most common position. The second is that, if you find that does not give you very stable outcomes, you tend to look at what is in the best interests of the children.

I think that, if this technique was used, it would be much easier to fit into those frameworks than surrogate pregnancy is, because it is the nuclear DNA that is usually used in tracking identity. It would be very surprising if anybody rushed into thinking this made it more uncertain than it was previously. There is a clear set of questions which lawyers in other countries would need to sort out. Because we know they have already grappled with them, I do not think they are a reason for our not taking that step, if there are other reasons why we would go in that direction.

The second concern Nuffield identified was around follow-up. Follow-up is clearly much less reliable if you lose touch with the families. There might be a number of ways you might deal with that. Depending on where people come from, you may be able to partner with centres that are providing support in other areas, but the most important thing about follow-up is to make sure we learn from the techniques and whether any safety concerns emerge. If you found that all the people using this technique were lost to follow-up, we should be concerned about it, but if you lose a few, that may be no different from the people who decline to participate. While there are things to work on, they do not seem to be reasons for not taking the step, if for other reasons it makes sense.

**Stephen Mosley:** Professor Montgomery, you went through my questions and answered them all, so I don't have any other comments.

**Q42 Chair:** On follow-up for people who are overseas, either British people who have left the UK and taken up residence elsewhere or people who have come here specifically for the treatment, obviously there is good clinical need for that follow-up, not just for the well-being of the patient but for the broader patient group. Have you given any thought to how you strengthen relationships with other countries so that you can get the follow-up data, or is it simply a matter of giving encouragement patient by patient, not quite as one of the conditions for treatment, but saying, "We really do want you to engage in follow-up"?

**Professor Montgomery:** I would have to take forward the discussions from the working group we held on this, because it was not elaborated in any detail. I think the answer lies in how the patients reach the treatment centres we are talking about. If they are referred because they are identified as having family histories, you can make a link with the referring clinicians and the referring centres. That is where I would start. You would expect the treatment centres to be building up partnerships, and then you would allow for follow-up in the places they came from.

The most important things to pick up will be any health issues that emerge for the children who are born, and you would expect that to be the focus in the places people go back to. If you have links with the hospitals or clinicians likely to be caring for them, you can hope they would seek those patients' permission to transfer the information. I think that is where you would build up the partnerships. Hoping to have something that is more legalistic or regulatory-based is unlikely to deliver anything better than those sorts of partnership arrangements.

**Robert Meadowcroft:** We are very fortunate in the UK that the science we are taking forward is exemplary; it is outstanding at times. This is an area where I think we are leading the world. It is first-class. We as a charity, thanks to the generosity and commitment of our supporters and patients with these conditions, have been able to fund research through Professor Turnbull's centre for more than 10 years, driven by the patients and their needs.

The point I want to add to the international dimension is that in other countries there are organisations like the Muscular Dystrophy Campaign who are watching what is happening in the UK. They will be keen to follow our lead, so in a sense I think this will play out in an entirely different way from the way it appears today.

**Chair:** That is a good point on which to finish. Gentlemen, thank you very much indeed.

### **Examination of Witnesses**

Witnesses: **Jane Ellison MP**, Parliamentary Under-Secretary of State for Public Health, Department of Health, and **Professor Dame Sally Davies**, Chief Medical Officer, Department of Health, gave evidence.

**Q43 Chair:** Minister and Professor Davies, welcome to the session this morning. This is the third panel. We have had a fascinating morning listening to the science community and the regulators. Minister, the Government announced that a number of further actions were necessary before regulations would be laid. Can you tell us a bit more about those actions, and when the Government intend to lay the regulations?

*Jane Ellison:* Thank you very much for inviting me and the Chief Medical Officer here. Perhaps I could take the Committee through what we said we would do and where we are. We published our response to the consultation on 22 July, and at that point we committed to giving further consideration to the recommendations of the expert panel, to refining the draft regulations to take account of changes identified during the consultation that we wanted to take forward, and to further discussions with the HFEA.

In addition, I was made aware pretty much at the end of the summer Session that we were going to have a debate at the very beginning of the September sitting. I was keen to wait on that because it would be the first full debate we had. As Minister, I had not responded to a full debate, or had the chance to hear that range of opinion before, so for me it was a step I wanted to take. The HFEA said they would undertake to produce a layman's summary around the science and the expert panel's view on some of the regulatory issues. I thought it would be very helpful to see that before deciding next steps, because there was some discussion around what some of the wording in the third report of the expert panel meant and what the implications were.

Having heard all that and having found the debate very useful, hearing from a very wide cross-section, I am now actively seeking cross-Government approvals and clearances and asking for parliamentary time in this Session to bring the regulations before the House. I cannot be more precise at this stage, because the process has not completed, but that is an update on the position I gave the House at the end of the debate, and I am actively seeking all of those things.

**Q44 Chair:** So “soon” genuinely means soon.

*Jane Ellison:* I am actively seeking both the approvals and the time, Mr Chairman. This is something I want to take forward.

**Q45 Chair:** Assuming the regulations are endorsed by Parliament through its normal procedures, when would you expect, following on from that, the first real in-person trials to proceed?

**Jane Ellison:** I do not think I am in a position to be precise about that, because from the point at which Parliament gave its approval the HFEA would have a series of processes to go through. I am sure you have been talking to them about that. They would then need to put the regulatory regime in place, but indicating that I am actively seeking to move things forward allows the HFEA to begin to move their thinking forward on that, so it would follow on from that. I do not think I am in a position to say exactly, but I am extremely conscious that there are real families waiting on the progress of this work. I have to make sure I go through a proper process and that I have done everything correctly. Like many other Members of Parliament, I have a family affected by this. I met their beautiful daughter Poppy who suffers from mitochondrial disease, so like every other Member of Parliament, with my constituency hat on, I am conscious that this is important to some people in our country and we need to keep up the momentum.

**Q46 Graham Stringer:** I took part in the debate and it seemed likely that the flavour of that debate was positive towards the regulations. Assuming Parliament agrees the regulations, what do you think are the implications for this country in being the first in the world to have regulations on mitochondrial replacement therapies?

**Jane Ellison:** I thank those members of the Committee who took part in the debate. I thought it was a very helpful debate. Occasionally, there is a sense in some of the public comment that Britain is going it alone and is isolated in this regard. That is something I have been exploring with my officials and have asked for information on. The UK is not an outlier in this area of medicine; we are pathfinders and innovators and I am very supportive of that. That came out in the debate.

In recent weeks we have received a lot of correspondence from researchers and scientists around the world—Germany, France, Holland, Sweden, Japan, Hong Kong and two states in Australia—all indicating support for and interest in what is being done here in advances in mitochondrial donation, and acknowledging that the introduction of our regulations, were Parliament to approve them, would influence the approach of those countries and states to the new technologies. That has been helpful to me to give a sense of where the UK sits in this area of science worldwide. It is extremely useful to put on record that Britain is not some sort of outlier or isolated case; we are pathfinders and innovators and I am extremely proud of that.

We also have a well-respected regulatory framework. Some of the comment elsewhere in the world is of great respect for our regulatory framework, and that is, if you like, an additional safeguard we are lucky to have. What came through in the debate, and in much of the comment I have been dealing with through a large number of parliamentary questions and so on, is that there is a very high degree of respect for the HFEA and the regulatory framework put in place by Parliament some years ago. It has more than stood the test of time, and in fact has gained respect as it has gone on. There has also been international comment about that framework.

**Q47 Graham Stringer:** By taking evidence today we are trying to get for the House of Commons an understanding of the science, so that it is there when we consider the regulations. We can do that as far as the science is concerned, but there is a big international debate going on out there which is about not just the science but the ethics. To summarise the

arguments against it, it is said that this kind of technique is incompatible with human dignity. There have been a number of discussions in international bodies about that. Have you taken into account, and can you reassure the Committee, that if the regulations are passed we will not be hit by a lot of disputes in international law? Have you fully considered all those issues?

*Jane Ellison:* I do not believe we will. Usually, there are one or two widely quoted examples of certain international bodies commenting, but all the advice I have is that we are proceeding in a perfectly legal way.

**Q48 David Tredinnick:** Could you tell us how many people in the United Kingdom you believe could benefit from these new techniques?

*Professor Davies:* In the first place, we think it is about 20 families that are very severely affected, but if it proves to be as safe as we believe it will be—only time will tell—we expect that may rise to about 80 families a year, if we go forward. Let me put on record that I hope we will, both scientifically and for those families; you would not want to deny that life-saving opportunity to families where children will die before they have become adults.

**Q49 David Tredinnick:** We are talking about a relatively small number of people—a small number of families. Would you consider making these treatments available to overseas citizens, Minister?

*Jane Ellison:* Over time, we might expect that the procedure might be offered by centres to overseas patients, but it would be for individual clinics to assess each case, and of course they would all have to work within the regulatory framework. The clinics would assess the cases and prioritise, but we would expect them to have a protocol for doing that to ensure that NHS patients were the priority. I would expect it to be something the HFEA would look at on a case-by-case basis, but our expectation would be that NHS patients would be the priority.

*Professor Davies:* Of course, overseas patients pay the full cost. The NHS would not be subsidising that treatment.

**Q50 David Tredinnick:** That is another question I had. Given the current debate, it is probably helpful to have that on the record. Who would be responsible medically and financially for the ongoing care of overseas citizens? You have already said that overseas citizens would be responsible for the full cost of the treatment. What about the responsibility for their long-term care? Is that responsibility divided, given what you have just said, into responsibility for cost and moral responsibility for the care of patients? Possibly an advisory service would write to make contact if they are uncertain about how they are.

*Professor Davies:* I do not see the children who are born as a result of this, as with Louise Brown, as patients; I see them as future healthy children and citizens, but we would like to follow up nationals and people who live in this country so that we get the data. I would expect that the centres, if they take overseas patients, would ask for follow-up, and will be



in close contact with the physicians who look after that family abroad, because they would need to be referred from a physician who looked after the family. We have a long and proud history of collaboration on research and follow-up between many countries through our academic networks. I think we would get some, if not all, of the data.

**Q51 Chair:** Adding together the two points you have made, Dame Sally, the overseas patient paying the full cost would have factored into that the costs of follow-up.

*Professor Davies:* I assume they would be followed up locally in their own countries, but if they come back here for follow-up as private patients they are not eligible for the NHS. Those who are not eligible for the NHS will have to pay.

**Q52 Stephen Mosley:** We have heard some criticism of the Government's working definition of genetic modification in humans. The Government's definition is that genetic modification involves a germline modification of nuclear DNA that can be passed on to future generations. Do you know how that definition was decided upon?

*Professor Davies:* Let me take responsibility for that. We had a lot of discussions. What was happening was that people were using terms like "genetic modification," "GM" and "germline," sadly, in rather mixed and odd ways. It seemed to us that, in order to have the discussion we were having, it was important to lay down working definitions. Germline is anything that is done to DNA that goes through the generations, and mitochondria go from woman to child through the generations. This is clearly a germline modification because it passes through, but we needed to make the distinction between nuclear DNA, which makes us who we are and how we are—our personalities, heights, weights and whether or not we get baldness—and the 37 genes in the mitochondria which are about energy for the cell, and which we describe as the power pack. That was why we adopted that working definition. No one to my knowledge has come up with a better definition so that we can have the conversations. It is not that that is what it is; it is so that we can have a conversation and know what we are talking about.

**Q53 Stephen Mosley:** We have seen a newspaper article from the summer in which it was suggested that the definition might have been because "the Government is doing all it can to contain and define these kinds of terms in ways that favour mitochondrial replacement being introduced as an uncontroversial therapy." Do you think that is a fair argument?

*Professor Davies:* No. I explained that we did it in order to clarify the discussion, so everyone knew what they were discussing.

**Q54 Stephen Mosley:** Is that definition still under review, and can people correspond with you or the Department about it?

*Professor Davies:* Please do, but unless they can come up with a better definition with absolute clarity so that we can continue our discussions, I would find it difficult to shift at this point. I am not saying that we will not shift, but we need definitions that give us clarity so the discussion is an honest, open and transparent one.

**Jane Ellison:** I think the rationale Dame Sally has presented for the definition is perfectly sensible and reasonable. If one had come up with a definition that did not have any science behind it and that you could not explain to a reasonable person, one might be accused of marking one's own homework, but that is not the case. As Dame Sally outlined, it is an entirely reasonable way to go forward. The same accusation can sometimes be made about headlines, articles or whatever that refer to GM babies and things like that, and which are extremely misleading. That is also something people should reconsider and be asked to justify. I am very comfortable that it is a reasonable definition that has helped us to have a sensible debate.

**Q55 Stephen Metcalfe:** I want to go back to follow-up. I think everyone accepts that follow-up is important. How do you envisage the Government getting involved in follow-up? Do you have a view on how follow-up data should be collected and then distributed?

**Jane Ellison:** I do not have a detailed view, because it is something I would expect HFEA to talk to scientists about. I do not think that at this stage we have to have all of that detail outlined. It is clearly a completely sensible thing for us to know, but at this point I do not think it is an essential piece of detailed planning to have in place to go to the next stage of the process. Any clinic licensed by the HFEA to do this technique would need to satisfy the regulator that they had thought it through and had a proper regime in place. That is why we have a regulator. I know that is something they would do. We have had conversations about the fact that, in principle, it would be part of the regime they would need to put in place.

**Q56 Stephen Metcalfe:** If there is a cost implication, are the Government willing to put in additional funds, or do you not see the scale of the treatment as so large that it requires funding?

**Jane Ellison:** We have not got to that stage of discussion yet, because we have not brought regulations before Parliament. It is a reasonable question to ask, and I think there will be a discussion, but because of the size of the potential cohort at the moment it is not a group so large that thinking ahead to that conversation would be a reason to say we need to stop and think about it. At the moment we know that we are talking about a relatively small group of people, and we have no reason to think it will change very quickly, but that is a conversation we would need to work through. Let's not forget that there is also an enormous cost in both human and financial terms in caring for children who are very sick and die young from dreadful diseases.

**Q57 Stephen Metcalfe:** There has been some suggestion that follow-up should be a condition of treatment, although I have not heard anyone agree with that here today. What is your view on treatment being conditional on agreement to follow-up?

**Jane Ellison:** I just do not think we are at a stage to have that discussion. We have not put regulations before Parliament yet. Clearly, discussions need to be had. Should Parliament pass the regulations, it is not the case that, the day after, all these things would suddenly be happening. The HFEA would need to put in place their own regulatory regime. The science is a continuum; it is an ongoing series of experiments, and that will continue. It is

not unreasonable to have not thought through all of those things at this stage. We have people and a process in place to make sure they have been thought through at the point when they need to be.

**Professor Davies:** I absolutely agree. As you know, I am a clinician and my subject was sickle cell disease, so I looked after disabled kids. My experience was that families wanted to know that their children were well after pre-implantation diagnosis and wanted them followed up. They also wanted to help future research. I would be surprised if our NHS patients did not want to join in.

**Jane Ellison:** We have seen that from some of the people we met through the Lily Foundation's work; they have been communicating with Members of Parliament, and families have been going to meet their Member of Parliament. I have been so impressed by how many of those families have a very good grasp of the science. They have been able to have good conversations with their Members of Parliament and help to get them to understand the debate.

**Q58 Mr Heath:** I think that the regulations you are bringing forward at the moment will allow for maternal spindle transfer and pronuclear transfer. I do not think they would allow for other techniques. Is that correct?

**Jane Ellison:** That is correct, at the moment.

**Q59 Mr Heath:** If we have a new development, as we now have in the HFEA addendum last week—polar body genome transfer—it has a few hurdles to get over first, but it would require a future change in regulations to be brought into use. Is that correct?

**Jane Ellison:** Yes, it would.

**Q60 Mr Heath:** The process would be that various safety concerns had to be satisfied, clearly.

**Jane Ellison:** It would follow the same process, which has been a rigorous one, and has been followed in the case of the two techniques that are currently the subject of discussion. I have the same understanding as you that there is a third technique, and I have had some layman's discussions with scientists about it. From my point of view, it is a little further back in the process of consideration, but it is clearly extremely interesting and encouraging. I would see it following a similar process, but it is just a little further back in the process we have been following on the other two techniques to date.

**Q61 Mr Heath:** On the two processes you are considering bringing within regulation, as far as you are concerned, the safety aspects have been satisfied. There may still be ethical considerations, but that is a matter for Parliament to decide.

**Jane Ellison:** There have been three expert panel reports during the course of this Parliament. My feeling is that we know all the things it is reasonable and possible to know at this stage. There are people who ask questions about safety and want to be satisfied, to

the extent it is possible to be satisfied given the sum of knowledge and the stage the techniques are at, which is that we have not yet done them, as it were, with women.

I think there is a body of opinion, and I respect their ethical concern, who express concerns about safety but in reality are opposed in principle. I would like people to be straightforward about that; it would be helpful to the debate. What I found particularly useful about the debate on 1 September was that I heard from a group of Members I do not think I had heard from before—people who did not have a strong view either way. They were not gung-ho at being at the forefront of science, nor were they opposed in principle. They came to it from the point of view of whether it was reasonable and sensible: are all the necessary steps and possible things that are knowable at this stage known? I found it very helpful that a number of Members in that third category were in favour of bringing forward the regulations.

In looking at the concerns people raise about safety, I always try to ask the question: are they actually opposed in principle? In other words, would the safety horizon always be just that, or is there another horizon, or are there reasonable questions to ask that can be answered at this stage? I think the latter stage is where we are with the third report, particularly when I read the layman's summary of the third expert panel report. There were certain words in it that caused public debate. I found it quite helpful to have that layman's summary explaining words like "critical," which were touched on, and what they meant, and to have it clarified that some of the experiments referred to in the third expert report could take place before or after regulations were made. I found that very helpful. That was what really tipped me towards thinking that I now needed to move forward actively.

**Q62 Mr Heath:** That is very helpful. When we were talking to the practitioners earlier we referred to the two techniques which are on the table, as it were. I put it to them that there was a discernible ethical difference between the two—one was using embryos rather than eggs—and perhaps it might be appropriate for patients to have an element of choice between two techniques. They might feel more satisfied with one rather than the other in ethical terms. They agreed with that. Would the NHS be able to encompass that?

**Professor Davies:** It may well be that the NHS can, but if you look at advanced technologies used with patients, whether it is in the NHS or elsewhere, success usually improves with practice. I would be worried if at the beginning you were doing one of this and one of that and flipping around. The outcomes are likely to be better, which means successful embryos coming through and children being born, rather than the safety of the technique, if you stick to one and get it to work successfully and then develop the other alongside if you want to offer choice. It is not that I am against choice, but pragmatically high technology usually has a practice curve to go up to get the best results.

**Q63 Mr Heath:** You want to back a winner, but you do not know which one it is going to be at the moment.

**Professor Davies:** That is absolutely true, but it is a practical issue that we should recognise.

**Q64 Jim Dowd:** There have been many references by yourself and others around the table to the earlier debate. You will know from that that some colleagues have reservations along the lines of the so-called slippery slope and designer babies, which are clichés much beloved by the tabloids. What reassurance can you give that by providing a legal platform for this kind of work we are neither on a slippery slope nor making it easier?

**Jane Ellison:** You are right; that is something that is said. Actually, in the debate I took the opportunity to give an example from the 1990s when legislation was put in place about the date up to which embryos could be used in experimentation. That has not changed. I gave an example of something put into statute that had not changed, yet debate at the time said it was a slippery slope; it would soon go and the date would stretch. It has not changed. Sometimes it is important to challenge easy assumptions, because particularly in my area of public health people make those assumptions all the time. It is quite important to go back and challenge them. I think we can give that reassurance because we can point to where it has not happened.

We also have a well-respected regulatory regime, and that is important. The regulator now has a lot more experience than when those debates on IVF were taking place. We should give the regulator credit for having given successive Governments and our population confidence that they can handle these issues in a sound and sophisticated way. That is the other reassurance people can have. There are some countries that do not have a similar regulatory regime, so you would have just a legislative framework and individual clinics. I think the fact that we have this important body sitting between the two is something from which everyone can take significant assurance.

**Professor Davies:** I think the HFEA have proved themselves in not allowing a slippery slope. They are there to protect all of us.

**Q65 Jim Dowd:** I certainly remember—I think the Chair does as well—those arguments around the embryology issue. They have not changed. You are satisfied that there are sufficient safeguards in place under the regulations as proposed to prevent any broader application or extrapolation of them. They are discrete and they are confined wholly and solely in addressing this issue.

**Jane Ellison:** Yes. The regulations are quite tightly drawn. In 2008 it was anticipated that this might be something on which we would want to bring forward regulation. As several people pointed out in the debate, it illustrates for how long careful consideration has been given to this issue. The regulations are carefully and thoughtfully put together. We have a regulator that not only has to license the places for doing it but has to look at each individual case and give approval on a case-by-case basis. I think that is a robust regime.

**Professor Davies:** Perhaps I could highlight—though the Minister would be better at speaking to it—that the Government have taken on board in the regulations a number of aspects that came up through the consultation, so they are changed in some small ways from where the Government started. Do you want me to list them?

**Jane Ellison:** We can list those for the Committee. I always think it gives people assurance that something is a genuine consultation, because as a result of the consultation

there have been amendments or whatever, so that is quite important. If Sally wants to run through those, I am very happy for her to do so.

*Professor Davies:* Would that be helpful?

*Jane Ellison:* I do not know whether the HFEA mentioned it earlier.

**Q66 Jim Dowd:** You might as well put it on the record.

*Professor Davies:* It includes amending the definitions to take account of the presence of polar bodies in eggs or embryos; modifying the consent provisions to ensure clarity; amending the determination required from the HFEA as to the risk of serious mitochondrial disease so that it can be made in relation to a specific woman rather than being needed for specific eggs or embryos; clarifying that there must be a significant risk that a person with those abnormalities would have, or develop, serious mitochondrial disease; and some other minor and technical drafting amendments.

**Chair:** Thank you, Minister and Dame Sally. The session today, when all the record is there, hopefully will help to inform the parliamentary process. For the record, we will publish from all the additional correspondence we have had, where we have the authority so to do, anything that has come to us that has not already been published elsewhere. Hopefully, the transcript of this morning's session, plus the additional correspondence that goes on our website, will help to inform the parliamentary process during the passage of the regulations. Thank you very much for your attendance this morning.