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To: Members of the European Parliament
Date: 5 February 2015
Re: Opinion on the legality of the draft Mitochondrial Donation Regulations (UK)

(a) Background

1. On 3 February 2015, British MPs voted to pass the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015³ with 382 votes for and 128 against. The instrument will next be voted on in the House of Lords and could come into force as early as October 2015.

The Biology

2. The regulations permit pronuclear and maternal spindle transfer to take place in the creation of human embryos with DNA from three parents in a bid to enable women with affected mitochondria to have genetically related children without the risk of passing on a mitochondrial disease. The new regulations would further empower the HFEA to grant licenses to allow mitochondrial donation.
3. Mitochondria are found in cells and contain a small amount of DNA, known as mtDNA. The majority of DNA is found within the nucleus (nDNA). At the point of fertilisation, the male gamete only provides the nDNA and so all the cells derived in the successive division processes will be carriers of mitochondria from the mother.
4. In pronuclear transfer (PNT), the nDNA of the embryo containing 'sick' mitochondria is transferred to another already existing embryo of a donor which has 'normal' mitochondria which it is hoped will result in the development of a healthy embryo which carries the nDNA (but not the mtDNA) of the woman seeking a child.
5. In Maternal Spindle Transfer (MST), the nucleus of the egg containing 'sick' mitochondria is transferred to the donor egg before being fertilised and it is only after the transfer that the 'hybrid' is fertilised with the father's sperm.

The Legislation

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³ Relevant excerpts of the law are set out in the Appendix.

6. Following the 1984 Report of the Warnock Committee,⁴ Parliament decided that because of an embryo's, "special status", it was essential to regulate the creation and use of human embryos. The result was the Human Fertilisation and Embryology Act 1990 which prohibits the creation, keeping or use of human embryos without a license from the Human Fertilisation and Embryology Authority. So doing, without a license, is a criminal offence.⁵
7. In 2009, a power was placed in the Human Fertilisation and Embryology Act 1990, as amended, to make new regulations to permit mitochondria donation.
8. Following this, the national regulator, the Human Fertilisation and Embryology Authority (HFEA), was asked to co-ordinate an expert group to consider the two proposed techniques (MST and PNT). The group considered there was insufficient evidence to guarantee the safety of either technique and recommended further research including requiring a crucial successful demonstration of PNT in a non-human primate model and follow up with those born as a result of these methods over an extensive period.⁶
9. We are asked to answer the following two questions. Helpful documentation and precedents :
 - (a) Is this proposed technique captured by the EU Clinical Trials Directive?
 - (b) Is Article 3 of the EU Charter of Fundamental Rights applicable?

(b) Is this technique captured by the EU clinical trials directive?

10. Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal product. The requirements for the conduct of clinical trials within the European Union are contained within Directive 2001/20/EC ("the clinical trials directive"). On 16 April 2014, the new Regulation EU No 536/2014 of the European Parliament and Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC was adopted. The regulation entered into force on 16 June 2014 but will apply no earlier than 28 May 2016.
11. The EU clinical trial directive of 2001 sets out certain processes and standards which must be adhered to in relation to "clinical trials" on "human subjects involving medicinal products." Medical products are defined as:

Any substance or combination of substances presented for treating or preventing disease in human beings or animals"; and, "any substance or combination of substances which may be administered to human beings or animals with a view to making a

⁴ Report of the Committee of Inquiry into Human Fertilisation and Embryology, Cmnd. 9314 (1984).

⁵ Human Fertilisation and Embryology Act 1990, s. 41.

⁶ HFEA, "Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception" (April 2011).

medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.⁷

The Government position

12. It is easiest to start with the question of whether clinical trials have been carried out given that a positive answer would, presumably, discharge the obligations contained within the directive. It is an easy question to answer given the position of the Department of Health.
13. The UK government has made a number of attempts to position the directive outside of the EU directive. In the first instance, in a letter sent to the Scottish Council on Human Bioethics, the Department of Health wrote:

The Clinical Trial Directive (2001/20/EC) is limited in scope to the regulation of the conduct of "clinical trials" as defined under the Directive. Mitochondrial donation is not undertaken for investigative purposes and is not therefore a clinical trial and is not governed by the Clinical Trials Directive, including Article 9.

14. More recently, during the course of the debate on 3 February 2014, the Parliamentary Under-Secretary of State for Health, argued that:

The clinical trials directive applies only to medicines. It does not apply to embryology, so it is not relevant in this case.⁸

Legal responses

15. There are two strong responses to these statements. The first surrounds the reagents used in the process as constituting medicines themselves. The fact that these are similarly regulated is made particularly clear in the notes accompanying the incoming 2014 clinical trials regulations which will repeal the 2001 directive. It states that:

Medicinal products intended for research and development trials ... include medicinal products used in the context of a clinical trial. They should be covered by specific rules taking account of their peculiarities. In establishing these rules, a distinction should be made between investigational medicinal products (the tested product and its reference products, including placebos) and auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products) ...⁹

16. Furthermore, the definition of "medical products", as set out above, is broad. This is seen even more strongly when taken viewed through the broad teleological lense mandated by the jurisprudence of the Court of Justice of the European Union

⁷ Defined by reference to Directive 65/65/EEC, Article 1.

⁸ HC Deb, 3 February 2015, c163.

⁹ Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, para. 54.

(CJEU.)¹⁰ This involves looking at the purpose to be achieved by the provision in question. Taking into account the breadth of the provision then it becomes clear that a physical and chemical intervention at the micro-medical level falls well within the ambit of the directive. That is a view shared by Lord Brennan QC, the Attorney-General for Northern Ireland and these authors.

17. Similarly, the interpretative tool of choice of the CJEU likewise dispenses with the argument that this technique will not be captured by the directive because “no trials are required.” That is akin to arguing that a statute setting out the lawful manner of buying a house is not offended in the case of an individual who steals the property.
18. The EU competences are defined in Article 2-6 of the Treaty on the functioning of the European Union (TFEU) and include areas of exclusive competence, shared competence, a competence to support and a competence to provide arrangements. Research, technological development and space appear within Article 4 TFEU as a shared competence. A shared competence means that member states can act only if the EU has chosen not to.
19. Given research is an area of shared competence, the EU enjoys a prior right to legislate in this area and it has done so. It is not open to the UK to bypass the clear terms of that legislation with a side step.

The prohibition in the directive

20. It is understandable why the UK is keen to act outside the directive. Article 9(6) of the directive provides that:

Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. *No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.*¹¹

21. This contains an explicit prohibition on activity which results in modifications to the subject's germ line – that is to say, the DNA which is passed on. Whilst the government has argued that this technique does not amount to genetic modification, they have long accepted that it does change a germ line. In MST, the germ line cells are manipulated or even human embryos to be manipulated directly (PNT) and these changes will be transmitted to the offspring.
22. The Parliamentarians voting on this were warned during the course of the preceding debate that “this legislation will open up research that is illegal [under] the EU clinical trials directive, which applies to all clinical work, states that no gene therapy trials

¹⁰ P Craig, “Pringle: Legal reasoning, text, purpose and teleology”, *Maastricht Journal of European and Comparative Law* (2013).

¹¹ Emphasis added.

may be carried out that result in modification to the subject's germline genetic identity. The HFEA itself has said that this procedure does."¹²

23. In his legal opinion on the regulations, Lord Brennan QC has said that they are caught by the clinical trials directive and that they are 'likely to be in breach of EU law'.¹³ Lord Brennan's opinion also anticipated the argument that this technique would not be subject to any requirement for clinical trials. He set out the relevant paragraphs from the 2011 report on safety from the review panel set up by the Secretary of State to monitor the procedures which says "Once assessed as safe to use in clinical practice, the panel strongly recommends that permission is sought from the parents of the children born from MST and PNT to be followed up for an extensive period" and that such permission should be sought from the children themselves once they are old enough. In the case of females, that should ideally be the next generation. This is intrusive and extensive monitoring, considered absolutely essential by those supporting the amendment, and amounts to a tacit acknowledgment that this legislation will permit clinical trials under the guise of clinical practice.
24. Considering the directive in light of its purpose – to ensure the safe provision of healthcare - given the express inclusion of these sort of technique and the explicit banning of any gene therapy trials then the proposed course of action in the UK will clearly fall within the prohibition, as it is likely to be interpreted by the UK. Furthermore, the provision will likely also be interpreted so as to prevent use in clinical practice without any investigation or trials first having taken place. To rule otherwise would negate the principle purpose of the directive.
25. In an open letter dated 2 February 2015, members of the European Parliament indicated that this matter may be brought before the European Commission which could consider infringement proceedings against the UK. The Commission would follow a set of formalized steps which have resulted in more than 85% of cases being resolved before the litigation stage.¹⁴

(c) Is Article 3 of the EU Charter of Fundamental Rights applicable?¹⁵

26. Following the entry into force of the Lisbon Treaty in 2009, the Charter has the same legal value as the European Union treaties. Article 51(1) of the Charter addresses, inter alia, EU member states when implementing EU laws providing that member States must respect the rights, principles and application of the Charter when "implementing Union law".

¹² HC Deb, 3 February 2015, c176.

¹³ S Connor, "New three-parent baby law 'is flawed and open to challenge', says senior lawyer", *The Independent* (14 January 2015); HC Deb, 3 February 2015, c177.

¹⁴ European Commission, "European Commission at work: Infringement procedure", (9 December 2014).

¹⁵ Note, there is also an argument that the regulations are ultra vires at a domestic level when considered in light of the parent Act. The argument is set out clearly in the Dr Elizabeth Allan's Written Evidence to the Secondary Legislation Scrutiny Committee.

27. The Charter contains some unusually explicit protections for human dignity and in relation to bioethics which appear in Articles 1-3¹⁶ which protect dignity, the right to life and the right to integrity of the person respectively. An action could potentially lie in relation to any of these three grounds which will now be set out.
28. Under Article 1, protecting dignity, the Charter contains a clear statement as to the inviolability of human dignity. Under this provision, the corpus of international soft law in relation to bioethics could be brought to bear. A further attraction to an argument under this provision is the fact that no potentially more controversial argument about personhood needs to be made. Dignity can be both an individual and a collective construct.
29. Similarly, under article 2, the right to life is protected. Whilst the European Court of Human Rights has struggled with the question of when life begins, the CJEU took an early position in the case of *Oliver Brüstle v Greenpeace eV*,¹⁷ holding that a human embryo is any human ovum after fertilisation given that the process of development of a human being starts at that moment. This is a favourable precedent and one that could be leveraged under Article 2.
30. Article 3 deals specifically with bioethics and protects the right to the integrity of the person. The Explanatory Notes to the Charter indicate that “the principles of Article 3 of the Charter are already included in the Convention on Human Rights and Biomedicine” and the Charter “does not set out to depart from those principles.”¹⁸ Even more helpfully, the official commentary to the Charter highlights the non-exhaustive nature of the list in Article 3 and notes that “other rights and principles laid down in the Biomedicine Convention and its two Protocols include ... [an] absolute prohibition of any modification in the genome of any descendants.”¹⁹

Legal status of the Charter

31. Article 6(1), gives the Charter “the same legal value as the Treaties” and prohibits the Charter from being used to extend “in any way” the competences of the EU. However, both Article 6 of the TEU, as amended, and Article 51(2) of the Charter constrain the Charter from extending the prior competences of the EU. A consequence is that individuals will be unable to take a member state to court for failing to uphold the rights in the Charter unless the State was implementing EU law.

The British Protocol

¹⁶ See Appendix for full provisions.

¹⁷ C-34/10.

¹⁸ [2007] OJ C303/18.

¹⁹ EU Network of Independent Experts on Fundamental Rights, “Commentary on the Charter of Fundamental Rights of the European Union” (June 2006), pp. 37-38; See further, the Convention on Biomedicine and Human Rights (though note the UK is not a signatory to the Convention itself).

32. Clouding the issue is the British protocol 30, secured in the leading up to the signing of the Lisbon Treaty.²⁰ The protocol states, in article 1(1), that the Charter:

Does not extend the ability of the Court of Justice of the European Union, or any court or tribunal of Poland or of the United Kingdom, to find that the laws, regulations or administrative provisions, practices or actions of Poland or of the United Kingdom are inconsistent with the fundamental rights, freedoms and principles that it reaffirms.

33. In *NS v. Home Secretary*,²¹ the CJEU ruled that the Protocol:

Explains Article 51 of the Charter with regard to the scope thereof and does not intend to exempt the Republic of Poland or the United Kingdom from the obligation to comply with the provisions of the Charter or to prevent a court of one of those Member States from ensuring compliance with those provisions.²²

34. Suggestions in Parliament that the protocol amounted to an “opt out” were rebuffed by the Secretary of State for Justice who has stated that”

[they] talk about an opt-out, but that is not what the Labour Government actually negotiated. They negotiated a protocol that stated that the charter would be applied only to EU law. That is the situation today, and it does not enable us to opt out of the charter. We are still subject to it in EU matters. [...] ²³

35. A March 2014 report by the House of Commons European Scrutiny Committee²⁴ seeks to clear up the confusion concluding that:

Protocol 30 was designed for comfort rather than protection: it is in no sense an opt-out Protocol; consequently, the Charter is directly effective in the UK with supremacy over inconsistent national law (as it is for all other EU Member States); it does not apply to all areas of national law, however, only those that fall within the scope of EU law, a test which the ECJ has interpreted broadly...²⁵

36. In *Aklagaren v. Fransson*,²⁶ the CJEU was called upon to decide whether imposing both administrative penalties for non-payment of VAT as well as criminal sanction breached the rule against double jeopardy contained within Article 50 of the Charter. The Court ruled that this did not breach the Charter but, more importantly, that the fundamental rights guaranteed in the legal order of the EU were applicable in all situations governed by such law, but not outside such situations. The Court had no

²⁰ P. Koutrakos, “Does the United Kingdom have a general opt out from the EU Charter of Fundamental Rights”, *European Law Review*, (2014) 39(1) at 1.

²¹ C-411/10 and C-493/10

²² Joined Cases C-411/10 and C-493/10, *N.S. v Home Secretary and M.E. v. Refugee Applications Commissioner* [2011] EUECJ C-411/10 (21 December 2011). Para. 120.

²³ HC Deb, 19 November 2013, col 1089.

²⁴ House of Commons European Scrutiny Committee, “The application of the EU Charter of Fundamental Rights in the UK: a state of confusion” (43rd Report of Session 2013-14).

²⁵ *Ibid.*, p. 5.

²⁶ C-617/10.

power to examine the compatibility with the Charter of national legislation lying outside the scope of EU law.

What does “implementing EU law” mean?

37. Having established that an action may lie where the UK has failed to properly respect the provisions of the Charter, the question which finally falls to be answered is whether “when implementing EU law” really means “acting within the scope of EU law.” David Anderson QC, commenting on the decision in *Fransson* reasoned that:

The significance of *Fransson* is not so much in concluding that the test to be applied under Article 51(1) of the Charter is whether Member State action is within the scope of EU law—that much is made plain by the Explanations; it is much more the ECJ’s conclusions on the national circumstances in which that test is met.

38. The CJEU held that its case law stated that EU fundamental rights are applicable “in all situations governed by EU law”²⁷ and that:

Since the fundamental rights guaranteed by the Charter must therefore be complied with where national legislation falls within the scope of European Union law, situations cannot exist which are covered in that way by European Union law without those fundamental rights being applicable. The applicability of European Union law entails applicability of the fundamental rights guaranteed by the Charter.²⁸

39. The *Fransson* threshold is a relatively low one and, in cases of uncertainty, the question should be ultimately answered by the CJEU.²⁹ Given our comments, above, in relation to the competence of the EU in this area, and given that the test does not require the legislation to be “implementing legislation”, it seems likely that the CJEU would find the relatively low threshold to be met in this case.

(d) Conclusion

40. Despite the UK government’s assertion to the contrary, it seems relatively clear that the regulations would be captured by the EU clinical trials directive. If they are so captured (whether based on the reagents used or a broader teleological interpretation), Article 9 is unequivocal in its prohibition on gene therapy which modifies the germ line – something which the government accepts is the result of these techniques. An action for infringement would lie in the hands of the Commission.
41. A separate course could be pursued by a different actor by way of challenge at the CJEU – if the legislation is passed – under the Charter of Fundamental Rights. The rights in the Charter are relatively untested and there is the additional complication

²⁷ Case C-617/10, para. 19.

²⁸ *Ibid.*, para 21.

²⁹ E Muir, “The fundamental rights implications of EU legislation: some constitutional challenges”, *Common Market Law Review* (2014) 51(1).

in relation to Britain's unique situation. That said, the legal position has settled upon a challenge against the UK under the Charter being possible so long as it falls within the scope of EU competence.

APPENDICES

(a) Department of Health Guide on the draft regulations (January 2015)³⁰

In summary, each regulation has the following effect:

Regulation 1: determines that, if approved by Parliament, the Regulations will be entitled The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 and that they will come into force on 29th October 2015.

Regulation 2: defines the terms used in the Regulations.

Regulation 3: enables an egg created by the use of a mitochondrial donation technique to be considered to be a “permitted egg” and suitable to be placed in a woman.

Regulation 4: prescribes the donation technique to be used for eggs. No technique that does not match this description may be used.

Regulation 5: prescribes the criteria that must be satisfied before a patient can be treated: that there is a particular risk that the patient’s egg will carry a mitochondrial DNA abnormality and that there is a significant risk that a child born from the use of that egg will have or develop a serious mitochondrial disease.

Regulation 6: enables an embryo created by the use of a mitochondrial donation technique to be considered to be a “permitted embryo” and suitable to be placed in a woman.

Regulation 7: prescribes the donation technique to be used for embryos. No technique that does not match this description may be used.

Regulation 8: prescribes the criteria that must be satisfied before a patient can be treated: that there is a particular risk that an embryo created using the patient’s egg will carry a mitochondrial DNA abnormality and that there is a significant risk that a child born from the use of that embryo will have or develop a serious mitochondrial disease.

Regulation 9: specifies that a clinic already holding a treatment licence from the HFEA, to carry out IVF, cannot provide mitochondrial donation treatment without specific prior approval to do so from the Authority.

³⁰ Department of Health, “The Draft Human Embryology and Fertilisation (Mitochondrial Donation) Regulations 2015, a guide on new regulations to enable the use of mitochondrial donation techniques in clinical practice” (January 2015).

Regulation 10: introduces modifications to provisions in the Human Fertilisation and Embryology Act 1990 and the Human Fertilisation and Embryology Act 2008 that will apply where an egg or embryo has been crafted as the result of the application of a mitochondrial donation technique.

Regulation 11: determines what information may be given to a mitochondrial donor-conceived person, on application to HFEA, about their mitochondrial donor. No identifying information may be disclosed.

Regulation 12: clarifies that a mitochondrial donor-conceived person cannot be considered as genetically related to the mitochondrial donor or any person who was born as a result of treatment services using genetic material from the person's mitochondrial donor for the purposes of requesting information about whether an intended spouse, civil partner or person with whom that person has or intends to have an intimate physical relationship is genetically related to them.

Regulation 13: provides that mitochondrial donors must not be informed that a young person born as a result of their donation has sought non-identifying information about them from the HFEA.

Regulation 14: determines what information can be given to a mitochondrial donor, on application to the HFEA, about children born as a result of their donation. No identifying information can be disclosed.

Regulation 15: clarifies that the mitochondrial donor cannot be considered to be a biological parent of a person born as a result of their donation for the purposes of section 31ZE of the Human Fertilisation and Embryology Act 1990, which means that two persons with the same mitochondrial donor are not to be regarded as genetic siblings.

Regulation 16: provides that a mitochondrial donor cannot withdraw their consent to their donated egg or embryo being used in the treatment of the affected patient once it has undergone the MST mitochondrial donation technique, even if the egg or embryo has not yet been placed in the patient.

Regulation 17: ensures that for the purposes of the consent provisions in the Human Fertilisation and Embryology Act 1990, the resulting egg or embryo is not to be treated as the egg or embryo of the person whose mitochondrial DNA was used to create it.

Regulation 18: provides that where a child has been born following treatment services a person who donated mitochondria is not eligible to apply for a parental order on the basis of that donation alone.

Regulation 19: amends the Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004 so that they do not apply to information requests under the Human Fertilisation and Embryology Act 1990 about mitochondrial donation.

(b) EU Charter of Fundamental Rights (Excerpts)

Preamble

Conscious of its spiritual and moral heritage, the Union is founded on the indivisible, universal values of human dignity, freedom, equality and solidarity;

Article 1

Human dignity

Human dignity is inviolable. It must be respected and protected.

Article 2

Right to life

1. Everyone has the right to life.
2. No one shall be condemned to the death penalty, or executed.

Article 3

Right to the integrity of the person

1. Everyone has the right to respect for his or her physical and mental integrity.
2. In the fields of medicine and biology, the following must be respected in particular:
 - (a) the free and informed consent of the person concerned, according to the procedures laid down by law;
 - (b) the prohibition of eugenic practices, in particular those aiming at the selection of persons;
 - (c) the prohibition on making the human body and its parts as such a source of financial gain;
 - (d) the prohibition of the reproductive cloning of human beings.

(c) Text of explanations relating to the complete text of the Charter

Article 3 – Explanation

The principles of Article 3 of the Charter are already included in the Convention on Human Rights and Biomedicine, adopted by the Council of Europe (ETS 164 and additional protocol ETS 168). The Charter does not set out to depart from those principles, and therefore

prohibits only reproductive cloning. It neither authorises nor prohibits other forms of cloning. Thus it does not in any way prevent the legislature from prohibiting other forms of cloning.

(d) EU Clinical Trials Directive (2001)³¹

Article 1

Scope

1. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC³²

[...]

Article 2

Definitions

For the purposes of this Directive the following definitions shall apply:

(a) 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

Article 9

Commencement of a clinical trial

[...]

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity. [...]

³¹ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

³² Article 1 of Directive 65/65/EEC defines a medicinal product as "any substance or combination of substances presented for treating or preventing disease in human beings or animals"; and, "any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product."