#### Mitochondrial donation: new case application form

1. Introduction

Please use this form if you wish to carry out a mitochondrial donation technique to treat a patient not previously authorised by the HFEA.

Before you begin your application please make sure the following statements are true:

* You hold a licence to carry out the mitochondrial donation technique (PNT and/or MST) intended for use in the treatment of this patient.
* You have identified a pathogenic mutation in the mtDNA of the patient.
* You have evidence that the patient has a significant risk of having a child who will have or go on to develop serious mitochondrial disease.

It is important that the language used in this application is clear and, as far as possible, understandable to non-specialists.

All abbreviations should be explained.

The application form has been designed to ensure that applying centres provide all of the information required to enable the Authority’s Statutory Approvals Committee to make its decision.  If the form is completed incorrectly or does not provide sufficient information it could delay the decision-making process.

The committee is aware that not all pieces of evidence asked for will be relevant to every case.

An independent assessment of the application may also be sought from clinical experts and may inform the Statutory Approvals Committee’s decision-making process.

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| The guidance outlined in the green boxes has been developed for centres licensed to carry out maternal spindle transfer (MST) and/or pronuclear transfer (PNT) that wish to apply for approval to perform mitochondrial donation for a new patient. Please refer to this as you fill in the application form. These applications are all considered on a case-by-case basis.   |

2. Current centre information

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| Person responsible |       |
| Centre name |       |
| Centre number |       |

3. Regulatory requirements

**Is this application from a centre licensed to carry out maternal spindle transfer (MST) and/or pronuclear transfer (PNT)?**

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| Only centres licensed to carry out mitochondrial donation (MST and/or PNT) are permitted to make an application. Please state whether or not the application is from an assisted reproduction clinic, licensed by the HFEA. |

[ ]  MST [ ]  PNT [ ]  No

**Will only an authorised embryologist who is named on the licence carry out the proposed mitochondrial donation technique (MST or PNT)?**

Only the authorised embryologists named on the licence are permitted to carry out MST or PNT in treatment. Please confirm that only an authorised embryologist named on your licence will carry out the proposed MST or PNT.

[ ]  Yes [ ]  No

**Which technique is intended for the treatment of this patient?**

[ ]  MST [ ]  PNT

**Has all the diagnostic genetic testing taken place in an accredited laboratory?**

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| Genetic testing should only be carried out by an accredited laboratory. If not, please provide an explanation as to why the genetic testing has not been carried out in an accredited laboratory. |

[ ]  Yes [ ]  No

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As the Person Responsible I confirm that the purpose of the application is to treat a patient with a pathogenic mtDNA mutation, and there is a significant risk of this resulting in a serious mitochondrial disease in their children.

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| Please confirm that the reason you want to carry out mitochondrial donation is for the statutory purposes. |

Please tick the box to confirm acceptance of the above statement: [ ] Confirmed

4. Patient details

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| Surname |       |
| Forename |       |
| Patient number |       |

 I wish to apply for authorisation for the patient/case [ ] Yes

5. Genetic cause

**Has a pathogenic genetic alteration to the mtDNA been identified in the female patient?**

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| Only female patients for whom a pathogenic mtDNA genetic alteration has been identified are considered to be at particular risk of passing on abnormal mtDNA to their children. |

[ ] Yes [ ] No

**Please give a description of this genetic alteration, i.e. point mutation, deletion, rearrangement and the tissue this was identified in**

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| Please describe the pathogenic genetic alteration present in the patient’s mtDNA, e.g. T8993T>G in ATP synthase subunit 6 (*MTATP6*) |

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**Please list any OMIM numbers associated with this mitochondrial disease**

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| If applicable also provide the OMIM (On Line Mendelian Inheritance in Man System) number for this mitochondrial disease. This is indicated by a hash (#) for phenotypes and a plus sign (+) for the description of a gene of known sequence and a phenotype. |

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6. Seriousness and significant risk: general information

In this section of the form we would like you to provide information based on scientific literature, which is **not patient-specific**, about the disease(s) caused by this genetic change and about the relationship between mutant mitochondrial load and disease manifestation.

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| When considering the seriousness of a condition, the Statutory Approvals Committee will consider non-case-specific evidence from the scientific literature, which you will provide in this section, as well as the case-specific information given in section seven. The committee will take the following factors into account. Please provide as much information as possible under each of these sections. Please include references. |

Where information about the disease(s) or genetic abnormality listed above is available please provide:

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| Please provide a summary of the genetic condition and, if applicable, all the types of the condition in non-technical / lay language. This should include a description of how the condition affects a person, if known, how mutant mitochondrial load correlates to clinical symptoms and, if applicable, whether any treatments for the condition are available. Please limit the word count for the lay summary to 200 words. |

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| Lay summary      |

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| Please describe the range of symptoms which an individual with this mitochondrial disease might have, indicating the worst possible outcomes.  |

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| Symptoms of the disease      |

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| At what age will the symptoms of the condition start to develop? Is the condition apparent at birth or does it manifest later in life? If so, at what stage, for example, childhood, early adulthood or later? Are symptoms likely to be static, once present, or progressive? |

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| Age at which symptoms are likely to develop      |

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| In this section, please include evidence about the effect the condition has on the quality of life of a child/adult (this might include the speed of degeneration in progressive disorders together with the extent of any physical and / or intellectual impairment). |

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| Effect on quality of life      |

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| If there is any evidence from the scientific literature to indicate the effect of mutant mtDNA load on the severity of disease, please include this information here. How does the mutant mtDNA load correlate to clinical symptoms? What is the mutant mtDNA load above which clinical symptoms become manifest? Are there any studies indicating how high the mutant mitochondrial loads were in women that have had children affected by mitochondrial disease? What is the lowest mutant mitochondrial load in a woman that has had a child affected by serious mitochondrial disease? |

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| Threshold level (or estimated threshold level) of mutant mtDNA necessary to cause symptoms      |

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| Please list any treatment options available. How invasive is the treatment or likely treatment? |

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| Available treatment options      |

7. Significant risk and seriousness: patient information

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| It is important that you explain to the patient why they are being asked to provide the information on their own medical history and that of their family. Explain to the patient that this information will be disclosed to the HFEA to assist in the Statutory Approvals Committee’s decision-making process and that all information will be treated confidentially by those to whom it is disclosed and will be stored securely. |

In this section please provide evidence that is **specific to the patient** named in this application.

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| The Committee may only approve the use of mitochondrial donation if it is satisfied that there is a particular risk that any egg extracted from the ovaries of the patient, or any embryo created with those eggs, may have mitochondrial abnormalities caused by mitochondrial DNA. The committee must also be satisfied that there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.Please explain why you think the patient's child, if conceived naturally, is at significant risk of having or developing a serious mitochondrial diseaseThe Committee may also only approve applications for patients who are (or are predicted to be) highly heteroplasmic or homoplasmic for a particular mtDNA mutation in their germ line and who have undergone assessment that deems PGD inappropriate or likely to be unsuccessful. This is in light of the Authority’s decision to approve the use of mitochondrial donation as a risk reduction strategy for patients for whom PGD would be inappropriate. When considering risk and seriousness, and the limitations of PGD for this patient, the Statutory Approvals Committee will take the following factors into account. Please provide as much information as possible under each of these sections.  |

**Is there a significant risk that a child born without mitochondrial donation will have or go on to develop a serious mitochondrial disease?**

[ ] Yes [ ] No

**Is the patient (or is the patient predicted to be) highly heteroplasmic or homoplasmic for a particular mtDNA mutation in their germ line?**

[ ] Yes [ ] No

**Has the patient undergone an assessment that deems PGD inappropriate or likely to be unsuccessful?**

[ ] Yes [ ] No

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| Please provide relevant details of the patient's medical history as well as pregnancy history. How does it provide evidence of risk and seriousness? How does this demonstrate that PGD is inappropriate for this patient or likely to be unsuccessful? You may wish to consider the following questions:* Does the patient have any symptoms? If so, how severe are they?
* Has the patient previously had any children affected by mitochondrial disease? If so, what were their symptoms? What was the age of onset? What was the effect on quality of life? Were any treatments available and what effect did they have? Would this manifestation of mitochondrial disease pass the seriousness test?
* Has the patient previously undergone preimplantation genetic diagnosis (PGD) to avoid transmission of mitochondrial disease? Was the PGD unsuccessful? What was the mutant mitochondrial load of the embryos tested? Did any of the embryos have a mutant mitochondrial load above the threshold level usually necessary for clinical manifestation of serious mitochondrial disease?
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| Please provide information on the patient’s medical history      |

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| Has the patient's mutant mtDNA load been assessed? How does it provide evidence of risk and seriousness? You may wish to address the following questions:* Is the patient homoplasmic or heteroplasmic for the mutation?
* What is the patient’s mutant mtDNA load and in which tissues?
* Have patients with similar mutant mtDNA loads had children affected by serious mitochondrial disease?
* How does the patient’s mutant mitochondrial load compare to the threshold level for clinical manifestation, if known?
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| Please provide information on the patient’s mutant mtDNA load      |

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| What is the patient's family history of mitochondrial disease? How does it provide evidence of risk and seriousness? You may wish to consider the following questions:* Does the patient have a family history of mitochondrial disease? How prevalent is mitochondrial disease in the family? How serious was the disease in affected family members: what were the symptoms, what was the age of onset, what was the effect on quality of life, were any treatments available and what effect did they have?
* What were the mutant mitochondrial loads of affected family members with severe mitochondrial disease and what were the mutant mitochondrial loads of their mothers? Are the mutant mitochondrial loads of female family members who have had severely affected children comparable to the patient?
* Describe the symptoms of affected family members, age of onset, effect on quality of life, their mutant mitochondrial load, if any treatment was available, what it was and what effect it had.

Note: Please ensure that you have either obtained consent before providing disclosure of family medical history that is capable of identifying an individual or take measures to ensure that confidentiality is not breached by providing family history as a narrative rather than describing individuals to a degree that they might be identified from your description. |
| If there is any additional information you feel provides evidence of risk and seriousness, please include it here. For example, you may wish to include a statement from the patient’s genetic counsellor, outlining the impact that mitochondrial disease has had on them and why they feel mitochondrial donation is the most appropriate treatment for them. |

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| Please provide information on the patient’s family history of mitochondrial disease       |
| Please provide any additional information to support this      |

8. Declarations

I consent to the HFEA processing the data that I have provided on this form and any supporting documentation submitted with it, for the purposes of considering my application; statistical analysis; and quality control.

I further consent to the HFEA sharing these data with any other body with whom there is an agreement to undertake inspections or other regulatory functions on behalf of, or in conjunction with, the HFEA.

I understand that these data will be stored securely by the HFEA and saved in accordance with the HFEA's published retention and disposal schedule.

I further understand that the HFEA will not disclose these data to any third parties except as specified above, or as permitted or required by law, and in particular by the requirements of the Data Protection Act 1998 and the Freedom of Information Act 2000.

Persons submitting this application should note that by Section 18(2) of the Human Fertilisation and Embryology Act 1990 (as amended) the Authority may revoke a licence if it is satisfied that any information given for the purposes of application for the grant of licence was in any material respect false or misleading. They should also note that under Section 41(3) provision of false or misleading information, knowingly or in a reckless manner is a criminal offence.

The information provided on this form is to the best of my knowledge true and accurate.

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| Please tick the box to confirm the declaration. This must be completed by the person responsible of the licensed centre applying for the treatment. The form should then be submitted to the HFEA by recorded delivery. |

**Check the box to confirm acceptance of the above statement** [ ]