Title: The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015	Impact Assessment (IA)
IA No: 3124	**Date: 12/09/2014**
	Stage: Final
Lead department or agency:	**Source of intervention: Domestic**
Department of Health	**Type of measure: Secondary legislation**
Other departments or agencies:	**Contact for enquiries: Steve Pugh**
NA	

Summary: Intervention and Options	**RPC Opinion:** RPC Opinion Status

Cost of Preferred (or more likely) Option				
Total Net Present Value	**Business Net Present Value**	**Net cost to business per year** (EANCB on 2009 prices)	**In scope of One-In, Two-Out?**	**Measure qualifies as**
£318.1m	£0m	£0m	Yes	ZNC

What is the problem under consideration? Why is government intervention necessary?

Serious mitochondrial DNA disease results from mutated mitochondrial DNA being passed from mother to child and affects the ability of cells to function, causing life-limiting diseases, such as heart and kidney failure. There are few effective treatments for mitochondrial DNA disease and no cure. Scientists in the UK have pioneered techniques by which faulty mitochondria of the mother is replaced by healthy mitochondria from a donor. However, it is illegal under current regulations to provide treatment of mitochondrial DNA disease based on these techniques. The Department of Health has been asked by researchers to introduce regulations under the section 3ZA of the Human Fertilisation and Embryology Act 1990 (amended through HFE Act 2008) to allow mitochondrial donation in treatment.

What are the policy objectives and the intended effects?

The intended effect of the proposal is to prevent serious mitochondrial DNA disease being passed from mother to child.

What policy options have been considered, including any alternatives to regulation? Please justify preferred option (further details in Evidence Base)

The policy options considered are as follows:
(1)   Do nothing
(2)   Create regulations that enable mitochondrial donation to take place
To do nothing would incur no additional costs, but would also mean that there is no method by which to prevent transmission of serious mitochondrial DNA disease from mother to child. Without intervention, the only option for those families who have children born with serious mitochondrial disease will be for healthcare to be provided to manage symptoms in whatever way is appropriate and possible. The only approach to achieving the objectives is by creating regulations to enable this activity (option 2). The Government has a regulation making power in the HFE Act 1990 (as amended) to redefine what is a "permitted" egg/embryo for use in assisted reproduction techniques. The regulation considered in this IA expands this definition to include eggs and embryos where unhealthy mitochondrial DNA is replaced by healthy mitochondrial DNA from a donor.

Will the policy be reviewed? It **will** be reviewed. **If applicable, set review date: 10/2019**

Does implementation go beyond minimum EU requirements?		N/A		
Are any of these organisations in scope? If Micros not exempted set out reason in Evidence Base.	**Micro** **No**	**< 20** **NA**	**Small** **NA**	**Medium** **NA**	**Large** **NA**
What is the CO$_2$ equivalent change in greenhouse gas emissions? (Million tonnes CO$_2$ equivalent)			**Traded:**	**Non-traded:**

I have read the Impact Assessment and I am satisfied that (a) it represents a fair and reasonable view of the expected costs, benefits and impact of the policy, and (b) that the benefits justify the costs.

Signed by the responsible Minister: Jane Ellison   Date: 12 September 2014

Summary: Analysis & Evidence   Policy Option 1

Description: Do nothing
FULL ECONOMIC ASSESSMENT

Price Base Year 2014	PV Base Year 2015	Time Period Years 10	Net Benefit (Present Value (PV)) (£m)		
			Low: 0	**High: 0**	**Best Estimate: 0**

COSTS (£m)	Total Transition (Constant Price) Years		Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low	Optional		Optional	**Optional**
High	Optional	NA	Optional	**Optional**
Best Estimate	NA		NA	**£0**

Description and scale of key monetised costs by 'main affected groups'
There will be no changes in costs or benefits to any groups.

Other key non-monetised costs by 'main affected groups'
N/A

BENEFITS (£m)	Total Transition (Constant Price) Years		Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	Optional		Optional	**Optional**
High	Optional	NA	Optional	**Optional**
Best Estimate	NA		NA	**£0**

Description and scale of key monetised benefits by 'main affected groups'
There will be no changes in costs or benefits to any groups.

Other key non-monetised benefits by 'main affected groups'
NA

Key assumptions/sensitivities/risks	**Discount rate (%)**	NA
The risk of selecting this option is that the objective will not be achieved.		

BUSINESS ASSESSMENT (Option 1)

Direct impact on business (Equivalent Annual) £m:			In scope of OITO?	Measure qualifies as
Costs:	Benefits:	Net:		

Summary: Analysis & Evidence   Policy Option 2

Description: Create regulations that enable mitochondrial donation treatment to take place

FULL ECONOMIC ASSESSMENT

Price Base **Year** 2014	PV Base **Year** 2015	Time Period **Years** 10	Net Benefit (Present Value (PV)) (£m)		
			Low: 110.3	**High:** 528.6	**Best Estimate: 318.1**

COSTS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low	NA		£0.4m	**£3.4m**
High	NA	1	£2.3m	**£19.7m**
Best Estimate	£0.1m		£1.3m	**£11.1m**

Description and scale of key monetised costs by 'main affected groups'

The main affected groups are the provider clinics who will carry out the mitochondrial donation treatment and the HFEA as regulators of mitochondrial donation, who will both regulate the clinics providing treatment and approve individuals considered for treatment on a case by case basis.

Other key non-monetised costs by 'main affected groups'

N/A

BENEFITS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	NA		**£13.2**	**£531.9m**
High	NA	NA	**£54.3**	**£130.0m**
Best Estimate	NA		**£33.5**	**£329.2m**

Description and scale of key monetised benefits by 'main affected groups'

The key benefits of the change to regulations will be QALY gains to the 20 individuals a year who will not have serious mitochondrial DNA disease. Estimates have also been made as to their gains in net production, as well as a saving in secondary (condition specific) healthcare costs.

Other key non-monetised benefits by 'main affected groups'

It is expected that families of the individuals that would otherwise have been affected by serious mitochondrial DNA disease will have an improved quality of life and make a larger contribution to the UK economy. Such expectations have not been quantified in this IA.

Key assumptions/sensitivities/risks	**Discount rate (%)**	3.5%

This IA relies on the expectation that 20 persons will benefit from mitochondrial donation treatment each year. Costs and benefits will change proportionately to the number of persons who receive these services.
There is also the assumption that there will be (at least partial) NHS provision and commissioning of this treatment. Should this not be the case then uptake may vary based upon willingness to pay for treatment.
Available evidence has been used estimate a 'typical' group of patients with serious mitochondrial DNA disease for purposes of analysis. Due to the inherent variability in the disease these are necessarily crude estimates.

BUSINESS ASSESSMENT (Option 2)

Direct impact on business (Equivalent Annual) £m:			In scope of OITO?	Measure qualifies as
Costs: 0	**Benefits:** 0	**Net:** 0	Yes	ZNC

Evidence Base (for summary sheets)

Problem under consideration & rationale for intervention

1. Mitochondrial disease results from mutation of mitochondrial DNA in humans. It affects the ability of cells to function and can cause a variety of diseases ranging from the relatively minor (lethargy, hearing loss) to severe (stroke, seizures, heart and kidney failure) – and can have substantial impacts on both life expectancy and quality of life. Mitochondrial DNA disease is passed on to future generations through the female line, through faulty mitochondrial DNA in eggs. These mutations affect the basic structure of human bodies, and to date, there are few effective treatments and there is no cure[1].

2. Scientists in the UK have pioneered techniques by which faulty mitochondria of the mother is replaced by healthy mitochondria from a donor [1].

3. Currently, it is legal to engage in research to prevent serious mitochondrial disease using human embryos or eggs, but it is *illegal* to provide treatment based on this technique. In 2010 the Department of Health was asked by researchers to introduce regulations to allow mitochondrial donation in treatment settings. The Department consequently asked the Human Fertilisation and Embryology Authority (HFEA), as regulators, to convene an Expert Panel to review the evidence of safety and efficacy of these new techniques. The panel found no evidence that the treatments were unsafe, but recommended further research. A further update is expected imminently. At the request of the Department of Health, the HFEA also undertook a public consultation and dialogue on the acceptability of mitochondrial donation. The outcome was support for it so long as the clinics providing the treatment are appropriately regulated, and treatments are approved for individuals on a case by case basis, seeking to treat only those mothers with a significant risk of having children with severe mitochondrial disease [2]. The Department of Health announced in 2013 that it intends to take forward regulations to allow mitochondrial donation to prevent the transmission of serious mitochondrial disease, under section 3ZA of the Human Fertilisation and Embryology Act 1990[2](amended through HFE Act 2008). A draft of the regulations was published for public consultation February to May 2014.

4. The rationale for Government intervention is that it is the Government that sets the regulatory framework that encompasses fertility treatment in the UK. It is intended to reduce the harm to individuals born with serious mitochondrial disease and reduce the impact of treatment on the NHS and personal care services.

Policy Objective

5. The intended effect of the proposal is to prevent serious mitochondrial DNA disease being passed from mother to child.

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[1]

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf

[2] http://www.legislation.gov.uk/ukpga/1990/37/contents

Description of options considered

6. The policy options considered are as follows:

(1) Do nothing

(2) Create regulations that enable mitochondrial donation to take place

7. The use of eggs or embryos with donated mitochondria in treatment is currently illegal. To do nothing (option 1) would incur no additional costs, but would also mean that there is no method by which to prevent transmission of serious mitochondrial DNA disease from mother to child. The only approach to achieving the objectives is by creating regulations to enable this activity (option 2). The Government has a regulation making power in the HFE Act 1990 (as amended) to redefine what is a "permitted" egg/embryo for use in assisted reproduction techniques. The regulation considered in this IA expands this definition to include eggs and embryos where unhealthy mitochondrial DNA is replaced by healthy mitochondria.

Monetised and non-monetised costs and benefits of option 1

8. Without intervention, the only option for those families who have children born with serious mitochondrial disease will be for healthcare to be provided to manage symptoms in whatever way is appropriate and possible. There would be no additional costs or benefits. This option acts as a counterfactual against which the costs and benefits of option 2 are compared.

Monetised and non-monetised costs and benefits of option 2

9. In 2010 medical researchers asked the Government to use their powers to introduce regulations to allow newly developed techniques to be used in prevention of serious mitochondrial DNA disease in the UK for the first time. The techniques would not treat or cure a person who already has a mitochondrial disorder. The intention instead is that the techniques will enable women who are the carriers of the disorder to have their own genetically related children, free of serious mitochondrial DNA disease [3].

10. The benefits of introducing the regulations (option 2) fall into the following categories:

    a. To the patients who will receive the treatment and their families

    b. There will be a benefit to business since creating these regulations would allow clinics to provide a service they would otherwise be unable to do and generate revenue from the process

    c. The NHS would benefit from a reduction in present costs of care for those affected by serious mitochondrial disease

    d. Finally, there would be a wider benefit from healthy people born (and/or their caregivers) making a larger contribution to the UK economy.

11. The costs of option 2 fall on:

    a. Those who will pay for the service. It should be noted at this point that this analysis is not intended as a cost effectiveness study for the commissioning of mitochondria donation. Further analysis would be required in order to confirm an appropriate commissioning route. However, based on preliminary conversations it is anticipated that NHS provision of these services will be paid for by NHS England, under specialised services commissioning arrangements[3], as is the case for in-vitro fertilisation (IVF) when combined with pre-implantation genetic diagnosis (PGD) [4]. A final decision on NHS England's position is not yet confirmed. In the meantime, it would fall to Clinical Commissioning Groups (CCGs) to make individual funding decisions, as for NHS IVF currently. Where these services were not commissioned by the NHS it could be expected that families may pay privately, as happens with IVF currently.

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[3] http://www.england.nhs.uk/ourwork/commissioning/spec-services/

b. There will additionally be administrative costs relating to the regulation of these services, both to the regulator, the Human Fertilisation and Embryology Authority (HFEA)[4] and the clinics who must comply with HFEA requirements.

12. Each of these cost and benefit groups will be discussed in turn.

Costs

13. This section will estimate the potential costs of mitochondrial donation treatment over a ten year period. As highlighted in the previous section, these will be made up of:

    a. Cost to clinics who will provide the treatment
    b. Costs to HFEA who will regulate clinics/providers of treatment (although this should be recovered in licence fees)

Costs of providing treatment

14. Serious mitochondrial DNA disease is estimated to potentially affect up to 1 in 6500 children born every year [21]. However, given that the treatment techniques are still under investigation and the further research required, it is not expected that all those who might potentially benefit would apply and/or receive this treatment. At present the best estimate of the number of persons who will receive mitochondria donation treatment, once available, is 20 persons per year, although this may increase to as many as 80 persons per year once processes are embedded [6]. Therefore, the initial estimate implies that over a ten year period 200 persons would benefit from the treatment. Whilst further research will be conducted to measure the efficacy of these treatment techniques, it is assumed for the purposes of this IA that they will be successful at removing risk of serious mitochondrial DNA disease for those treated.

15. Efforts have been made to estimate the costs of mitochondrial donation treatment through looking at present costs of similar fertility treatment and consultation with experts within the Wellcome Trust Centre for Mitochondrial Research, based in Newcastle. As it is likely that their clinic (the Newcastle Mitochondrial Clinic[5]) will be the sole providers of such treatment in the first few years of the policy, they are best source of a cost estimate at this time.

16. Mitochondrial donation techniques cover pro-nuclear transfer (PNT) and maternal spindle transfer (MST) and have been used in the UK for many years for research purposes. In terms of the necessary resources, whilst slightly different in nature, both treatments require cycles of IVF treatment, which involves removing eggs from the ovaries and fertilising in the laboratory, before placing the fertilised egg (embryo) inside the woman's womb. Additionally, expert opinion explains that performing the technique of extracting the donor's nuclear DNA and transferring the patient's nuclear DNA to the enucleated egg/embryo would involve resources similar to Pre-implantation Genetic Diagnosis (PGD) which can be carried out in conjunction with IVF treatment. PGD is a technique that allows embryos to be tested for genetic conditions before being placed in the woman.

17. The Wellcome Trust centre have estimated that the costs of carrying out one course of PNT would be £13,000, whilst a course of MST is estimated as costing £14,000, being slightly more complex to implement. Assuming an equal use of both methods, we estimate the cost of treatment as £13,500. These costs are broadly made up of:

    a. Three courses of IVF: two for potential mothers to collect enough oocytes, one for the mitochondria donor
    b. Pronuclear or metaphase 2 spindle transfer
    c. Equipment costs, assuming 20 procedures per year

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[4] http://www.hfea.gov.uk/index.html
[5] http://www.newcastle-mitochondria.com/service/mitochondrial-clinic/

18. Whilst this will be the source of our best estimate, it should be borne in mind that treatment costs are likely to vary around the country. To give an indication of how treatment costs vary across the country, we use the variation calculated using the Market Forces Factor (MFF) from the NHS Payment by Results tariff [7]. The MFF adjusts payments to NHS organisations on the basis of the cost of inputs in that region. The average MFF is 1 and Newcastle has an MFF just below the national average (at 0.96). National variation means costs can be up to 8% cheaper than the national average or up to 20% higher. This variation will be used to uprate the cost estimates to create a nationally representative range for providers in England as a whole. Table 1 demonstrates the calculations.

Table 1: Estimated cost of mitochondrial donation treatment, per individual course of treatment

Parameters, (rounded to nearest 1,000)	Cost estimate	
Newcastle PNT cost estimate	£	13,000
Newcastle MST cost estimate	£	14,000
Newcastle market forces factor (MFF)		0.9595
Central estimated PNT cost	£	14,000
Central estimated MST cost	£	15,000
Lowest estimated MFF		0.9263
Highest estimated MFF		1.2020
Lowest estimated treatment cost (based upon PNT)	£	**13,000**
Highest estimated treatment cost (based on MST)	£	**18,000**
National estimated treatment cost (average of PNT and MST)	£	**14,500**

19. As shown in table 1, the national (central) estimated cost for mitochondria donation is an average of the cost of PNT and MST treatment methods, which have been calculated based on an uprating of the Newcastle estimates, based on their MFF. As presently both methods have equal likelihood of being used, it makes sense to assume a single average estimate, weighting the costs of both methods equally[6]. As it is being assumed that these services will be NHS commissioned in the first instance, costs by private providers have not been estimated here, but are covered later in the IA.

20. A further point to take into consideration is the number of treatment courses that are necessary for successful conception and live birth. It has been suggested that treatment success will mirror that of IVF treatment. According to an HFEA report from 2012, IVF will typically result in a live birth 25% of the time, i.e. following the fourth course of IVF treatment [8]. This success rate varies in relation to a number of factors, such as age of the mother.

21. Given these assumptions, the treatment costs per person per year may range between £13,000, assuming the lowest possible treatment cost and that one cycle results in a live birth, to £108,000 assuming the treatment takes place in a more high-cost area and 6 cycles are required before a live birth is achieved. The estimate of 6 is based upon a range of fertility clinic IVF success rates as taken from the HFEA website [22]. Whilst it is incredibly difficult to

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[6] The lowest estimated cost is an estimate based upon using the PNT method only, in the area with the lowest MFF, to represent to lowest possible cost for mitochondria donation. The highest estimate, in contrast, assumes complete use of the MST method, in the area with the highest MFF, representing the highest possible cost of treatment within the NHS areas.

ascertain a realistic upper range (for example, there are large differences in success rates depending on age of the mother,), colleagues at the Wellcome Trust have confirmed that this is a reasonable upper estimate, bearing in mind that the success rate will vary from patient to patient, as will their response should treatment be unsuccessful (e.g. some individuals would continue to request treatment to the point that a live birth is reached, whereas others would cease attempts after a given number of courses). As a best estimate it is assumed that four cycles (i.e. the national average) should be sufficient to achieve a live birth[7]. Table 2 highlights these results.

Table 2: Estimated cost of mitochondrial donation per patient

Parameters	Cost estimate (see table 1)		
	High	**Low**	**Central**
Treatment cost per person, one course	£ 18,000	£ 13,000	£ 14,500
Treatment cost per person, six courses	£ 108,000	£ 78,000	£ 87,000
Treatment cost per person, four courses	**£ 72,000**	**£ 52,000**	**£ 58,000**

22. Calculating the annual cost for 20 persons per year, this would mean that for 20 cases per year, the estimated cost is likely to be **£1.16m**. If the number of cases were to expand to 80 per year, this would multiply costs further. This is presented in annex A.

Table 3: Estimated costs of mitochondrial donation treatment per year

Parameters	Value (£)
High estimate: highest cost x six courses x 20 persons	£2,160,000
Low estimate: lowest cost x one course x 20 persons	£ 260,000
Central estimate: central cost x four courses x 20 persons	**£1,160,000**

Costs of regulating mitochondrial donation

23. In addition to costs relating to the treatment itself, there will be costs associated with regulating mitochondrial donation treatment. The HFEA will be responsible for regulating the use of these techniques. They will thus have a burden associated with assuring that treatment providers are acting in accordance with their statutory requirements. In turn, the clinics will also have the burden of complying with these requirements.

24. The costs involved will allow HFEA to grant a licence to a clinic who wishes to carry out mitochondrial donation techniques, and approve individual patients to receive such treatments from these licensed providers.

HFEA Transition

25. There will be preparatory costs incurred by HFEA to enable them to carry out their regulatory responsibilities. Having consulted with members of the HFEA, it is believed that the financial burden of setting up a process to be able to assess a clinic's suitability to carry out mitochondrial donation techniques will be negligible, since much of the work will fit into their existing business model, mirroring the regulation of existing techniques.

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[7] It should be noted that this IA is not making an assumption (at this stage) as to how many courses of mitochondrial donation may be commissioned by the NHS – rather, it is seeking to derive an estimate of the overall costs of carrying out treatment for 20 persons, regardless of the commissioning route. Potential commissioning scenarios are discussed later in this analysis.

26. Areas where costs will initially be incurred is through setting up licensing procedures including consultation with experts and developing guidance materials, such as a 'decision tree' similar to that existing for PGD decision-making [9]. Costs cannot be estimated in exact terms, but for the purposes of this IA it has been suggested, in consultation with colleagues in HFEA, that HFEA staff time might considered at a rate of £2,000 a day for 30 days [10]. When compared to HFEA's latest annual report this would equate to approximately 10 staff members working on materials for 30 days [11]. Additionally there are expected to be costs from expert opinion elicitation. These may be estimated based upon the latest convening of their expert panel, the total cost of which was £32,073 [12]. As this was part of an overall consultation process that will have incurred some cost additional to the expert opinion component, this will be rounded down to an estimated cost of £30,000. As shown in the table below, the combination of staff time and the cost of further assessing treatment safety would bring the estimated HFEA set up costs to within the region of **£90,000**.

Table 4: Estimated HFEA transition costs

Parameter	Value (£)	Calculation
Estimated daily HFEA resource	£2,000	a
Number of days set-up	30	b
Expert opinion costs	£30,000	c
Sub-Total	**£90,000**	d = (a x b) + c

Licensing providers to carry out mitochondrial donation treatment

27. Once processes are set up to allow HFEA to regulate mitochondrial donation effectively, providers should be able to apply for a licence to carry out these techniques.

28. All clinics require a 'treatment and storage' licence in order to carry out any kind of fertility treatment. Such clinics would undergo a number of stages, including an application form followed by an inspection visit. This would then be followed up by a consideration panel within HFEA, following which the provider would receive an inspection report and confirmation of whether or not their application has been approved. Once a clinic has an approved licence there will be follow-up inspections from time to time, particularly when the licence is renewed. Licence renewal may be required every year or every two to three years [26].

29. The present HFEA fee for a clinic to apply for a treatment and storage licence is £500 [27]. However, an HFEA consultation suggests that the actual burden on HFEA to process such an application is greater than this figure, approximately £15,000 per licence [13]. There will of course also be additional internal costs to the clinics as they carry out activities to comply with HFEA licensing requirements.

30. It is expected that intitially there will be only one provider ready to carry out these techniques and thus apply for a licence within the first ten years of the scenario. This prospective provider, the Newcastle Mitochondrial Clinic, already has a 'treatment and storage' licence to carry out IVF and PGD techniques. To carry out mitochondrial donation treatment it is expected that rather than apply for a new and separate licence, they would instead apply to 'vary' their existing licence to add these new techniques [31]. Generally the fee to a clinic to vary their licence in this way is £0 [27]. This is because the cost to HFEA to process such a variation to add an additional existing treatment is minimal. It will also present lower levels of burden to the clinic since many of the statutory and licensing requirements necessary for a new fertility treatment will be the same as for those they already carry out. However, in the case of mitochondrial donation, a new technique, it is likely that the HFEA would act cautiously in licensing clinics to carry out this procedure. To take into account this caution, it is assumed that the HFEA burden to license clinics will be similar to that necessary to approve a

new licence. For clinics, whilst simpler than applying for a completely new licence, they will still have to present a quantity of evidence to satisfy HFEA's requirements.

31. The Newcastle Mitochondria Clinic have estimated that to prepare evidence, ensure standard operating procedures are in place and to complete the necessary application forms, they would expend approximately ten hours of consultant time and four hours of administrative staff time. If an additional inspection visit were required as part of the application they would spend an additional eight and four hours in preparation time for these staff respectively.

32. The 'Personal Social Services Research Unit' (PSSRU) estimate the unit costs of various services relating to health and social care [28]. Based on their 2013 estimates, the average cost of a (non-London-based) medical consultant would be approximately £85,000 per year, with the cost to their non-medical staff being approximately £20,000 a year. They also estimate that on average these professionals and their staff work 43.3 hours per week for 42.3 weeks per year. Using these components, it is estimated the cost for the time spent complying with HFEA's licence application requirements in year 1 would be approximately £1,000.

Table 5: Estimated costs to clinics to comply with licensing process

Parameter, rounded	Cost	Calculation
Cost of medical consultant time, per year	£85,000	a
Cost of administrative staff, per year	£20,000	b
Number of working hours in year	1800	c = (43.3hrs x 42.3wks)
Number of hours time spent on application, medical consultant	18	d
Number of hours time spent on application, administrative	8	e
Compliance costs to vary licence (Year 1)	**£1,000**	**h = ((a/c) x d) + ((b/c) x e)**

33. The overall cost to HFEA and providers of obtaining a licence to carry out mitochondrial donation treatment is provided in the table below, estimated to be approximately £16,000. HFEA fees to clinics are noted below but not included in the totals, since they provide compensation for a proportion of the HFEA burden and thus to include these as well as the total HFEA burden would result in double-counting.

Table 6: Estimated cost to vary licence to carry out mitochondrial donation

Parameter	Cost	*Calculation*
Cost to HFEA to vary licence	£15,000	a
Clinic fee of varying licence	*£500*	b
Net cost to HFEA	*£14,500*	c = (a-b)
Clinic compliance cost per licence application	£1,000	d
Total cost	**£16,000**	e = (a+d)

On-going annual costs for mitochondrial donation treatment, per patient

34. Once a provider has a licence to carry out mitochondrial donation treatment, the remaining and on-going costs will consist of approving the procedure to be carried out for individual patients.

35. Whilst not all details have been confirmed by the HFEA, the mitochondrial donation regulations stipulate that the HFEA should assess all potential families on a case by case basis, similar to that of pre-implantation tissue typing (PTT):

"For PTT the HFEA approves embryo testing on a case-by-case basis involving a specific patient... In making its decision, the HFEA will consider a referral from the child's treating clinician to ensure that the treatment is necessary and all other options have been considered." [25]

36. For such new and complex decisions, the HFEA typically assembles a licencing panel of up to six members [29]. Panel members would be required to read research regarding the case in advance, before meeting the remaining panel members to consider the case in detail. In advance of a meeting the panel would spend approximately a day reading research material and a day in discussion. Dividing this by the number of cases discussed by the panel during the day (which will fall across various treatments besides mitochondrial donation) it is assumed that panel members would spend two hours reading research material for a particular case, in preparation for an hour's panel discussion time.

37. The PSSRU has also been relied upon to provide estimates of cost relating to decision-making panels, accepting that costs for particular panel members may differ depending on distinct expertise. For example, the cost of a panel member has been estimated at £47 per hour.

38. In addition to the decision-making panel time, it has been assumed that two further days of HFEA staff time is spent approving each case. This remaining decision-making time has been costed, as previously suggested for transition costs, at £2,000 per day (see paragraph 25). This accounts for the time spent publishing applications on the HFEA website for public consultation and taking opinion from 'Genetics Alliance', which takes time to seek and receive [10].

39. In terms of costs to the provider clinic, the HFEA typically charge £75 to providers to cover the administrative burden per case (e.g. data storage). It is further assumed that for cases to be considered by the panel the clinic will have to provide evidence to explain why their case should be considered. It is estimated that the time necessary to do this may be equivalent to the time spent preparing for a licence, without the additional costs relating to inspection preparation. This is approximately a further £500 per case considered (see paragraph 30).

40. The estimated cost to approve a case for mitochondrial donation treatment is thus summarised in the table below. Again, the £75 fee has been subtracted from HFEA's total burden to prevent double-counting.

Table 7: Estimated cost to approve a case for mitochondrial donation treatment

Parameter, rounded to nearest 1,000	Cost	Calculation
Number of licensing panel members	6	a
Number of administrative staff	1	b
Cost of panel member, per hour	£47	c
Cost of admin member, per hour	£28	d
Length of panel time - 1hr discussion plus 2hrs pre-reading	3	e
Average no. of working days to process single application	2	f
Cost of daily HFEA time	£2,000	g
Cost to HFEA of approving a single case for treatment	£5,000	h = ((a x c)+(b x d) x e) + (f x g)
Cost to clinics to prepare case for consideration	£1,000	i
Per treatment licence fee for clinics	£75	j
Overall estimated cost per case	**£6,000**	k = (h + I - j)

Number of treatments per year	20	l
Total annual cost for 20 patients per year	**£120,000**	m = k x l

41. Based upon the estimated regulatory costs specified in the tables above, the overall burden due to treatment regulation is summarised below. It is assumed that the overall transition costs, including HFEA preparation and the initial licensing of the Newcastle Mitochondrial Clinic, will cost approximately £106,000. Beyond this the costs will only fall on the costs to approve individual cases per year, approximately £120,000.

42. It should be noted that whilst the provider will need to renew their licence every one to two years, this burden has not been counted in years 2 to 10 of this scenario. This is because the Mitochondrial Donation Clinic, who already carry out fertility treatments other than of mitochondrial donation, already expend the effort to prepare for their licence renewal, as does the HFEA to inspect their premises. The licence renewal burden for a new provider would be estimated to be £15,500, consisting of the costs to HFEA to inspect the clinic (£15,000), plus the time for the clinic to prepare for this visit (£500). However, in the case of the Newcastle Mitochondrial Clinic this represents 'business as usual'.

Table 8: Summary of regulatory costs

Parameter	Year 1	*Years 2-10*
HFEA transition cost (Year 1 only)	£90,000	£0
Burden associated with licence application	£16,000	£0
Per treatment (case) approval costs	£120,000	£120,000
Total annual cost	**£226,000**	**£120,000**

43. As with treatment costs, if the policy were to be expanded to allow treatment of 80 persons per year, this would affect the burden on the regulator in terms of the number of clinics and treatments they would be required to assess. Please see Annex A for details.

Costs Summary

44. This section has covered the costs that may be incurred from allowing mitochondrial donation treatment. The table below summarises these costs on a 'per patient' basis. Our best estimate would suggest that it would cost around £58,000 per patient for treatment, with an additional £6,000 covering the burden placed on HFEA to approve their individual case. As previously, it should be noted that these costs do not include the total costs as they do not include the transition costs to HFEA and the provider clinic, those necessary to set-up processes to regulate and license clinics for mitochondrial donation. These costs would be incurred even if no patients were then considered; therefore they cannot be estimated on a per patient basis.

Table 9: Estimated cost per patient (not including transition costs) annual estimate

Parameter	Cost estimate		
	High	Low	Central
Cost of treatment	£108,000	£13,000	£58,000
HFEA case consideration cost	£6,000	£6,000	£6,000

45. The second summary table below estimates the total costs of the policy over a ten year period, including the total costs to HFEA, assuming that 20 patients receive mitochondrial

donation every year in the period. These costs have been discounted over the period at a rate of 3.5% [16].

Table 10: Total estimated costs, discounted over 10 years, assuming 20 patients per year

Policy year	Year	Total cost estimates, rounded		
		Low	High	Central
0	2015	£486,000	£2,386,000	£1,386,000
1	2016	£367,000	£2,203,000	£1,237,000
2	2017	£355,000	£2,128,000	£1,195,000
3	2018	£343,000	£2,056,000	£1,154,000
4	2019	£331,000	£1,987,000	£1,115,000
5	2020	£320,000	£1,920,000	£1,078,000
6	2021	£309,000	£1,855,000	£1,041,000
7	2022	£299,000	£1,792,000	£1,006,000
8	2023	£289,000	£1,731,000	£972,000
9	2024	£279,000	£1,673,000	£939,000
Total		**£3,378,000**	**£19,731,000**	**£11,123,000**

46. Based on these values it is estimated that the policy will cost approximately £1.39m in the first year and £11.12m overall.

Benefits

47. So far it has been summarised that the costs of mitochondrial donation treatment will be made up of:
    a. Cost to clinics who will provide the treatment
    b. Costs to HFEA who will regulate clinics/providers of treatment

48. This section will summarise the benefits of mitochondrial donation treatment. These will be made up of:

    c. Pure lifetime benefit to patients, as measured in QALYs (Quality adjusted life years,) as a result of no longer living with serious mitochondrial disease
    d. An increase in the 'net production' each recipient can expect to achieve in their lifetime as a result of being healthier and living longer, thus consuming less care resources and having potential to gain employment.
    e. Savings to be made for the health system from a reduction in mitochondrial disease-specific healthcare costs

Benefits to patients

49. Naturally, the greatest benefit of mitochondrial donation treatment will be to patients who will be able to live longer and healthier lives free of serious mitochondrial DNA disease, and to their families who will not have to care for children with such disease.

50. These benefits can be looked at in terms of the pure value a person places on having a healthier longer life. The quality of life for a person suffering mitochondrial disease will be highly variable, even when considering only those with the most serious conditions. These diseases span a range of physical and cognitive impairment, which naturally result in a huge

difference on how an individual perceives their own quality of life. The age of disease onset and life expectancy also varies between conditions although all are seen as limiting [5].

51. The Wellcome Trust centre provided some key data from a small group of patients with serious mitochondrial DNA disease whilst in secondary care. Quality of life (QoL) weights were provided for each patient, measured by the SF-12 survey and translated into the SF-6D. There are many articles showing the efficacy of using SF-6D within economic assessment [14]. QoL weights range from a value of 0 corresponding to a state which the patient considers equivalent to death, to 1 representing 'perfect' health. In this cohort the QoL weights ranged from 0.44 to 0.74. This wide range is to be expected within patients with mitochondrial disease due to the high variability in its presentation amongst individuals. For the purposes of this IA, an average of these scores will be used to estimate the 'best estimate' of quality of life with those with mitochondrial disease, 0.61.

52. Placing these values into context, the University of York investigated quality of life amongst the UK population [15]. From this they generated estimated quality of life weights for an average (UK) male and female across the life span, ranging from .94 at birth to .71 (females) and .74 (males) towards the end of life.

53. Using these estimates in conjunction with ONS cohort life expectancy data, it is possible to estimate the number of QALYs a person may achieve across their life course. For example, a female born in 2014 may expect a quality adjusted life expectancy of 80.4 years (see Annex D for an example calculation). However, to take into account social time preference these years of life following birth will be discounted at a rate of 1.5% [16]. As such, the average female could expect a discounted a quality adjusted life expectancy of 44.7 years.

54. An equivalent calculation can be created for those with mitochondrial disease. As stated above, even amongst those with serious mitochondrial disease the life expectancy and conditions presented are highly variable. As such it is difficult to generate an estimated value of an 'average' mitochondrial disease patient. Based upon the data provided by the Wellcome Trust centre for Mitochondrial Research, four main patient categories have been proposed, specified in the table below.

Table 11: Four example mitochondrial disease patient categories, based on expected age at onset of disease and mortality

Parameters	Age of disease onset	Average life expectancy
Patient group 1a	0	20
Patient group 1b	0	40
Patient group 2a	20	50
Patient group 2b	20	90

55. As shown in the table, these patient categories can be split broadly into two types of patients with mitochondrial disease. The first is those with an early onset and short life expectancy, such as those with Pearson Syndrome, MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), NARP (Neuropathy, ataxia, and retinitis pigmentosa), Myopathy and diabetes, and Leigh syndrome are represented by groups 1a and 1b [3]. Groups 2a and 2b, in contrast, represent those conditions that may emerge later in life and persist for the remainder of life, such as with conditions like LHON (Leber's hereditary optic neuropathy), MIDD (Maternally inherited diabetes and deafness), and CPEO (Chronic progressive external ophthalmoplegia) [3]. The inclusion of sub-groups (a and b) are created purely to take into account the fact that the exact life expectancy will vary across individuals and conditions.

56. In order to measure the QALY benefit that individuals will gain from receiving mitochondrial donation treatment, the quality adjusted life expectancy for those with mitochondrial disease will be calculated in the same way as for the 'average' population demonstrated above. Comparing the values for 20 individuals with mitochondrial disease and 20 individuals without disease will then demonstrate the benefits that the policy can produce per year. The table below demonstrates the number of QALYs a person may have in each category[8]. For each category it is assumed that the quality of life from onset to through to the end of life is 0.61. In reality it is likely there would be some form of deterioration in condition over time, but there is insufficient data available to estimate this with any accuracy, therefore the single estimate will be used for each year of life. For those with a later onset of disease (2a and 2b,) it will be assumed that the average quality of life experienced in our 'average' group will also be experienced by these individuals prior to the age of disease onset.

Table 12: Indicative estimated quality adjusted life years per patient category over lifespan

Parameter	Value (QALYs)
Quality adjusted life expectancy of the 'average' person	44.3
Quality adjusted life expectancy of a mitochondrial donation patient, 1a	11.0
Quality adjusted life expectancy of a mitochondrial donation patient, 1b	18.7
Quality adjusted life expectancy of a mitochondrial donation patient, 2a	27.5
Quality adjusted life expectancy of a mitochondrial donation patient, 2b	35.3

57. As would be expected there is considerable variation amongst the four mitochondrial disease groups. In any year the 20 individuals benefiting from mitochondrial donation may benefit to different degrees, dependent upon the condition they may have had without treatment. To demonstrate the potential benefit of the policy in any given year a range will be presented. The low end of the range will assume that all 20 recipients would have been in category 2b, thus the difference in QALY gain will be smallest. The upper estimate will assume that all 20 recipients are from category 1a, thus benefiting the most from the treatment as a result of the number of additional life years achieved. As a central estimate, it will be assumed that the 20 recipients will be made up of five persons from each category. These assumptions and the associated QALY gain are represented in the table below.

Table 13: Annual estimated QALY gain, per person, from implementation of mitochondrial donation regulations

Parameter	Estimate range (QALYs)		
	High	Low	Central
QALYs of person of 'average' health	44.3	44.3	44.3
QALY person with mitochondrial disease	11.0	35.3	23.2
QALY gain per person	**33.3**	**9.0**	**21.2**

58. It is generally accepted that a QALY represents a value of £60,000. Therefore this QALY gain can be represented by its monetary value, as in the table below. The estimated value over a

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[8] Each 'QALY per person' value is made up of an average of the values assumed for males and females. These values are evenly weighted, assuming that the policy will benefit both males and females equally.

year, gained purely from living longer healthier lives, is **£25.4m**, assuming 20 persons benefit from mitochondrial donation treatment.

Table 14: Annual estimated QALY value from implementation of mitochondrial donation regulations

Parameter, rounded	High	Low	Central
QALY value of 20 persons of 'average' health	£53,163,000	£53,163,000	£53,163,000
QALY value of 20 persons with Mitochondrial Disease	£13,236,000	£42,392,000	£27,781,000
Total QALY gain from policy	**£39,927,000**	**£10,771,000**	**£25,382,000**

59. It should be noted that whilst this IA only quantifies the estimated QALY gain to the patients themselves, mitochondrial disease also has a devastating effect on the families who have a child with an incurable and potentially life-limiting disease. Kim et al (2010) measured the health-related quality of life of mothers of children with severe mitochondrial disease, using a number of measures, including the medical outcomes short-form 36 (SF-36). They found that these mothers had a greatly reduced health-related quality of life, particularly with respect to role limitation and mental health, based upon the stress of having a family with mitochondrial disease and the need to provide care [17]. These effects persisted even when compared to mothers of children with intractable epilepsy.

Wider benefits to society and the economy

60. In addition to the personal value of a healthy life to the patient, one can also look at the benefits to wider society of having individuals without life-limiting disease – for example if they are able to work and contribute to Government and family finances, or if they no longer require care, by their family or in nursing homes. This impact assessment estimates the total impact of the policy on the wider economy using the wider social benefits model [18].

61. A wider social benefit approach calculates a person's economic impact on society based upon ICD 10 classification of disease, age, gender and quality of life. The calculation estimates 'net production' of an individual by estimating the resources a patient contributes, or produces, net of the amount they consume. Any production in excess of consumption will provide resources that are available for others to consume and benefit from. Conversely, any excess of consumption over production must be met by resources that are therefore not available for others to benefit from. These estimates are based upon numerous data sources. The diagram below, taken from the guidance document for this model, shows the essential categories that make up these 'production' and 'consumption' components. One point to note is that the 'care' included in the model covers social or residential care, it does not calculate a patient's healthcare costs for their condition. These will be considered separately in the next section.

$$\text{Net production} = \text{production}$$

= paid production
+ unpaid production
− consumption
= formal care consumption
+ informal care consumption
+ private paid consumption
+ private unpaid consumption
+ government consumption

Diagram 1: Description of the components of net production [18]

62. According to the model and applying the assumptions regarding the 'average' population as specified in the previous section, an average person in the population would consume approximately £1.4m worth of resources during their lifetime. This quantity is made up of the expected consumption in each year of life, discounted and taking into account probability of survival at each year of age. A similar calculation tells us that the same average person would produce resources valued at approximately £1.1m over their lifetime[9]. For further details of the calculation of the impact of the policy on individuals' net production, see Annex D.

63. It is expected that a person with severe mitochondrial disease, even if they live to working age, will not be in a sufficient state of health to achieve sustained employment. Additionally, consumption may be greater in some cases due to greater care needs, although this will be balanced against the care requirements upon reaching old age in the general population. Therefore, it is expected, even with the quantity of care consumed by the average person, that there is a wider economic gain from implementing the policy – as individuals will provide more resources, and use less. The resulting net gain in resources will benefit others in society.

64. To compare an 'average' population cohort against those with mitochondrial disease, a similar approach will be used to that used in the previous section; the same four categories of mitochondrial disease patient will be used to produce a range of potential benefits to society from the policy. The results presented below show that providing treatment for an individual should generate additional resources valued at approximately £360,000, taking into account the expected reduction in consumption and increase in production, particularly an expectation of employment that would not otherwise have been possible.

Table 15: Estimated annual net production gain, per person, in response to implementing mitochondrial donation regulations

Parameter	High estimate	Low estimate	Best estimate
Net production of average person	-£276,000	-£276,000	-£276,000
Net production of person with mitochondrial disease	-£878,000	-£389,000	-£635,500
Difference in net production	**£602,000**	**£113,000**	**£359,500**

Impact on healthcare costs

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[9] This indicates that the average person consumes £300,000 more over their lifetime than they ultimately produce. This is to be expected, since only part of total production is attributable to labour (and affected by health). The remainder is attributable to capital (and is unaffected by health – as even if a person dies, the capital they own will remain, and will produce output). Because all production is ultimately consumed, total consumption (and therefore average consumption) should be expected to exceed the output attributed to labour (and therefore the average production attributed to labour) (see annex D).

65. As stated previously, whilst the wider social benefits model provides an estimate of the consumption of an individual, this does not cover healthcare costs associated with the particular condition they are suffering from (though it does encompass the healthcare costs of average individuals). Patients with serious mitochondria disease cannot be 'cured' but their conditions still require management and care, which can incur considerable cost. This means that where patients can avoid serious mitochondrial disease through receiving mitochondrial donation, the NHS will save on these condition-specific healthcare costs. The dataset provided by the Wellcome Trust centre in Newcastle showed a range of secondary healthcare costs for individuals with serious mitochondrial disease. An example case history is presented in the table below. The example shows that costs are primarily based on inpatient and outpatient admissions, with lesser costs attributable to tests, condition-specific procedures (such as sleep study or testosterone injections, though there were no costed procedures for this particular patient,) and medications. This split of costs is typical across the sample cohort provided.

66. As specified in the four broad categories used for estimation in previous sections of this IA, there was great disparity between the patients presented and thus the costs per patient. Of the patients (including patient A, below) who were deceased at the time the data was collected, it is apparent that the decline in these types of condition is sudden and there is then a sharp increase in healthcare costs as the patient reaches end of life. This is observable in patient A, who in their final year of life required admission to hospital at a cost of £212,000, where previously outpatient admissions were sufficient.

Table 16: Secondary healthcare costs of a patient with serious mitochondrial disease

Patient A	Inpatient admissions	Outpatient admissions	Tests	Genetic tests	Medications	Total cost per year
Year 1	£ -	£ 176	£ -	£ -	£ -	£ 176
Year 2	£ -	£ 176		£ 65	£ -	£ 241
Year 3	£ -	£ 646	£ -	£ -	£ -	£ 646
Year 4	£ -	£ 538	£ -	£ 65	£ -	£ 603
Year 5	£ -	£ 714	£ 30	£ -	£ -	£ 744
Year 6	£ -	£ 664	£ 30	£ 65	£ -	£ 759
Year 7	£ -	£ 533	£ -	£ -	£ -	£ 533
Year 8	£ 795	£ 1,252	£ -	£ -	£ -	£ 2,047
Year 9	£ -	£ 3,698	£ 117	£ -	£ -	£ 3,815
Year 10	£ -	£ 673	£ -	£ 540	£ -	£ 1,213
Year 11	£ -	£ -	£ -	£ -	£ -	£ -
Year 12	£ 211,648	£ -	£ 480	£ -	£ 2	£ 212,130
Total per category	£ 212,443	£ 9,070	£ 656	£ 735	£ 2	£ 222,906

67. Using the case histories provided, an average annual healthcare cost was derived for each of the four broad patient categories across their relative lifespans. Despite the variability in the categories, the predicted lifetime healthcare costs do not greatly differ between categories, ranging from approximately £100,000 to £300,000 per patient in each category. This is because in general the longer-lived conditions require lower annual healthcare costs (though as shown in the WSB model these patients will likely consume more social/residential care) than the conditions that considerably shorten life expectancy. The primary differences in the range cover the 'end-of-life' increase in costs, which is predicted to be between £100,000 and £200,000. Like all lifetime costs, the costs over time need to be discounted to produce an estimated saving that takes into account the number of years over which the benefit will be realised. The discount per year will be 3.5%. The estimated healthcare cost saving per

patient, as might be saved if the policy were to be implemented, is presented as a range in the table below. Further explanation of calculation is presented in Annex D.

Table 17: Estimated lifetime healthcare cost savings per mitochondrial donation patient

Parameter	Value (£)
High estimate (category 1a)	£117,000
Low estimate (category 2b)	£13,000
Central estimate (average of each category)	**£50,400**

68. Our best estimate suggests that a further £50,000 might be saved on healthcare costs for each patient who receives mitochondrial donation. However, it should be noted that this may not include all healthcare costs that might be saved as a result of the regulations (see upside risks, para 64). It covers what can be estimated based on available evidence.

Benefits summary

69. This section of the IA has presented the range of benefits that may be realised as a result of allowing mitochondrial donation treatment, made up of QALY gains and an increase in net production, i.e. people will live longer, be healthier, consume less health and social care costs and have the potential to gain employment. The benefits of the policy (before costs) are summarised, per patient, in the following table.

Table 18: Annual estimate of policy benefits, per patient

Parameter	Benefit estimates		
	High	Low	Central
QALY benefit (QALYs)	33.3	9.0	21.2
Net production gain (£)	£602,000	£113,000	£359,500
Healthcare cost savings (£)	£117,000	£13,000	£50,400

70. Once the QALYs per person are valued and aggregated (£60,000 per QALY,) over the first ten years of the policy it is estimated that these benefits will reach approximately £329m, approximately £33m per year.

Table 19: Total benefits of the policy, discounted over a 10 year period, assuming 20 patients per year

Policy year	Year	Benefit estimates		
		High	Low	Central
0	2015	£54,307,000	£13,291,000	£33,580,000
1	2016	£54,045,000	£13,234,000	£33,428,000
2	2017	£53,804,000	£13,158,000	£33,284,000
3	2018	£53,542,000	£13,102,000	£33,133,000
4	2019	£53,321,000	£13,046,000	£33,000,000
5	2020	£53,060,000	£12,971,000	£32,846,000
6	2021	£52,839,000	£12,916,000	£32,719,000

7	2022	£52,518,000	£12,742,000	£32,475,000
8	2023	£52,377,000	£12,808,000	£32,450,000
9	2024	£52,116,000	£12,734,000	£32,295,000
Total		**£531,929,000**	**£130,002,000**	**£329,210,000**

Combining the costs and benefits

71. As a final step in this analysis, it is necessary to combine the costs and benefits estimated in the previous sections to demonstrate the expected net benefit of the policy option. The following table shows that, on a per patient basis, there is expected to be a net benefit of £1.6m. Again, it should be noted that this figure does not include the full extent of the HFEA costs, since these cannot be expressed on a per patient basis.

Table 20: Estimated net benefit of the changes to mitochondrial donation regulations, per person, in the first year of the policy

	Value (Yr 1)
Highest estimated net benefit	£2,702,300
Lowest estimated net benefit	£556,500
Central estimated net benefit	£1,620,950

72. Scaling up to 20 persons a year and including the full extent of the HFEA burden, it can be seen that the policy option is still expected to be hugely beneficial, with approximately **£32m** net benefit in the first year.

Table 21: Estimated net benefit of the changes to mitochondrial donation regulations in the first year of the policy

	Value (Yr 1)
Highest estimated net benefit	£53,933,000
Lowest estimated net benefit	£11,017,000
Central estimated net benefit	£32,306,000

Risks and assumptions

73. Whilst all efforts have been made to consult with experts and use relevant evidence to source the estimates made in this analysis, there are numerous underpinning assumptions that affect the estimated costs and benefits presented. Risks may occur on both the benefits and cost side of mitochondrial treatment. A summary of these risks are stated in this section.

General assumptions

74. It has been assumed for this analysis that 20 persons will benefit from this treatment every year. The costs and benefits will thus change proportionately if a decision is taken to reduce or increase this number. The change in response to an increase to 80 cases per year is presented in annex A.

75. It has further been assumed that initially there will be only one active clinic providing mitochondria donation treatment. If this changes and further clinics provide treatment, this

may impact on the price of the offered treatment, the market share (i.e. 20 cases split between providers) this will incur further costs/fees in terms of HFEA regulation than just one clinic.

76. It is difficult to predict the number of persons who may benefit from mitochondrial donation treatment in future. Long-term follow-up research on cases will be needed to ensure that the treatment is working as expected. Until such a time it is not expected that the market will expand beyond the estimated 20 cases per year. However, if the treatment is successful and well-researched, the market may expand and further providers may carry out treatment to more cases where serious mitochondrial disease is present. The greater the number of cases, it is reasonable to assume that private sector providers may carry out this treatment as well as NHS providers, similar to practices with IVF. However, it is presently only assumed that the services may expand to 80 cases per year, which in itself is unlikely to result in a large change to how services are commissioned. Longer term predictions carry too much uncertainty to be included within the primary analysis.

Upside risks

77. Costs of mitochondrial donation treatment are based upon the cost of a single course of treatment. However, it is possible that providers might operate economies of scale, such as those that exist for multiple cycles of IVF treatment. For instance, one clinic offers one cycle of IVF for £3,350 whereas three cycles cost £8,400 [19]. This might mean that costs are lower than predicted.

78. Whilst efforts have been made to gather evidence regarding healthcare costs for individuals with serious mitochondrial disease, these are considered conservative estimates of the real costs. This is in part due to the inability of the Wellcome Trust centre to cost certain isolated procedures. More importantly, these estimates only cover secondary (hospital) care costs. The costs to the primary care system were unable to be estimated but are likely to be considerable. The inclusion of such costs would serve to increase the potential benefit of this policy option.

79. The use of QoL weights for those with serious mitochondrial disease is an indicative measure of perceived quality of life. As made clear in the text the experiences of those with serious mitochondrial disease will be highly variable. Those with cognitive impairments, in particular, may have difficulty reflecting on their quality of life relative to someone with a more physical ailment such as muscular dystrophy. Whilst this is a typical outcome of a self-reported measure of quality of life, this may explain some of the higher QoL scores where these would not necessarily be expected. It is thus expected that the average QoL weight used is a conservative measure, since it predicts a greater quality of life for those affected by the disease than might actually be the case, thus making the differential between those with disease and those within is smaller than might actually be the case.

80. Analysis of the impact of serious mitochondrial disease upon the families of sufferers is equally difficult to predict with accuracy. Children born with serious mitochondrial disease will require differing levels of care and with varying conditions. It is not possible to predict with accuracy how parents will react or how childcare will be affected/provided in these conditions. This may have an impact on the economic productivity of parents, not included in the main analysis. Inclusion of such costs would further increase the net benefit of the policy.

Downside risks

81. The costs of treatment are based upon the estimates of a single provider. This was deemed appropriate since this will be the most likely initial provider of this treatment. However, it is not possible to know the prices that may be set should other providers enter the market.

82. The costs of providing mitochondrial donation treatment may be higher than expected as only trained embryologists would have the necessary skills to perform this procedure. Further, as there will be very few viable providers of this treatment in the short-term, these providers could exploit its monopoly status in the early stages of this market opening up and raise the price of treatment, though this is seen as unlikely.

83. The probability of success for mitochondrial donation treatment could be substantially different to that for standard IVF. In the absence of other information, the statistics from standard IVF offer a reasonable proxy.

84. The long-term follow up research by providers of mitochondrial donation, as mentioned above, will incur a cost that has not been estimated in this IA. The Wellcome Trust centre has suggested that this will not be a large cost and would broadly fit within routine costs to the clinic. Such costs would certainly not outweigh the large benefits outlined within the analysis.

85. The use of the wider social benefits model provides the best factual estimate of the actual impact of health conditions and treatments on society. However, the mechanism is under continuous review and the calculations are continuously updated as further evidence becomes available [18]. It is therefore important that the estimates generated are treated as such; they are not based on an actual sample of consumption costs from patients with mitochondrial disease.

86. It is assumed that, given the number of cases involved and the severity of conditions concerned, that NHS provision of these services will be paid for by NHS England under specialised services commissioning arrangements, in a similar format to IVF when combined with PGD. In the meantime it would fall to CCGs to make funding decisions. Where services are not provided by the NHS it might be expected that families will pay privately for mitochondrial donation treatment, as happens with IVF (see next section). However, there is no data available to date to show how much a family would actually be willing to pay to prevent mitochondrial disease transmission where risks are present, as opposed to other options (such as adoption, for example). Uptake of treatment could be affected accordingly.

One In Two Out Status

87. The changes in regulations presented in this IA would allow any provider, approved by HFEA, to carry out mitochondrial donation. Since private sector providers could apply for a licence to provide these services and the associated costs are less than £1m per year, this piece of regulation has been considered eligible for the fast track process.

Funding mitochondrial donation

88. In the first instance it is assumed that NHS provision of these services will be funded centrally by NHS England under specialised services commissioning[10]. NHS England centrally funds such services based upon four factors [20]:

- the number of individuals who require provision of service
- the cost of providing the service or facility
- the number of persons able to provide the service or facility
- the financial implications for Clinical Commissioning Groups (CCGs) if they were required to commission the service or facility themselves.

89. If all mitochondrial donation treatment were to be provided by the NHS in this way, the direct costs and benefits to business would be £0.

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[10] However, this will not be confirmed prior to regulation change, nor without further cost-benefit analysis.

90. It is expected within the Newcastle clinic that a small number of patients (or treatment cycles) will be privately funded. They have provided an estimated cost of treatment for the two techniques under private funding of £16,000 and £17,000 respectively, an increase of approximately 20% in the cost relative to the publically funded cost. These privately funded treatments may stem from international interest; the Newcastle Clinic currently receives requests for analysis each year, which may become a basis for treatment if regulations are passed. Further, it is not expected that the NHS will fund unlimited cycles of treatment per patients, and therefore families who do not conceive on their first few attempts may choose to fund further cycles privately[11]. However, it is difficult to predict the number of cycles this would involve and in the first 10 years of treatment it is expected that these numbers would be very small. It is not possible to confirm the number of cycles that NHS England would fund until they have completed their own analysis, though for IVF with PGD this is currently three cycles per patient [4]. As such, the direct costs and benefits to business as a result of these cases are not counted for this IA.

Future providers of mitochondrial donation treatment

91. In the future it is expected that the regulatory change will allow new providers to carry out mitochondrial donation treatment techniques. It is reasonable to assume that in the long term the market will be split in a similar manner to that of IVF. The present IVF market is split between 40% public and 60% private sector funding [22]. However, as there are no providers currently ready to carry out these treatments and it is not expected that these new providers will surface until after the first ten years of the scenario, the costs and benefits of these potential new providers are considered indirect for OITO purposes and will not be estimated here.

92. Under 'One In Two Out' methodology, the impact on business is the Equivalent Annual Net Cost to Business (EANCB) and includes both annually recurring net costs and net transitional costs as a result of changing regulations [24]. As the uptake of mitochondrial donation treatment in the private sector is expected to take longer than ten years to occur, the EANCB for the present regulation change is estimated to be £0, i.e. zero net cost.

Summary

93. This impact assessment has presented the policy options available for those suffering with serious mitochondrial disease. It has been established that, despite healthcare options that might manage symptoms as best as possible, the disease cannot be cured. The only option available that will help those with a significant risk of serious mitochondrial disease is to change regulations to allow mitochondrial donation treatment techniques.

94. The analysis presented has demonstrated that this policy option is extremely beneficial, adding years of life and improved health to potential sufferers. Our best estimate states that the policy, if treatment were carried out for 20 patients per year as expected, would result in an annual net benefit of approximately **£32m** per year, **£318m** over ten years.

Table 22: 'Best estimate' of the total costs and benefits of mitochondrial donation policy option, discounted over a ten year period, assuming 20 treated patients per year

Policy year	Year	Benefits	Costs	Net benefit
0	2015	£33,580,000	£1,386,000	£32,194,000
1	2016	£33,428,000	£1,236,715	£32,191,285
2	2017	£33,284,000	£1,194,894	£32,089,106
3	2018	£33,133,000	£1,154,487	£31,978,513
4	2019	£33,000,000	£1,115,446	£31,884,554
5	2020	£32,846,000	£1,077,726	£31,768,274

6	2021	£32,719,000	£1,041,281	£31,677,719
7	2022	£32,475,000	£1,006,068	£31,468,932
8	2023	£32,450,000	£972,047	£31,477,953
9	2024	£32,295,000	£939,176	£31,355,824
				£318,086,161

95. The primary risk to consider regards how services will ultimately be commissioned. Initial conversations with NHS England have led to the assumption that in the first instance, where only 20 (to a maximum of 80) persons/families are expected to receive mitochondrial donation treatment, services will be NHS-commissioned centrally under specialised services commissioning. However, further cost-benefit analysis would need to be conducted before such a decision was made. If NHS England were to not fund these services it would be for CCGs to make individual commissioning decisions, which may vary depending on local commissioning policy. Uptake of the treatment could be affected accordingly.

96. Given the assumption that most cases will be provided by the NHS and the number of persons who will receive the treatment, it is not anticipated that the changes to regulations will generate a large revenue stream to private sector business in the first ten years of the policy. With the evidence available our estimated EANCB is that there will be a zero net cost to business (£0). However it is important to note that the changing of the regulations provides an opportunity for the private sector. Whilst it is not expected that the market share will be large in the short-term, this could change in future to be similar to that of IVF.

97. Tables presenting the complete net present costs and benefits over the policy 10 year period are presented in Annex B.

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Annex A: Expansion of cost and benefit estimates if the service were to be expanded to 80 patients per year

98. As stated in the main analysis, it is expected that the regulations proposed in this IA will benefit 20 persons a year. However, the Wellcome Trust have proposed that once processes are embedded this may be expanded to 80 persons a year. Whilst this would not make substantial differences to the policy as a whole, this annex is provided to demonstrate how the costs and benefits of the regulations might change in response to this potential expansion.

Costs

Cost per treatment

99. The price of treatment is not anticipated to change[12] in response to the relatively small change in number of cases each year. The act of carrying out more treatment will therefore increase proportionally with the number of persons receiving it, using the same price and success parameters, from the original estimate of £1.2m to £4.6m each year (before discounting).

Table 23: Estimated costs of mitochondrial donation treatment per year, given 80 patients per year

Parameters	Value (£)
High estimate: highest cost x six courses x 80 persons	£8,640,000
Low estimate: lowest cost x one course x 80 persons	£1,040,000
Central estimate: central cost x four courses x 80 persons	**£4,640,000**

Regulatory burden

100. The set-up and licensing costs would be the same regardless of the numbers of people who ultimately receive mitochondrial donation treatment. The main change to the regulatory burden would be in terms of assessing additional individual cases for significant risk of serious mitochondrial disease. These costs would therefore increase proportionate to number of additional cases considered. Since the cost per case considered was estimated to be £6,000, this increases the estimated cost of case consideration from £120,000 a year (£6,000 x 20 cases) to £480,000 (£6,000 x 80 cases).

Table 24: Estimated on-going regulation costs, given 80 patients per year

Parameter	Year 1	Years 2-10
Total average annual regulation cost	£480,000	£480,000
Set-up and licence-granting costs to provider & HFEA	£106,000	£0
Total regulatory burden (rounded)	**£586,000**	**£480,000**

101. Placing these two changes together, the overall estimated costs would become **£5m** each year, compared to the present estimate of approximately **£1.2m**. The £4.7m excludes the costs of the first year of the policy where HFEA set up costs would take place, since it is not

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[12] There may be a slight increase in equipment costs, which were initially estimated based upon 20 patients per year. However this is considered to be a small proportion of the overall cost of the treatment.

expected that this change will take place in the first year. A further £90,000 would be added to the total if this were the case.

Benefits

QALY gains

102.   In the event that 80 persons a year were to receive mitochondrial donation treatment, an additional 60 persons would gain from a life without serious mitochondrial disease. Using the same mitochondrial disease patient categories proposed in the main analysis, this would lead to a proportional rise in benefits. From an original estimated QALY benefit of £25m, it would now be estimated that the policy would result in a QALY gain of £102m.

Table 25: Annual estimated QALY value from implementation of mitochondrial donation treatment regulations, given 80 persons receiving treatment per year

Parameter, rounded	High	Low	Central
QALY value of 80 persons of 'average' health	£212,654,000	£212,654,000	£212,654,000
QALY value of 80 persons with MD	£52,945,000	£169,569,000	£111,124,000
QALY gain from policy	**£159,709,000**	**£43,085,000**	**£101,530,000**

Net production

103.   Again, because net production is calculated per person, the benefits to the economy would increase proportionally to the number of people who receive mitochondrial donation treatment. As such, if 80 persons were to receive mitochondrial donation treatment, the benefits of their expected increased net production would rise from £7.2m (the estimate for 20 recipients) to £28.8m.

Table 26: Estimated annual net production gain in response to implementing mitochondrial donation regulations, assuming 80 patients treated per year

Parameter	High estimate	Low estimate	Best estimate
Net production of average 80 persons	-£22,080,000	-£22,080,000	-£22,080,000
Net production of 80 persons with mitochondrial disease	-£70,240,000	-£31,120,000	-£50,840,000
Net production gains	**£48,160,000**	**£9,040,000**	**£28,760,000**

104.   Finally, as would be expected, the secondary healthcare cost savings would also increase proportionately to the number of persons who no longer require condition-specific healthcare. The savings, should 80 persons receive mitochondrial donation treatment, would increase from an estimated £1m to a central estimate of £4m.

Table 27: Estimated lifetime secondary healthcare cost savings per patient with serious mitochondrial disease (that receives donation treatment)

Parameter	Value (£)
High estimate (80 patients from category 1a)	£9,360,000
Low estimate (80 patients from category 2b)	£1,040,000

Central estimate (20 patients from each category)	**£4,030,000**

105.   Combining the benefits before costs together, these would increase from the present estimate of approximately £33m per year to £134m per year.

106.   Putting all these elements together, the final tables below demonstrate the effect the expansion would have on the costs and benefits as a whole. It is estimated the net benefit of the policy would be £1,273m over 10 years, approximately £128m each year.

Central estimated costs and benefits

Policy year	Year	Benefits	Costs	Net benefit
0	2015	£134,320,000	£5,226,000	£129,094,000
1	2016	£133,714,000	£4,946,860	£128,767,140
2	2017	£133,138,000	£4,779,575	£128,358,425
3	2018	£132,534,000	£4,617,947	£127,916,053
4	2019	£132,000,000	£4,461,784	£127,538,216
5	2020	£131,387,000	£4,310,903	£127,076,097
6	2021	£130,875,000	£4,165,123	£126,709,877
7	2022	£129,903,000	£4,024,274	£125,878,726
8	2023	£129,802,000	£3,888,187	£125,913,813
9	2024	£129,182,000	£3,756,703	£125,425,297
				£1,272,677,645

Annex B: 10-year impact - combining the costs and benefits of the policy

High estimate

Policy year	Year	Benefits	Costs	Net benefit
0	2015	£54,307,000	£486,000	£53,821,000
1	2016	£54,045,000	£367,150	£53,677,850
2	2017	£53,804,000	£354,734	£53,449,266
3	2018	£53,542,000	£342,738	£53,199,262
4	2019	£53,321,000	£331,148	£52,989,852
5	2020	£53,060,000	£319,950	£52,740,050
6	2021	£52,839,000	£309,130	£52,529,870
7	2022	£52,518,000	£298,677	£52,219,323
8	2023	£52,377,000	£288,576	£52,088,424
9	2024	£52,116,000	£278,818	£51,837,182
				£528,552,079

Low estimate

Policy year	Year	Benefits	Costs	Net benefit
0	2015	£13,291,000	£2,386,000	£10,905,000
1	2016	£13,234,000	£2,202,899	£11,031,101
2	2017	£13,158,000	£2,128,404	£11,029,596
3	2018	£13,102,000	£2,056,429	£11,045,571
4	2019	£13,046,000	£1,986,888	£11,059,112
5	2020	£12,971,000	£1,919,699	£11,051,301
6	2021	£12,916,000	£1,854,781	£11,061,219
7	2022	£12,742,000	£1,792,059	£10,949,941
8	2023	£12,808,000	£1,731,458	£11,076,542
9	2024	£12,734,000	£1,672,907	£11,061,093
				£110,270,475

Best estimate

Policy year	Year	Benefits	Costs	Net benefit
0	2015	£33,580,000	£1,386,000	£32,194,000
1	2016	£33,428,000	£1,236,715	£32,191,285
2	2017	£33,284,000	£1,194,894	£32,089,106
3	2018	£33,133,000	£1,154,487	£31,978,513
4	2019	£33,000,000	£1,115,446	£31,884,554
5	2020	£32,846,000	£1,077,726	£31,768,274
6	2021	£32,719,000	£1,041,281	£31,677,719
7	2022	£32,475,000	£1,006,068	£31,468,932
8	2023	£32,450,000	£972,047	£31,477,953
9	2024	£32,295,000	£939,176	£31,355,824
				£318,086,161

Annex D: Expansion on calculations

Calculation of QALY benefits

1. The table below shows an example of the quality-adjusted life expectancy for females with mitochondrial disease scenario '1a', as an illustration of the calculations used across all scenarios. Category 1a presents the group with the shortest life expectancy and therefore has been chosen for practical reasons of table length, otherwise calculations are identical across categories.

Table 28: Calculation of the quality adjusted life expectancy for a female with serious mitochondrial disease (scenario 1a)

1	2	3	4	5	6	7	8	9	10
Age	Survivors at the age shown, from a starting population of 100,000 (females)	No. years lived in the age band per survivor at the start of the age band (females)	No. of years lived in the age band (females)	QoL Female	Discounting factor (1.5%)	QALY female	Life expectancy (female)	Undiscounted QALE (female)	Discounted QALE (female)
0	100,000	1	100,000	0.61	1.0000	61,000	20.91	12.75	11.04
1	99,639	1	99,639	0.61	0.9852	60,780	19.98	12.19	10.62
2	99,603	1	99,603	0.61	0.9707	60,758	18.99	11.58	10.16
3	99,592	1	99,592	0.61	0.9563	60,751	17.99	10.97	9.70
4	99,582	1	99,582	0.61	0.9422	60,745	16.99	10.36	9.23
5	99,574	1	99,574	0.61	0.9283	60,740	15.99	9.76	8.75
6	99,566	1	99,566	0.61	0.9145	60,735	14.99	9.15	8.26
7	99,559	1	99,559	0.61	0.9010	60,731	13.99	8.54	7.76
8	99,553	1	99,553	0.61	0.8877	60,727	12.99	7.93	7.26
9	99,547	1	99,547	0.61	0.8746	60,724	12.00	7.32	6.75
10	99,542	1	99,542	0.61	0.8617	60,721	11.00	6.71	6.23
11	99,537	1	99,537	0.61	0.8489	60,718	10.00	6.10	5.71
12	99,532	1	99,532	0.61	0.8364	60,715	9.00	5.49	5.17
13	99,526	1	99,526	0.61	0.8240	60,711	8.00	4.88	4.63
14	99,520	1	99,520	0.61	0.8118	60,707	7.00	4.27	4.08
15	99,513	1	99,513	0.61	0.7999	60,703	6.00	3.66	3.53

16	99,504	1	99,504	0.61	0.7880	60,697	5.00	3.05	2.96
17	99,495	1	99,495	0.61	0.7764	60,692	4.00	2.44	2.39
18	99,485	1	99,485	0.61	0.7649	60,686	3.00	1.83	1.80
19	99,474	1	99,474	0.61	0.7536	60,679	2.00	1.22	1.21
20	99,462	1	99,462	0.61	0.7425	60,672	1.00	0.61	0.61

2. The first column describes the age of the person over their expected lifetime (0-20 in this group). Column 2 shows the expected number of 'survivors' at each age. These numbers are taken directly from ONS cohort life tables and are calculated based upon current and projected mortality rates over time [23]. Interpreted directly it shows, of a hypothetical birth cohort of 100,000 people, how many are expected to 'survive' at each year of age. These numbers could alternatively be converted into a probability of mortality or survival, as is done in the wider social benefits approach (see next section). The two columns beside the survival numbers convert the number of survivors into a number of years 'lived' in the age band. Because each row represents a single year of age, here the resulting number of years lived is the same.

3. The final three columns represent the expected number of life years remaining for an individual (in the birth cohort) at each age. The number of years remaining in the first row (e.g. from birth, age 0) shows the average life expectancy at birth for those in this mitochondrial disease category – the main life expectancy column shows that on average, persons in this group will live to the age of 20.9. This is calculated by summing the total number of years expected to be lived from birth (column 4) and dividing by the number of persons in the birth cohort (100,000 from column 2). The final two life expectancy columns are adjusted estimates of life expectancy. 'Undiscounted QALE' represents the quality-adjusted life expectancy of these individuals. This means that the number of years lived are adjusted by the quality of life expected in each year, so showing that 20 years of life at a QoL of 0.61 is equivalent to 12.75 years of life in 'perfect health' (QoL=1). This has effectively converted the expected life years into quality adjusted life years (QALYs) which is a standard measure that can then be valued. The final column discounts the quality-adjusted life expectancy figures further, taking into account social time preference (the fact that we value a year of life now more than we value the promise of life 10 years from now) and discounting accordingly by 1.5% per year. Once discounted, the number of QALYs expected for a female with this category of mitochondrial disease is estimated as 11.04. This is reflected in the average 'person' QALYs (i.e. an average of males and females in each category) presented in the main analysis (tables 10 and 11).

4. The table above estimates the life expectancy and the QALYs for a person born with serious mitochondrial disease in 2014, as a hypothetical comparison for someone who might benefit from mitochondrial donation treatment in the first year of the regulations. These tables are replicated for each year of the policy, using the survival figures (column 2) from ONS from 2014-2023 as appropriate.

Calculation of wider social benefit

5. The wider social benefits model has numerous components, data sources and assumptions, and it would be inappropriate to attempt to cover all of the details here when guidance for the model is publically available [18]. The components of the model are split into those of production, which include paid

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and unpaid labour, and of consumption, which includes social/residential care costs, household consumption, and general consumption of other resources such as education, childcare, and government resources. The table below shows the values for each of these separate components, for an 'average' person in the population and for a person under each of the mitochondrial disease categories used within this IA, over their lifetime.

Table 29: The expected net production for the 'average' person and persons with serious mitochondrial disease (1a-2b)

	Average population	Mitochondrial Disease, 1a	Mitochondrial Disease, 1b	Mitochondrial Disease, 2a	Mitochondrial Disease, 2b
Total Consumption	£1,394,000	£467,000	£832,000	£975,000	£1,372,000
Formal Care	£11,000	£0	£0	£0	£12,000
Informal Care	£9,000	£2,000	£17,000	£22,000	£31,000
Private Paid Consumption	£509,000	£140,000	£286,000	£342,000	£497,000
Private Unpaid Consumption	£636,000	£230,000	£391,000	£454,000	£613,000
Childcare Consumption	£17,000	£17,000	£17,000	£17,000	£17,000
Government Consumption	£212,000	£77,000	£120,000	£139,000	£201,000
Total Production	£1,118,000	£78,000	£209,000	£323,000	£494,000
Paid production	£521,000	£0	£0	£0	£0
Unpaid Production	£597,000	£78,000	£209,000	£323,000	£494,000
Net production per person	**-£276,000**	**-£389,000**	**-£623,000**	**-£652,000**	**-£878,000**

6. The model estimates these components based upon a number of inputs: age, gender, QoL weight and ICD10 code. The outputs are inevitably estimates, and the model is being continuously updated. However, where more is known about a specific condition some components can be overridden. For this IA the model has been run based on a person with QoL of 0.61, for patients with disease category 'G' from ICD10. The model assumes that, post 16 years of age, such persons may be in paid employment (albeit with a greater level of sickness absence than the average population). However, consultation with experts suggests that those with serious mitochondrial DNA disease are to be employment, whether this is due to severe physical disabilities or cognitive impairment. Therefore the paid labour element of the model is overridden to zero for those with mitochondrial disease. However, the unpaid labour component remains, which might include such activities as self-care, which holds a value even though it is not a paid form of activity. It may be that those with mitochondrial disease are fully dependent upon carers, but with such variability in conditions it is felt that it is fairer to keep these elements of production within the model. This means that the net benefit of the policy might actually be higher than that produced in this IA.

7. The following table shows a more detailed breakdown of the calculation that produces the 'lifetime estimate', based on a female from category 1a. Note that because the 'person' values above are derived from an average of male and female outputs, the totals will differ from the 1a column presented in the previous table. The model generates monthly estimates of consumption and production based on the model inputs (in this case, a female, input at each age as below over the expected lifespan (0-20.) with QoL of 0.61 and ICD10 category G) which are multiplied by 12 to generate annual estimates for each year of life. To generate a single 'lifetime' estimate, the values are adjusted in a similar way to the QALY estimates produced in the previous section. Each year's value is multiplied by the probability that an individual will 'survive' to the specific age. These survival probabilities are directly converted from the survival numbers used in the table above (e.g. 99,639 females out of 100,000 are expected to survive to age 1, therefore 99,639/100,000=0.99639.) It is then also multiplied by the discounting factor, again used to take into account the social time preference of values as they become more and more distant from the present. Ordinarily values for consumption and production would be discounted at a rate of 3.5%. However, the model being used provides estimates of consumption and production based on current circumstances. Since this analysis goes far into the future it is reasonable to assume that technology improvement would be expected to change production and consumption substantially over time. For example, paid and unpaid production is valued at the present median wage, which is not likely to remain the same over time. Since it is assumed that the economy grows at a rate of 2% over the long term, this is reflected in the discount rate, which has been amended to 1.5%. Once appropriately adjusted, each annual estimate is aggregated to form a lifetime estimate.

Table 30: The lifetime estimated net production of a female with serious mitochondrial disease (scenario 1a)

Age	Survival probability	Discounting Factor	Consumption, rounded	Unpaid Production, rounded	Net production, rounded
0	1	1.0000	£27,600	£3,400	-£24,200
1	0.99639	0.9852	£27,100	£3,300	-£23,800
2	0.99603	0.9707	£26,700	£3,400	-£23,300
3	0.99592	0.9563	£26,300	£3,500	-£22,800
4	0.99582	0.9422	£25,900	£3,600	-£22,300
5	0.99574	0.9283	£22,500	£3,700	-£18,900
6	0.99566	0.9145	£22,200	£3,800	-£18,400
7	0.99559	0.9010	£21,900	£3,800	-£18,000
8	0.99553	0.8877	£21,500	£4,400	-£17,200
9	0.99547	0.8746	£21,200	£4,400	-£16,800
10	0.99542	0.8617	£20,900	£5,000	-£15,900
11	0.99537	0.8489	£20,600	£4,700	-£15,900
12	0.99532	0.8364	£20,700	£5,000	-£15,800

13	0.99526	0.8240	£20,400	£5,200	-£15,300
14	0.9952	0.8118	£20,100	£5,300	-£14,900
15	0.99513	0.7999	£20,100	£5,000	-£15,100
16	0.99504	0.7880	£19,800	£5,300	-£14,500
17	0.99495	0.7764	£19,900	£5,700	-£14,200
18	0.99485	0.7649	£19,600	£5,400	-£14,200
19	0.99474	0.7536	£19,500	£5,400	-£14,200
20	0.99462	0.7425	£22,700	£5,700	-£17,000
Total	**NA**	**NA**	**£467,200**	**£95,000**	**-£372,200**

8. A further point to note is that the model assumes that production will curtail at age 60-65 based on current rates of retirement. This is another element that is likely to change over time. No amendments have been made in response to this in the analysis. Instead, it is accepted that the lifetime production value of the 'average' person is likely to be an underestimate, since it is likely they will retire later than 60-65 years of age. This will make estimates of benefit more conservative in nature.

9. Finally, it should be known that this model only includes consumption and production components where they are affected by health. It is not an exhaustive sum of total value a person may contribute to society. For example, the production element includes labour but does not include capital, such as the assets that a person may own, since these would continue to hold some value even if the owner's health were to decline. Similarly, consumption, as covered in the main analysis, does not include condition-specific healthcare costs, since these are likely to be highly variable and thus difficult to estimate in a model that has use across a wide range of conditions.

Example of healthcare gain estimates

10. Finally, this section provides a brief explanation of the calculations of healthcare costs. The main analysis already demonstrated an example of patient healthcare costs (table 14) that for ease has been replicated below.

Table 31: Secondary healthcare costs of a patient with serious mitochondrial disease

Patient A	Inpatient admissions	Outpatient admissions	Tests	Genetic tests	Medications	Total cost per year
Year 1	£ -	£ 176	£ -	£ -	£ -	£ 176
Year 2	£ -	£ 176	£	£ 65	£ -	£ 241

Year 3	£ -	£ 646	£ -	£ -	£ -	£ 646
Year 4	£ -	£ 538	£ -	£ 65	£ -	£ 603
Year 5	£ -	£ 714	£ 30	£ -	£ -	£ 744
Year 6	£ -	£ 664	£ 30	£ 65	£ -	£ 759
Year 7	£ -	£ 533	£ -	£ -	£ -	£ 533
Year 8	£ 795	£ 1,252	£ -	£ -	£ -	£ 2,047
Year 9	£ -	£ 3,698	£ 117	£ -	£ -	£ 3,815
Year 10	£ -	£ 673	£ -	£ 540	£ -	£ 1,213
Year 11	£ -	£ -	£ -	£ -	£ -	£ -
Year 12	£ 211,648	£ -	£ 480	£ -	2	£ 212,130
Total per category	**£ 212,443**	**£ 9,070**	**£ 656**	**£ 735**	**2**	**£ 222,906**

11. There was great disparity amongst the health care costs per patient. The table below summarises some of the main findings, demonstrating the approximate split of costs amongst different aspects of secondary care and showing the wide variation in costs on an annual basis. A further complication within the data is that a number of the case histories concerned patients who were still alive at the time of reporting, which means that the full extent of healthcare costs are still to be determined.

Table 32: Summary information regarding secondary healthcare costs of those with serious mitochondrial disease

Parameter	Value, rounded
Mean annual cost	£1,800
Median annual cost	£300
Max annual cost	£200,000
Min annual cost	£0
% cost of inpatient admissions	75.0%
% Cost of outpatient admissions	17.0%
% Cost of test	6.6%
% Cost of procedures	0.4%

% Cost of additional genetic tests	0.9%
% Cost of medications	0.1%

12. With all of these considerations in mind, I selected three annual cost estimates for patients within each of my four scenario groups. An example is provided below for a patient from group 1a. As can be seen, the costs increase over their expected lifetime, with a sharp increase in care costs at the point where their health deteriorates. This is an example of the central estimate – the lower and higher estimates differed only in the healthcare costs at the 'end of life' stage, which varied between £100,000 and £200,000 respectively. The costs were dispersed proportionately across the number of years between disease onset and end-of-life for each of the other three scenarios.

Table 33: Example of the average secondary healthcare costs calculation for those with serious mitochondrial disease, scenario 1a

Age	Cost	Discount 3.5	Discounted cost, rounded
0	£100	1.0000	£100
1	£100	0.9662	£100
2	£100	0.9335	£100
3	£100	0.9019	£100
4	£1,000	0.8714	£900
5	£1,000	0.8420	£800
6	£1,000	0.8135	£800
7	£1,000	0.7860	£800
8	£1,000	0.7594	£800
9	£1,000	0.7337	£700
10	£1,000	0.7089	£700
11	£1,000	0.6849	£700
12	£2,000	0.6618	£1,300
13	£2,000	0.6394	£1,300
14	£2,000	0.6178	£1,200
15	£2,000	0.5969	£1,200
16	£2,000	0.5767	£1,200

17	£2,000	0.5572		£1,100
18	£2,000	0.5384		£1,100
19	£2,000	0.5202		£1,000
20	£150,000	0.5026		£75,400
Total	**£174,400**	**NA**		**£91,400**