Authority meeting - agenda

15 December 2016

Venue: Etc Venues Victoria, 1 Drummond Gate, London SW1V 2QW

Agenda item		Time
1.	Welcome, apologies and declaration of interests	10:00am
2.	Previous Authority Minutes **HFEA (15/12/16) 817** For decision	10:05am
3.	Mitochondrial Donation **HFEA (15/12/16) 818** For decision	10:10am
4.	Any other business	11:45am
5.	Close	12:00pm

Minutes of Authority meeting 16 November 2016

Strategic delivery:	☐ Setting standards	☐ Increasing and informing choice	☐ Demonstrating efficiency economy and value
Details:			
Meeting	Authority		
Agenda item	2		
Paper number	HFEA (15/12/2016) 817		
Meeting date	15 December 2016		
Author	Charlotte Keen, Information Access and Policy Manager		
Output:			
For information or decision?	For decision		
Recommendation	Members are asked to confirm the minutes as a true and accurate record of the meeting		
Resource implications			
Implementation date			
Communication(s)			
Organisational risk	☐ Low	☐ Medium	☐ High
Annexes			

Minutes of the Authority meeting on 16 November 2016 held at ETC Venues, Victoria, 1 Drummond Gate, London SW1V 2QW

Members present	Sally Cheshire (Chair) Rebekah Dundas Dr Andy Greenfield Yacoub Khalaf Margaret Gilmore	Ruth Wilde Dr Anne Lampe Anthony Rutherford Kate Brian Anita Bharucha
Apologies	Bishop Lee Rayfield	
Observers/Presenters	(Department of Health)	
Staff in attendance	Peter Thompson Nick Jones Juliet Tizzard Catherine Drennan Paula Robinson	Charlotte Keen

Members

There were 10 members at the meeting, 6 lay members and 4 professional members

1. Welcome, apologies and declarations of interest

1.1. The Chair opened the meeting by welcoming Authority members and members of the public to the sixth meeting of 2016. As with previous meetings, it was being audio recorded and the recording would be made available on the HFEA website to enable interested members of the public who were not able to attend the meeting to listen to the HFEA's deliberations.

1.2. Apologies were received from Bishop Lee Rayfield.

1.3. Declarations of interest were made by:

- Kate Brian (Regional organiser for London and the South East for Infertility Network UK)
- Yacoub Khalaf (Person Responsible at a licensed centre)
- Anthony Rutherford (Consultant in Reproductive Medicine and Gynaecological Surgery at a licensed centre)
- Ruth Wilde (Senior Fertility Counsellor at a licensed centre).

2. Minutes of Authority meeting held on 14 September 2016

2.1. Members agreed the minutes of the meeting held on 14 September, subject to a minor amendment, for signature by the Chair.

3. Chair's report

3.1. The Chair welcomed Richard Sydee to his first Authority meeting as Director of Finance and Resources. Richard joined the HFEA on 1 November and is the shared Director between the HFEA and the Human Tissue Authority (HTA), replacing Sue Gallone.

3.2. The Chair provided members with a summary of events that she had attended with organisations in the IVF sector and the wider health and care system since the last Authority meeting.

3.3. On 15 September, the HFEA marked its 25th anniversary. The HFEA was the first regulator of IVF and human embryo research and it was testimony to all those involved that it had stood the test of time so well and was considered to be the standard against which regulation in the field was judged. The event provided a chance to celebrate those achievements in more detail with past colleagues and some of the HFEA's most important stakeholders. The Chair thanked all those who attended and a particular thanks to HFEA staff who helped put the event together.

3.4. On 28 September, the Chair attended the Department of Health's arm's length bodies (ALBs) chairs and non-executive directors (NEDs) policy context seminar on accelerated access, and on 10 October she attended the ALB chairs and NEDs Ministerial round table meeting at the Department of Health with the Parliamentary Under Secretary of State for Health, Lord Prior of Brampton.

3.5. On 18 October, the Chair, together with the Chief Executive, had an introductory meeting with the new Parliamentary Under Secretary of State for Public Health and Innovation, Nicola Blackwood.

3.6. On 11 November, the Chair, together with the Chief Executive attended a meeting on the cost of publically funded IVF, involving NHS England, representatives from the sector and the Department of Health.

3.7. Finally, the Chair advised members that she had been working with the Department of Health on the appointment of two new Authority members. Shortlisting took place in late September, with interviews in October. As ever, the recruitment attracted a number of high quality candidates and Cabinet Office approval of the appointment of the successful candidates should follow shortly.

4. Chief Executive's report

4.1. The Chief Executive advised members that, on 21 September, he, together with the Chair of the Authority's Audit and Governance Committee, appeared before the Department of Health's Risk and Audit Committee meeting, one of a number of meetings involving all ALBs to look at system wide risks and how they could best be managed.

4.2. On 27 September, the Chief Executive spoke at Health and Social Care Leadership Scheme seminar, and on 27 October he participated in a peer review workshop on managing talent. The Health and Social Care Leadership Scheme brings together the Department of Health and all of the Chief Executives of the health sector's ALBs to identify senior talent within the system.

4.3. On 1 November, the Chief Executive attended a meeting at the Academy of Medical Science (AMS), held to assess the regulation and governance of health research five years on since the AMS report which had led to the establishment of the Health Research Authority (HRA).

4.4. On 3 November, the Chief Executive, together with the Interim Head of Regulatory Policy, spoke to a Norwegian delegation about the HFEA's work on mitochondrial donation, embryo research, donation and other issues.

Press coverage

4.5. The Chief Executive advised members that there had been a busy period for press coverage since the last Authority meeting. The National Fertility Awareness week had generated a lot of coverage and the Director of Strategy and Corporate Affairs would go into more details in item six. There were two other issues which were of particular importance.

4.6. Samantha Jeffries case: the Chief Executive reminded members that Samantha Jeffries was seeking permission to continue to store embryos made with her and her dead husband's gametes. Mrs Jeffries believed that she and her husband had consented to storage for ten years but that this had been changed by the clinic to two years to match the period of time for which there was NHS funding and she sought to restore the ten-year consent through the courts. The HFEA had agreed with her position, as did the clinic. Judgement had been handed down about six weeks ago and the Judge accepted that it was the true intention of the husband to consent to storage for ten years. The Judge had therefore ruled that Mrs Jeffries had effective consent for ten years.

4.7. The Chief Executive emphasised that there was a clear lesson for clinics to follow the HFEA's long-standing advice that the statutory storage period to which patients were entitled must not be overwritten by any separate agreement about the funding of storage, whether paid for by the NHS or the patients themselves.

4.8. Baby born using mitochondrial donation in Mexico: there had been considerable media interest in this story. The baby was now five months old and healthy. The American doctors had made it clear they had gone to Mexico precisely because there were no rules governing mitochondrial donation there. The Chief Executive commented that it was for individuals to judge the ethics of such an approach.

5. Committee chairs' updates

5.1. The Chair of the Statutory Approvals Committee reported that the committee had met on 29 September and 27 October. There had been four preimplantation genetic diagnosis (PGD) applications on 29 September, three of which were approved and one adjourned pending further information. At the meeting on 27 October, there had been one PGD application, which was approved, and two Special Directions applications, one of which was approved and one refused.

5.2. The Chair of the Licence Committee reported that the committee had met on 10 November, when the committee received two executive updates. The minutes of the meeting had not yet been published.

5.3. The Director of Strategy and Corporate Affairs advised members that the Executive Licensing Panel (ELP) had met four times since the last Authority meeting; on 23 September, 7 and 19 October and 4 November. For the first three meetings, the panel had considered 17 items in total, all of which were approved and noted. There was one renewal licence application; nine interim inspection reports; five licence variations, one appliction for HLA tissue typing and one progress report. At the meeting on 4 November, the minutes of which had not yet been published, the

panel had considered 4 items. There was one interim inspection report; two licence variations and one progress report.

5.4. The Chair of the Audit and Governance Committee (AGC) advised members that the committee had met on 21 September, and had received reports on:

- A Directorate update and contribution to the HFEA strategy, from the Director of Strategy and Corporate Affairs
- Risks, including staffing and patient/stakeholder engagement, from the Director of Strategy and Corporate Affairs
- An IFQ update on managing risks, from the Director of Compliance and Information
- Strategic risks, from the Head of Business Planning
- Updates from the Internal and External Audit teams
- A progress report on the implementation of audit recommendations
- Cyber security, from the Head of IT
- Updated reserves policy from the Head of Finance

5.5. The Chair of the Scientific and Clinical Advances Advisory Committee (SCAAC) reported that the committee had met on 17 October and had considered the following items:

- The multiple births strategy
- A paper and presentation on in-vitro derived gametes from Professor Azim Surani from Gurdon Institute in Cambridge
- HFEA website content review – treatment 'add-ons'
- The NICE IUI guideline review.

6. Strategic performance report

6.1. The Director of Strategy and Corporate Affairs reminded members that National Fertility Awareness week had taken place between 31 October and 6 November. Fertility Network UK ran a campaign called 'Hidden Faces' which was a series of short films with people who were going through, or had had, fertility treatment and their experiences or having treatment and their journey, regardless of the outcome. The Director of Strategy and Corporate Affairs presented one of the films to members which could be found on YouTube at https://www.youtube.com/watch?v=6OK5mqXGPek.

6.2. The Director of Strategy and Corporate Affairs advised members that there had been a lot of public discussion about fertility during National Fertility Awareness week, which had culminated in the Fertility Show on 5 and 6 November in London, which attracted 3,000 visitors. We met many of those visitors at our stand, distributing 500 'Getting Started' guides and showing them Choose a Fertility Clinic (CaFC). The Director of Strategy and Corporate Affairs also gave a talk on how to understand IVF statistics. The Fertility Show was a good opportunity for the HFEA to engage with people at all stages of the IVF process and for them to have access to all the information the organisation could provide to assist them in making informed choices.

6.3. The Director of Compliance and Information highlighted key points within his Directorate from the Strategic Performance Report. Firstly, the time taken for the licensing process to be complete was

the lowest it had been, with the average time being 50 days from start to finish. Secondly, in terms of PGD applications received from clinics who were seeking to test for a new condition which had not already been approved, the time taken to process those applications was also down to around 50 days, which demonstrated very good progress at this time.

6.4. The Director of Finance and Resources gave a brief overview of financial performance. Over the last six months there had been a slight increase in the treatment fee income against that which had been forecast. There was no obvious reason or pattern but the Director of Finance and Resources emphasised that the Executive were very sighted on the increase.

6.5. Following a discussion, members noted the latest strategic performance report.

7. Information for Quality: update

7.1. The Director of Compliance and Information explained that the IfQ programme was a comprehensive review of the information that the HFEA held, the systems that governed the submission of data, the uses to which it was put and the ways in which the information was published. It included:

- The redesign of the HFEA's website and Choose a Fertility Clinic (CaFC) function
- The redesign of the 'Clinic Portal' used for interacting with clinics
- Combining data submission functionality
- A revised dataset and data dictionary which would be accredited
- A revised Register of treatments, which would include the migration of historical data contained within the existing Register
- The redesign of the HFEA's main internal systems that comprised the Authority's Register and supporting IT processes.

7.2. The Director of Compliance and Information explained that this presentation was to update members on:

- Progression to a fully live HFEA website and Clinic Portal
- 'Release two' progress – data submission system development
- Information policy
- IfQ programme conclusion
- Programme timelines and budget.

7.3. HFEA website and CafC: the Director of Compliance and Information advised members that these two products were released to public beta in July 2016 and feedback had been positive. However, as reported at the September Authority meeting, it was felt that both the website and CaFC should not proceed to live until February 2017. This was in recognition of the Judicial Review, which was scheduled to take place on 19 and 20 December, and the need to secure final GDS approval, currently planned for late January 2017.

7.4. For the purposes of the programme, the Director of Compliance and Information advised members that the website and CaFC was largely concluded, and the additional design and development work that needed to take place was already included within the existing contract.

Subject to assessment, the product would be live in February 2017, and the current HFEA website decommissioned.

7.5. Clinic Portal (release one): the Director of Compliance and Information reminded members that this element of the portal would allow clinics to conduct all transactions with the HFEA other than treatment data submission. Members noted that the report to the September Authority meeting confirmed that the portal was released in beta form on 12 July, and anticipated that the GDS assessment was scheduled to take place on 28 October.

7.6. A consequence of the beta testing was the identification of issues and bugs and the Director of Compliance and Information informed members that the resolution of these had required more time and effort than anticipated. As a consequence, the Executive had decided to reschedule the GDS assessment for 21 November so that further and final user testing could be undertaken on 3 November.

7.7. For the purposes of the programme, the Director of Compliance and Information advised members that the Clinic Portal, subject to GDS assessment, was largely concluded. It was anticipated that the Clinic Portal would be released as live in December and current portal decommissioned.

7.8. Clinic Portal (release two): the Director of Compliance and Information reminded members that this was the component that replaced the current clinic data submission application. This was a substantial undertaking requiring both extensive foundational work and a new 'front end' service that would be experience by clinic users. Much of the foundational work was well advanced, as had previously been reported to members. A new Register database had been designed with a new data structure, with each item defined in a data dictionary, which was in the process of being accredited by NHS Digital. Cleansing of vital data prior to the migration of the current Register database was in the process of being finalised, with a Register migration strategy in place. A set of new expectations as regards clinics' information management arrangements was also being developed.

7.9. The Director of Compliance and Information informed members that challenges remained with this aspect of the programme. Whilst much of the foundational work had progressed well, it was likely that the remaining work would absorb the majority of the remaining time and resource attached to the programme.

7.10. Release two (data submission development): the Director of Compliance and Information advised members, as outlined above, that there had been much progress, with more to do, on the necessary foundational work in transforming the data submission system. This included the data dictionary and accreditation, Register data migration and the information policy.

7.11. Information policy: the Director of Compliance and Information advised members that, since there had been a substantial investment by the HFEA in developing a new information architecture, the Executive wanted to develop a set of principles to underpin the HFEA's approach to information and how those principles supported the delivery of the organisations' strategic objectives. Members noted that a draft information policy would be presented to them at the January 2017 meeting and would encapsulate the following reasoning:

- A new information architecture was being created
- There would be an easier process for clinics to submit data and check or verify the accuracy of their data

- This was an opportunity to establish much clearer accountabilities with a new information bargain with clinics
- The emerging policy would make that bargain transparent – substantial proposals would be presented in January
- An extant policy was in place until the new policy was adopted.

7.12. Timelines and budget implications: the Director of Compliance and Information reminded members that a revised programme plan had been finalised and signed off by the IfQ Programme Board in January 2016, in line with the overall £1.134m agreed by the Authority. The Executive did not anticipate the programme exceeding this figure at 31 March 2017, although the consequences of the revised timeline, and the financial implications of this, were being worked through.

7.13. The variance in September was explained by an underspend originally forecasted for the security consultant and this underspend should balance in the coming months once the work was completed and invoiced.

7.14. Following a discussion, Authority members noted:

- Progress since the last Authority meeting, noting the launch of the HFEA website and clinic portal
- The delays to 'Release Two' – the new data submission system
- The conclusion of the programme in March 2017
- The HFEA's emerging information policy
- Programme timelines and budget implications.

8. Choose a fertility clinic

8.1. The Director of Strategy and Corporate Affairs presented this item and reminded members that a major strand of work within the IfQ programme was the redesign of the HFEA website, incorporating the Choose a Fertility Clinic (CaFC) service. The current CaFC service is used by 15,000 patients each month to research and select a licensed clinic for their fertility treatment. However, the current CaFC was last redesigned in 2009 and is dated, overly complex and built on old technology. The new service, currently in its beta phase, had a fresh new design with new features and a much simpler presentation of birth statistics.

8.2. The Director of Strategy and Corporate Affairs reminded members that they had made a number of policy decisions in January 2015 about how birth statistics would be calculated. Whilst developing CaFC for the past year, a number of presentational decisions had also been made about the birth statistics and members would now be asked to make final decisions about how births statistics would be calculated and presented. Following those decisions, the Executive would then redesign CaFC, ready for the launch of the live service early next year.

8.3. The Director of Strategy and Corporate Affairs reminded members that the new CaFC was built on the following principles:

- Birth rates are not the only measure of quality in a clinic
- Information about each clinic should be clear and helpful

- CaFC should be the go-to place for birth statistics.

8.4. The Director of Strategy and Corporate Affairs advised members that the point of the beta feedback period was to receive public feedback and to test with individual users so that improvements could be made before the live version was launched. In order to inform decisions during the meeting, members had been presented with reports from the beta feedback period and members noted they should give consideration to this feedback in order to inform their decisions.

8.5. The Director of Strategy and Corporate Affairs emphasised that it is important to bear in mind some peculiarities in the fertility sector in the UK:

- With 60% of patients self-funding, clinics compete to attract patients
- Patient case mix variation – most of which is not captured in the HFEA's data – affects outcomes
- The size of the clinics across the UK varies enormously
- Therefore, presenting meaningful data is complex and difficult.

8.6. The Director of Strategy and Corporate Affairs informed members that the most reliable statistics are calculated from national data, which is based on nearly 70,000 treatments each year. Once data is presented clinic by clinic, however, statistical reliability became a real issue. For the larger clinics, chance variation does not have a significant effect on outcomes, but this is an issue for small clinics and even medium sized ones.

8.7. For this reason, confidence intervals in the CaFC data had been included since it was first launched in 2009. Without them, the data would be misleading. In the beta CaFC, the term 'reliability range' is used, which shows how confident the HFEA is that a clinic will repeat its success rate in the future. Although, patients found this difficult to understand, the advisory group had discussed this issues and agreed that such an important health warning should not be abandoned. Instead, the HFEA should seek to increase clarity and understanding through the design and wording on the page, using feedback from user testing.

8.8. The Authority considered the options and recommendations in the paper. The Chair advised members that decisions would be taken by exception (ie, only if someone did not agree with the recommendation would they let the Chair know). The Authority was asked to consider the IfQ advisory group's recommendations and alternative options.

Births per embryo transferred

8.9. The Director of Strategy and Corporate Affairs reminded members that, in January 2015, based on advice from the IfQ advisory group, Authority members decided that the primary headline birth rate for IVF should be births per embryo transferred. Adopting this rate would mean a greater emphasis on the clinical and embryological practices of the clinic and would promote the HFEA policy on single embryo transfer, as a double embryo transfer would reduce a clinic's birth rate in this calculation. The beta CaFC service uses this birth rate measure.

8.10. However, some respondents during the beta feedback survey argued against births per embryo transferred, claiming it acts as a disincentive to replace the number of embryos that are clinically indicated and is difficult for patients to understand as it does not give them a picture of their overall chance of success.

8.11. Looking at the views expressed during the beta feedback period in the round, the HFEA was of the view that there was no case for changing the policy of having births per embryo transferred as the headline measure for the following reasons:

- It promotes good practice around embryo transfer
- It reinforces the HFEA's policy to reduce multiple births
- It is understandable to patients if explained well
- It is supported by the majority of professionals, the advisory group and the BFS.

8.12. Members were asked to consider the IfQ Advisory Group recommendation to retain births (ie, birth events) per embryo transferred as the headline IVF birth rate on CaFC or to consider using a different birth rate.

8.13. **Decision**: All members agreed to retain births (birth events) per embryo transferred as the headline IVF birth rate on CaFC.

Presenting the headline statistic at the top of the page

8.14. The Director of Strategy and Corporate Affairs advised members that, in the beta feedback period, users were asked for their views about whether CaFC should have a headline statistic at the top of the page. Thoughts about this were:

- Most people supported a headline measure, so long as it was aggregated
- It should be something which enables a comparison between clinics
- A few suggested showing more than one age group at this point
- The advisory group thought that a simple 'consistent with the national average' tick would be more meaningful.

8.15. The Director of Strategy and Corporate Affairs therefore asked members to consider how the HFEA should present the headline IVF birth rate at the top of the page and in search results from the following three options:

- Remove birth rate information altogether
- Present only where or not the rate is consistent
- Present the clinic rate as a percentage, alongside the national rate (as it is now in beta).

8.16. Members were asked to choose between the three options for how the IVF birth rate should be presented at the top of the clinic profile page and in search results.

8.17. **Decision**: All members agreed to accept the recommendation of the Advisory Group, that the HFEA presents only whether or not the rate is consistent with the national average. This needs to be appropriately labelled to show what the underlying calculation is.

What should be included in the headline birth rate calculation?

8.18. The Director of Strategy and Corporate Affairs advised members that users were asked for their views about what types of IVF and what ages should be included here. The key points were:

- Age aggregation and treatment aggregation as done in beta CaFC are very unpopular
- Because of the impact of age on success, grouping all ages may disadvantage some clinics treating older patients

- Some treatments are used for different reasons to standard IVF
- Both may make the birth rate less meaningful to patients.

8.19. The Director of Strategy and Corporate Affairs asked members to consider the following recommendation and options about what types of IVF treatment should be included in the calculation:

- **Recommendation**: only fresh IVF and ICSI cycles with the patient's own eggs
- **Option 1**: exclude natural (unstimulated) IVF
- **Options 2**: include natural IVF.

8.20. Members were also asked to consider the following recommendation and alternatives about age banding:

- **Recommendation**: present the statistics for just under 38s
- **Alternative one**: present it for the 'gold standard' patient
- **Alternative two**: present it for both under 38 and 38 and over
- **Alternative three**: present it for more age categories.

8.21. Members were asked to consider the IfQ Advisory Group recommendation that the IVF birth rate calculation should use only fresh IVF and ICSI cycles with the patient's own eggs. Members were also asked whether or not unstimulated (natural) IVF should be included.

8.22. **Decision:** All members agreed that the IVF birth rate calculation should use only fresh IVF and ICSI cycles with the patient's own eggs. All members agreed that unstimulated (natural) IVF should not be included in this calculation. Natural IVF is treatment with no drug stimulation at all. Mild stimulation falls into the stimulated IVF statistic. It was decided that it is important to make it clear that any reference to IVF excludes natural IVF – this being consistent with the decision to exclude egg donor IVF and PGS/PGD.

8.23. Members were asked whether they agreed with the recommendation from the IfQ Advisory Group to present, at the top of the page and in search results, the statistic for just under 38s or to consider one of the alternative approaches.

8.24. **Decision:** All members agreed that with the recommendation from the IfQ Advisory Group to present, at the top of the page and in search results, the statistic for just under 38s. There should be an explanation that this is a quality measure of clinics and not an indicator of a patient's own chances of success. All members agreed that, further down the page, the IVF birth rate should continue to be shown as 'all ages', 'under 38' and '38 and over'.

Births per egg collection time period

8.25. The Director of Strategy and Corporate Affairs advised members that a few respondents had suggested the HFEA review the time period for the births per egg collection calculation, so that it can be aligned with the time period for births per embryo transferred. The advisory group discussed the issue and recommended that the HFEA should retain the current time period of two years from the time of egg collection. They felt that their original recommendation had been made after lengthy deliberation and they could not see a compelling reason for departing from this decision.

8.26. The Director of Strategy and Corporate Affairs asked members to consider the following recommended and alternative option in relation to the time period for births per egg collection:

- **Recommended option**: advisory group recommendation: retain the two-year time period
- **Alternative option**: reduce the time period to one year to align with births per embryo transferred.

8.27. Members were asked whether they agreed with the IfQ Advisory Group recommendation to retain the two-year time period for births per egg collection.

8.28. **Decision:** All members agreed to retain the two-year time period for births per egg collection.

9. Annual review of SCAAC work

9.1. The Scientific Policy Manager gave an update of the work of the Scientific and Clinical Advances Advisory Committee (SCAAC) in 2016. The work of the committee is integral to the HFEA; we rely on the group of the experts to provide highly technical and specialist advice on advancements in the field in order to ensure the HFEA makes robust and sensible decisions.

9.2. The Scientific Policy Manager advised members that SCAAC met three times each year to consider advances in science and clinical practice, which were relevant to the Authority's work. The committee kept the HFEA up to date with a fast moving area and consisted of Authority members and external advisors.

9.3. The committee continued to include a broad range of clinical and scientific expertise in its membership, including:

- Obstetrics
- Gynaecology
- Embryology
- Andrology
- Clinical genetics
- Preimplantation genetics
- Stem cell biology
- Epigenetics.

9.4. SCAAC has a number of key functions which included:

- Horizon scanning functions
- Updates on key areas of research
- Patient information
- Policy development
- Novel processes.

9.5. The Scientific Policy Manager advised members that SCAAC carried out its horizon scanning function annually, with the aim of identifying issues that could have an impact on the field of assisted reproduction or embryo research. Issues were identified by thoroughly reviewing all

journal articles from the previous year and issues were prioritised according to criteria including the HFEA's remit, potential patient demand, technical feasibility and ethical or public interest issues.

9.6. Issues identified as high priority were incorporated into the HFEA's business plan and work plan for the Executive, SCAAC and the Authority.

9.7. The Scientific Policy Manager advised members that the annual horizon scanning international panel meeting was held, as is usual, at the annual meeting of the European Society of Human Reproduction and Embryology (ESHRE) which this year was in Helsinki, Finland. The panel discussed the HFEA's egg freezing data, noting that this was a unique data set. The panel also discussed the planned treatment add-ons work of the HFEA and provided an update on recent issues from their respective countries. This enabled the Executive to pick up on pioneering and quickly progressing areas of research to bring to SCAAC. One area that was noted as progressing significantly this year was that of in-vitro derived gametes.

9.8. Researchers were investigating whether it was possible to develop eggs and sperm in the laboratory using early germ cells, embryonic stem cells or other human cells. Eggs and sperm derived from such cells in the laboratory were called in vitro derived gametes or artificial gametes. It was not legal to use these types of gametes in treatment in the UK but they could be used for research purposes. The research was thought to be valuable in a research in terms of understanding embryo development and developmental biology.

9.9. The Head of Regulatory Policy advised members that SCAAC considered three standing items on an annual basis:

- Alternative methods to derive embryonic stem (ES) cells or embryonic-like stem (ES-like) cells
- Health outcomes in children conceived using assisted reproductive technologies
- Embryo culture media.

9.10. For some time, the committee had focussed on the first two items and, more recently the third item. However, there had also been an increasing focus on SCAAC providing significant input into patient advice, in line with the HFEA's commitment, as an organisation, to ensure that patients had access to high quality, meaningful information. An example of this was the HFEA's work on drafting new information on treatment add-ons.

9.11. The Scientific Policy Manager reminded members that one of the HFEA's key strategic aims was to improve the information about treatments that was available to patients. Media coverage in this area highlighted that there was much controversy around which add-ons clinics provided and the extra cost to the patient.

9.12. The HFEA's aim in this area was to:

- Provide clear, impartial information about certain treatment add-ons on the new website
- Introduce a 'traffic-light' system for communicating the level of evidence for each add-on.

9.13. The Executive planned to provide easy to understand information on the following topics:

- Endometrial scratching
- Time lapse imaging

- Elective freeze-all
- Embryo glue
- Assisted hatching
- Reproductive immunology
- Egg activation
- Intrauterine culture
- PGS.

9.14. This information would be regularly monitored through the HFEA's horizon scanning function and would therefore be an evolving and constantly changing area of the website.

9.15. The Scientific Policy Manager reminded members of the HFEA's plans to reinvigorate the multiple births policy. In order to do this, advice had been sought from SCAAC. In 2008, multiples births from ART was one in four. It was now about one in seven live births, with the current target being one in ten. In 2008, the vast majority of patients received double embryo transfers. However, elective single embryo transfer (eSET) was now more common, and, since 2009, multiple births had gradually decreased whilst pregnancy rates were maintained.

9.16. Following discussion, SCAAC members:

- Highlighted the potential risks of double blastocyst transfer
- Suggested further analysis could further explore cumulative data sets (taking more than one year)
- Emphasised more work on highlighting the negative impact of multiple births.

9.17. The advice from SCAAC would be fed back to the multiple births stakeholder group.

9.18. In conclusion, the Scientific Policy Manager advised members that SCAAC played a key role in ensuring that the HFEA was up-to-date with scientific advances and would also play a key role in the HFEA's focus on improving patient information. The Executive would use the committee to ensure that patients understood the evidence base for given treatments.

9.19. In 2017, in addition to the committee's standing items, SCAAC would focus on:

- New technologies in genetic testing
- Gene editing
- ICSI – best practice.

9.20. Members noted and welcomed the presentation and agreed that it would be helpful to circulate it more widely.

10. Draft business plan 2017/18 and strategic risk register

10.1. Members noted the two items and the Chair invited members to send any comments to the Head of Business Planning.

11. Any other business

11.1. The Chair confirmed that the next regular meeting would be held on 18 January at Church House Westminster, Dean's Yard, Westminster, London SW1P 3NZ. Members were asked to confirm their attendance to the Executive Assistant to the Chair and Chief Executive as soon as possible.

12. Chair's signature

I confirm this is a true and accurate record of the meeting.

Signature

Chair

Date

Introducing mitochondrial donation into clinical practice

Strategic delivery:	☒ Setting standards	☐ Increasing and informing choice	☐ Demonstrating efficiency economy and value
Details:			
Meeting	Authority		
Agenda item	3		
Paper number	HFEA (15/12/2016) 818		
Meeting date	15 December 2016		
Author	Anna Rajakumar, Policy Manager		
Output:			
For information or decision?	For Decision		
Recommendation	Agree recommendations on the introduction of mitochondrial donation into clinical practice.		
Resource implications	Minor staffing resource implications (across the Executive)		
Implementation date	December 2016		
Communication(s)	Press release, Clinic Focus and Code of Practice update		
Organisational risk	☐ Low	☐ Medium	☒ High
Annexes	Annex 1: Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update Annex 2: Amended draft mitochondrial donation Code of Practice guidance note Annex 3: Mitochondrial donation: Explanatory note for statutory approvals committee. Annex 4: Amended General Directions 0008 - Information to be submitted to the HFEA as part of the licensing process		

1. Introduction

1.1. Mitochondrial malfunction caused by mutations in mitochondrial DNA (mtDNA) is a significant cause of several serious multi-organ diseases. Until recently, many families with such inherited diseases had no effective treatment options for avoiding transmission of these diseases to offspring. However, two new techniques, maternal spindle transfer (MST) and pronuclear transfer (PNT) now offer, for the first time, the prospect of preventing such serious diseases through the use of assisted conception. This paper asks the Authority to decide whether research on MST and PNT has progressed to such a point where it would be appropriate to offer either technique in clinical practice in the UK. Whilst recent reports refer to the use of mitochondrial donation techniques in other countries, this would be the first time the techniques would be offered in a fully regulated environment.

1.2. Before considering the issues raised it is important to briefly remind ourselves of some of the history and the broad structure of the legislative scheme. After a policy process stretching back some four years, in February 2015 the UK Parliament approved The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 ('the Regulations'), making mitochondrial donation techniques (MST and PNT) to avoid serious mitochondrial disease a lawful treatment. The Regulations came into force on 29 October 2015, as did our own system for licensing clinics to use mitochondrial donation and for approving individual applications.[1]

1.3. The Regulations prescribe the requirements UK clinics must meet before they can offer this new treatment, using either MST or PNT. Decisions on whether a clinic is competent to offer mitochondrial donation will be made by the HFEA Licensing Committee. The Regulations also prescribe that such techniques can only be approved on a case-by-case basis. In other words, a clinic licensed to provide either MST or PNT must, by law, apply to the HFEA for approval of the use of either technique for each patient it wishes to treat. These patient-level decisions will be made by the HFEA's Statutory Approvals Committee (SAC). It should also be noted that the clinical use of MST or PNT for infertility purposes is not legal in the UK.

1.4. The HFEA reconvened an expert panel to review the latest evidence of safety and efficacy for the two mitochondrial donation techniques – MST and PNT. The panel first met in 2011 and met subsequently in 2013 and 2014. In these three separate reports[2] the panel recommended a number of experiments

[1] HFEA Authority paper - Regulating mitochondrial donation. (16th September 2015). Accessed at: http://www.hfea.gov.uk/9862.html

[2] The four reviews undertaken by the panel are listed below (including an addendum on polar body techniques in 2014):

- HFEA 2011 Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. Accessed at: http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF.
- Annex VIII: Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update. Accessed at: www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf.
- Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception:2014 update. Accessed at: http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf.

which it believed should be completed to achieve sufficient reassurance of safety and efficacy. The Authority therefore agreed it would only accept applications once the expert panel were satisfied that the outstanding safety and efficacy recommendations had been satisfied.

1.5. Earlier this year, two research groups published studies which showed significant progress in addressing the recommendations previously set out by the expert panel (Hyslop et al 2016; Yamada et al 2016). The expert panel was therefore reconvened in July 2016 to assess the current state of the research, with particular reference to whether the 2014 experimental recommendations had been met. A third directly relevant paper, Kang et al 2016, was also considered by the expert panel prior to its publication in November 2016. The Executive Summary of the expert panel's report is at Annex 1 of this paper[3].

1.6. This paper outlines the expert panel's recommendations and asks members to decide whether mitochondrial donation should now be made available to patients in the UK. Whilst the passing of the mitochondrial donation Regulations was a significant milestone, it is the Authority that will decide whether or not patients will be able to access these new treatments.

1.7. In view of the recommendations of the expert group, the Authority is invited to decide whether the techniques are sufficiently safe and efficacious to be used in the treatment of patients. If the Authority decides to approve the use of mitochondrial donation in clinical practice (section 2), the paper then sets out how we can implement this into our regulatory mechanisms (section 3). Lastly, the paper also outlines a number of other clinical recommendations (section 4) and embryologist competency requirements for the Authority to consider (section 5).

2. Safety and efficacy and patient selection criteria

2.1. The expert panel carried out an evidence-based scientific review[4] as an independent group of experts, liaising extensively with specialists in this area, providing a comprehensive overview of the research to date. In doing so, they came to the conclusion that **it is appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients.**

2.2. The expert panel suggests that MST and PNT should in the first instance be offered to selected patients for whom preimplantation genetic diagnosis (PGD) would be inappropriate, and likely to be unsuccessful. Like PGD undertaken for mtDNA mutations, MST or PNT can be used as a risk reduction strategy[5], in

- Addendum to the 2014 update - Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease. Accessed at: http://www.hfea.gov.uk/docs/2014-10-07_-_Polar_Body_Transfer_Review_-_Final.PDF.

[3] The scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update can be accessed at: http://www.hfea.gov.uk/docs/Fourth_scientific_review_mitochondria_2016.PDF

[4] See Annex C of the 2016 review for details relating to the methodology.

[5] Bredenoord AL, Dondorp W, Pennings G, De Die-Smulders CE, De Wert G. PGD to reduce reproductive risk: the case of mitochondrial DNA disorders. Human reproduction. 2008 Nov 1;23(11):2392-401.

those patients in whose germ line there are likely to be high levels of heteroplasmy or homoplasmy for the abnormal mtDNA (this means they have either a high proportion of abnormal mtDNA or all abonormal mtDNA). These patients would therefore be unlikely to have any suitable embryos for transfer following PGD.

2.3. Pre-treatment assessment would need to take into account the particular mutation involved, the inheritance pattern in the family, the likely clinical manifestations of disease, the efficacy of any previous treatments such as PGD, and the patient's understanding of the risks and limitations of what is being offered.

2.4. In short, the expert panel believes that the most recent research it has seen suggests that this treatment is sufficiently safe and efficacious to be offered to selected patients – those for whom PGD is inappropriate and likely to be unsuccessful. It should be noted that this is a more restricted group of patients than the regulations allow for. If the Authority approves the use of these techniques today and they subsequently prove to be safe when used in these patients (ie, there is no significant reversion to the carried-over mtDNA haplotype), the Authority can review the decision and could consider extending the application of the techniques to other patients in future. The reasons for the expert panel's view can be summarized as follows.

2.5. Recent research on embryonic stems (ES) cell lines derived from embryos generated using these techniques indicates that, in a minority of cases, mtDNA carried over with the maternal spindle or parental pronuclei can come to predominate after extended periods of culture *in vitro*. Whilst it is difficult to interpret the significance of these data, since ES cells are far from a perfect model of postimplantation development *in vivo* and there is no established mechanism to account for the observed data, they raise the possibility that an embryo/fetus generated by MST or PNT might develop high levels of abnormal mitochondria carried over in the process. This carries the potential risk, albeit small, that a child might be born with a mitochondrial disease following use of MST/PNT. It is with this evidence in mind that the expert panel recommends the cautious, limited implementation of MST and PNT in a clinical setting. It suggests that MST and PNT should, in the first instance, be offered to patients for whom preimplantation genetic diagnosis (PGD) would be inappropriate because it is likely to result in an affected child. For these patients, MST/PNT offer a greater chance of success in preventing mitochondrial disease in their genetically related children.

2.6. Whilst it is difficult to summarise a complex set of clinical considerations, PGD is a suitable treatment option for patients with low levels of abnormal mtDNA in their eggs (also known as low level heteroplasmy). However, it is not a suitable option for those whose eggs have a high degree of heteroplasmy or those whose eggs areas homoplasmic. It is this group of patients who the panel recommend should be eligible for MST or PNT treatments.

2.7. The expert panel acknowledges the potential risk of elevated abnormal mtDNA in a small proportion of individuals born following MST or PNT. Therefore, they believe that it would currently be inappropriate to offer these treatments to patients who are likely to have an unaffected child using PGD and embryo selection. However, the expert panel thinks that MST and PNT would be appropriate for those wishing to have their own genetically related child, but whose prospective offspring are at high risk of severe or lethal mitochondrial disease due to high levels of abnormal mtDNA in mother's eggs, based on predicted homoplasmy or high levels of heteroplasmy. For such patients PGD would be unlikely to be successful, therefore MST and PNT represent the only viable risk reduction strategy for the avoidance of mitochondrial disease. Currently, it is known that there will be patients awaiting treatment who belong to this group.

2.8. In reaching this view it is important to note that, with further research and clinical data, our understanding of the risk of pathogenic levels of abnormal mtDNA arising in embryos/fetuses following MST or PNT is likely to change. It may be the case that such a phenomenon – referred to as 'reversion' in the report – is not observed after clinical use of these techniques. If it turns out to be a clinical concern, then future refinements of the techniques might eliminate it. However, unless and until the appropriate evidence appears, the panel recommends a cautious approach. It also recommends that patients who become pregnant following MST/PNT should be offered prenatal testing.

2.9. The Authority is therefore asked to consider whether it can now support the use of these techniques in clinical treatment. As the panel discusses in its report, all novel treatments pose essentially the same medical question: when is a treatment safe to offer? In reaching a view it is important to recognise that research can never answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time in the clinic. It can only serve to reduce the risk, for example by highlighting areas that need close attention. Patients must understand those risks and accept them before proceeding.

2.10. Maternal spindle transfer (MST) and pronuclear transfer (PNT) will fall under the HFEA's licensable activities of "processing gametes" and "processing embryos/creating embryos".

Recommendations

2.11. Today the Authority is asked:

- In light of recent research and the recommendations in the expert panel report, to consider the safety and efficacy of the techniques and decide whether research on MST and/or PNT has progressed to such a point where it would be appropriate to allow either technique in clinical practice.

Further to this, if the Authority agree the above, they are asked to consider:

- If these techniques should initially be offered only to a narrower cohort of patients, who meet specific criteria identified in the expert panel's report?

3. Implementing the patient selection criteria

3.1. If the Authority decides to approve the use of mitochondrial donation in clinical practice for a specified group of patients, we will need to make some changes to our guidance and agreed scheme for approving individual patient applications.

3.2. The Regulations (and corresponding licence conditions) specify that any clinic licenced to perform MST and/or PNT must also apply to the HFEA for approval to treat each and every patient. As noted above, these applications will be considered by SAC. If granted, the approval will be for the treatment to be applied for the particular patient, in the circumstances described in the Regulations. Two decision trees for SAC reflecting the Regulations and an Explanatory Note have been developed to aid its decision making and were noted by the Authority in October 2015. To support an application, a clinic will need to submit patient-specific information to enable an assessment of 'significant risk' and 'seriousness' to be made.

3.3. Given the patient criteria identified by the expert panel, we propose introducing a requirement in our Code of Practice guidance, that mitochondrial donation can only be offered to patients for whom PGD is not appropriate. Further to this, an additional requirement is proposed in General Direction 0008 and the Code of Practice Guidance will be reflected in the Guidance Note for use by SAC. These additions will support the explicit narrowing of the scope to those for whom PGD is not clinically prescribed or recommended. The additional wording provides guidance around the threshold for such patients i.e. in what circumstances we would say it was reasonable to say that PGD is not suitable, but ultimately this will be a clinical decision.

3.4. There will also be a need for SAC to assess whether the patient criteria are met. To this end, we propose amending the patient application form to explicitly require the treating clinician to make a formal assessment of why PGD may be inappropriate or likely to be unsuccessful for the specific patient. The Committee will be provided with a peer review assessment of this rationale to aid their decision, ensure that this consideration has been undertaken and that they can proceed through the decision tree. SAC would also be able to consult with an appropriate expert further, should they need to.

3.5. Given the novelty of this technique, and the recommendations of the panel, we feel that this approach strikes the right balance of allowing these techniques to be used in treatment given they are lawful in the UK as of the introduction of the Regulations, yet safeguarding patients for whom the use of the MST and PNT might be more likely to result in the birth of a child affected by mitochondrial disease than were they to use alternative treatment options.

3.6. If the Authority agree this approach, decision trees and accompanying aids for decision making will need to be reviewed and amended. These include the decision trees and explanatory note for the Licence Committee and the

Statutory Approvals Committee. The Authority is invited to delegate the approval of these amendments to the appropriate committees. Changes to the guidance note and General Direction will be published as part of the Code of Practice April 2017 update.

Recommendation

3.7. If the Authority is satisfied that mitochondrial donation can be used in clinical practice for a specified cohort of patients, members are asked to:

- agree the proposed approach for considering patient selection as set out in section 3.
- agree changes to the Code of Practice Guidance Note 33 on Mitochondrial donation (highlighted in yellow at paragraphs 33.6 and 33.7(a), Annex 2) and referenced explanatory note designed to aid the Statutory Approvals Committee (Annex 3)
- agree changes to paragraph 7 General Direction 0008 (highlighted in yellow at Annex 4) and
- agree that the amendments of any relevant decision trees and patient application form are delegated to the appropriate Committees.

4. Other clinical recommendations

4.1. The expert panel was also of the view that particular precautions should be made for specific areas of practice, including haplogroup matching, follow-up reporting, and prenatal testing - the first two of which were already incorporated into our regulatory framework in October 2015. The panel's thinking can be summarised as follows.

Haplogroup matching

4.2. The panel continues to recommend that consideration is given to mitochondrial DNA haplotypes[6] or haplogroup[7] matching[8] as a precautionary step in selecting donors. This is a complex topic, with some potential risks or benefits associated with choosing a specific donor mitochondrial DNA haplotype/haplogroup. At present, the panel believes any risks associated with a mtDNA - nuclear DNA (mito-nuclear) mismatch are very low, but it recommends that if these techniques are used clinically, the latest evidence regarding how mtDNA haplogroups/haplotypes affect mito-nuclear interactions should be considered in order to inform the donor selection process. The panel also noted that in assessing this risk the treating clinician should be mindful of parallels with potential mito-nuclear mismatches in natural reproduction.

[6] A group of genes inherited as a single unit from a parent.
[7] A haplogroup is a term used to define a group of similar haplotypes. Mitochondria from separate human lineages can be classified according to similarities or differences in their DNA sequence into many different haplogroups. The more evolutionary distant the separation of two maternal lineages, the greater the differences between mitochondrial haplogroups.
[8] see section 5 of the Report, on clinical recommendations.

4.3. This requires no further action from the Authority as this was incorporated into the Code of Practice guidance agreed in 2015, where it states:

"Centres should ensure that they keep up to date with relevant literature and professional guidance, such as on refinements to the techniques to improve their efficacy in treatment. Centres should also keep up to date with emerging research relevant to mitochondria haplogroups/haplotype matching and consider matching the haplogroups/haplotypes of donors with recipients where possible."

Follow-up reporting

4.4. The panel have long been of the view that there should ideally be follow-up reporting for all those who are born as a result of mitochondrial donation. As stated in the Authority paper in 2015, clinics will be required to have in place a documented process for monitoring children born following mitochondrial donation, where patients have given their consent to participating in follow-up. In addition, clinics should submit an annual report on patient uptake of follow-up studies and non-patient-specific information on the outcomes.

4.5. This requires no further action from the Authority as these requirements are outlined in General Directions 0005 and the mitochondrial donation follow-up information sheet that must be submitted.

Prenatal testing

4.6. The panel discussed ways of predicting the potential for disease presentation during the pregnancy. Prenatal testing by amniocentesis or fetal blood sampling was suggested; however, neither sample type would necessarily be representative of all tissues. Amniocentesis would be preferable, as the cell types present in amniotic fluid come from embryonic lineages whereas fetal blood cells are entirely mesodermal[9] in origin, and therefore may not be as informative. In addition, the risk of miscarriage following the procedure is extremely low for amniocentesis. It would be important to counsel patients on the miscarriage risk associated with these techniques. The panel suggested that prenatal testing should be offered to all women undergoing treatment, but recognised that it is unlikely that all women will accept this offer and they are of course under no obligation to do so.

4.7. When using these techniques (MST or PNT) patients would have to be counselled as to the risk that they would be taking because of the theoretical risk of amplification of carried-over mtDNA. To reflect this recommendation, we have proposed minor amendments to the mitochondrial donation Code of Practice guidance note at Annex 2 (see 33.13 b, highlighted in yellow).

[9] Mesodermal cells are located in the middle layer of cells or tissues of an embryo; these cells form components such as connective tissue, bone, cartilage, muscle, blood and blood vessels.

Recommendation

4.8. The Authority is asked to agree changes to the Code of Practice Guidance Note 33 on Mitochondrial donation (paragraph 33.13(b)) at Annex 2) recommending prenatal testing to all those who undergo mitochondrial donation.

5. Assessing embryologists' competency

5.1. Due to the complexity and skill set involved in conducting these techniques, it was agreed by Authority that not only should the PR be required to demonstrate that their MST/PNT embryologists have experience of performing the techniques on human gametes and embryos, but the PR must also demonstrate that the individual can perform the techniques in line with a pre-determined set of performance indicators. The Licence Committee will assess embryologist competency as part of the clinic's application to vary a licence for mitochondrial donation techniques. This is set out in General Direction 0008 (see annex 4, 7.b.ii and iii).

5.2. In October 2015, Authority agreed that the performance indicators should be based on embryo survival rates, blastocyst development, and rate of carryover of mtDNA. For example, the ability of the embryologist to create embryos following MST or PNT with a low rate of carryover of mtDNA may directly affect whether or not any child is born free from mitochondrial disease. The Authority agreed to postpone the decision on the specific thresholds for these performance indicators until it had taken into account the advice of an expert panel following consideration of the latest research.

5.3. Following advice from the panel, and consideration of the recently published work by Hyslop et al. (2016), we recommend the following thresholds be applied:

- **Embryo survival rates** - must exceed 70%. (Hyslop et al have shown a 92% survival rate using early PNT so this is achievable).
- **Blastocyst development rates** - which must be no less than 50% of that observed in the control embryos at day 5. Where possible, controls should be age-matched to the karyoplast donor.
- **Rates of carryover of mtDNA** - should not on average exceed 2% and no greater than 10% per embryo. (Hyslop et al - After optimization, mtDNA carryover was reduced to <2% in the majority (79%) of PNT blastocysts so this is achievable) [10]

[10] Autologous transfers may be used in this assessment due to supply of material required for this aspect of training. The assessment of mtDNA carryover will inevitably require heterologous transfers and carryover data from cleavage stage embryos as well as blastocysts could be included. In the case of cleavage stage embryos, it would be informative to get a measure of variation between blastomeres where possible.

5.4. These have been reviewed by the panel who agree that they are appropriate benchmarks for conducting mitochondrial donation techniques, based on current published work. However, it was noted that these serve as a minimum requirement and with further refinement of the techniques these parameters may also be refined. For this reason, the panel note that they will need to be reviewed, as the techniques develop.

5.5. In order to facilitate the assessment of competence we would expect clinics to make clear and demonstrate how they have determined the reliability and quality of the assessment process for judging competency. This requires that they are familiar with the literature on assessing the quality of MST/PNT-derived human embryos. The clinic should decide on the methods of assessment and be able to provide a justification for its selection e.g. if they were to carry out autologous transfers to assess embryo manipulation skills. They should ensure assessments are in line with current professional standards for existing embryology competencies. We recommend that they submit full data, including the raw data figures relating to these assessments and a justification for the methods used as well as established methods that have been omitted.

Recommendation

5.6. The Authority is asked to approve the proposed thresholds for the key performance indicators, and that these will be added to paragraph 7 of General Directions 0008. The key performance indicators will be reviewed periodically by the HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) to ensure they best reflect the minimum requirements expected for practitioners of these techniques

Annex 1: Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update

Executive summary

The panel continues to see clinical value in maternal spindle transfer (MST) and pronuclear transfer (PNT) to mitigate or prevent the inheritance of mitochondrial disease. It recommends that, in specific circumstances, MST and PNT are cautiously adopted in clinical practice where inheritance of the disease is likely to cause death or serious disease and where there are no acceptable alternatives. The report describes the reasoning behind this decision and provides guidance regarding circumstances in which MST and PNT could be considered.

In February 2015 the UK Parliament approved regulations to permit the use of maternal spindle transfer (MST) and pronuclear transfer (PNT), collectively 'mitochondrial donation', to avoid serious mitochondrial disease. The regulations, which came into force on 29 October 2015, enable licensed fertility clinics in the UK to apply to the Human Fertilisation and Embryology Authority (HFEA) for a licence to perform mitochondrial donation treatments.

Although the regulations make it lawful to use mitochondrial donation in the clinic, the HFEA must be satisfied that the techniques involved are sufficiently safe and efficacious before any clinic can apply for a licence to offer mitochondrial donation. This report to the HFEA considers the scientific data relevant to an assessment of the safety and efficacy of MST and PNT and makes recommendations on whether either technique should be introduced into clinical practice. The final decision will rest with the HFEA board.

The process leading to a change in the law in the UK has a long history. The Human Fertilisation and Embryology (HFE) Act 1990 was amended in 2008 to allow for regulations to be passed to permit techniques that prevent the transmission of serious mitochondrial disease due to deleterious mutations in mitochondrial DNA (mtDNA), in recognition of research that had taken place over several years. In 2011, the Government asked the HFEA to examine the safety and efficacy of these techniques and in response the HFEA established a scientific panel, with broad-ranging scientific and clinical expertise, to examine the evidence[11]. Two further reviews were carried out in 2013[12] and 2014[13,14]. In addition, the HFEA was asked in January 2012 to carry out a public dialogue[15] on the social and ethical impact of making these techniques available to patients.

MST and PNT have the potential to avoid transmitting serious mitochondrial disease from mother to child. In its clinical application, MST involves transferring the nuclear DNA from an oocyte with abnormal

[11] HFEA 2011 Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. Accessed at: http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF.
[12] Annex VIII: Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update. Accessed at: www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf.
[13] Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update. Accessed at: http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf.
[14] Addendum to the 2014 update - Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease. Accessed at: http://www.hfea.gov.uk/docs/2014-10-07_-_Polar_Body_Transfer_Review_-_Final.PDF.
[15] HFEA Public Dialogue: Medical frontiers: debating mitochondria replacement. Accessed at: http://www.hfea.gov.uk/9359.html.

mitochondria and placing it into an oocyte with healthy mitochondria. PNT involves transferring the pronuclei from an embryo that has abnormal mitochondria and placing them into an embryo that has healthy mitochondria.

Reconvening the expert panel in 2016

This fourth scientific review of the safety and efficacy of mitochondrial donation follows a similar structure to the earlier reviews. As before, the aim is to provide a comprehensive overview of the scientific issues raised by mitochondrial donation and an assessment of the current state of the research. The panel was tasked with reviewing the latest evidence of safety and efficacy for the two mitochondrial donation techniques – MST and PNT, with particular reference as to whether the recommendations outlined in the 2014 scientific report have been met. However, whereas the previous reports were commissioned by the Government to inform a decision about whether to change the law, the context for this report is different: Parliament has changed the law and this report has been commissioned by the HFEA as part of an internal assessment of whether mitochondrial donation is ready for clinical practice.

In deciding to change the law Parliament has always been clear that neither MST nor PNT should be introduced into clinical practice until they were judged sufficiently safe. Before the first application for licensing can be received, the outstanding safety and efficacy experiments recommended in the 2014 scientific mitochondria review (see Box 1) need to be considered by the panel and then by the HFEA[3].

Box 1: The conclusions and recommendations listed in the 2014 scientific review were as follows:

- MST using human oocytes that are then fertilised (not [artificially] activated): It is still important for some follow-up experiments to be carried out, notably to improve efficiency, if possible, and further corroborative experiments would be valuable.
- Experiments comparing PNT using normally-fertilised human oocytes with normal ICSI fertilised human oocytes: The method continues to be developed and appears promising. Further work will be published in the near future and those results will need assessing before they can be incorporated into recommendations.
- PNT in a non-human primate model, with the demonstration that the offspring derived are normal, is not critical or mandatory.
- MST and PNT should both be explored and that, as yet, it did not consider one technique to be preferable to the other.
- Consideration should be given to mtDNA haplogroup matching (see section 3.7.20 of the 2014 report) as a precautionary step in the process of selecting donors.

This fourth review was commissioned in response to recent publications reporting significant progress in addressing the recommendations above[16,17,18]. Whilst these publications were the trigger, the review also

[16] Hyslop LA, Blakeley P, Craven L, Richardson J, Fogarty NM, Fragouli E, Lamb M, Wamaitha SE, Prathalingam N, Zhang Q, O'Keefe H. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature. 2016 Jun 8 534: 383-386.
Hyslop LA, Blakeley P, Craven L, Richardson J, Fogarty NM, Fragouli E, Lamb M, Wamaitha SE, Prathalingam N, Zhang Q, O'Keefe H. Corrigendum: Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature. 2016 Jul 27 538, 542.
[17] Yamada M, Emmanuele V, Sanchez-Quintero MJ, Sun B, Lallos G, Paull D, Zimmer M, Pagett S, Prosser RW, Sauer MV, Hirano M. Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes. Cell stem cell. 2016 Jun 2;18(6):749-54.

took into account other relevant studies conducted since the previous review, in order to consider whether the techniques are now ready to be used in clinical practice and, if so, what clinical issues should be taken into account.

This review builds on the findings of the previous three reviews (including the addendum to the third review, exploring polar body transfer techniques), and is not written as a stand-alone summary of current scientific knowledge. For full details of areas reviewed, please refer to the previous reports. An updated timeline highlighting the key developments in the consideration of mitochondrial donation in the UK is at Annex B.

As noted above, the science relevant to the safety and efficacy of mitochondrial donation has been considered in detail by this panel a number of times since 2011. This has allowed the direction of travel to be assessed in addition to the current state of the methodology. On each occasion, the panel has reviewed evidence from experts directly in the field, both in the UK and abroad, and taken account of unpublished as well as published data and opinions. The panel's reports to Government in 2011, 2013, 2014, and now this one to the HFEA in 2016, reflect this composite evidence.

In 2016 the panel considered submissions received as a result of the call for evidence and reviewed new literature in this area, as set out in Annex C. The panel met on five occasions to allow some of those who had submitted evidence to present their work and take part in a roundtable discussion. These individuals or groups had been selected because of the direct relevance of their work to the methods being considered. The panel was therefore able to consult with a number of relevant research groups and additional experts in order to inform their conclusions on the progress of current research.

Progress on essential experiments and clinical data

The panel agreed that good progress had been made in experiments recommended in previous reviews and that additional clinical data should also be considered:

- MST using human oocytes that are then fertilised (not artificially activated): There has been significant progress in this area of research from the group of Professor Shoukrat Mitalipov and his collaborators[8] demonstrating an increase in the efficiency of these methods using oocytes carrying pathogenic mtDNA mutations as well as from controls. Carryover of mtDNA was below 1% in MST blastocysts (Kang et al 2016). Whilst Yamada et al. (2016) used artificially activated rather than fertilised oocytes following MST, they report that the process of oxidative phosphorylation (OXPHOS) was normal in differentiated cell types from embryonic stem (ES) cells derived from MST embryos, despite using mtDNA combinations from distinct haplogroups. Similar results were also obtained by Kang et al (2016). Yamada et al. (2016) further corroborated these conclusions by studying ES cells derived from somatic cell nuclear transfer (SCNT) blastocysts.
- Experiments comparing PNT using normally-fertilised human oocytes with normal ICSI-fertilised human oocytes: Hyslop et al., (2016) demonstrated that PNT undertaken shortly after *in vitro* fertilisation resulted in the generation of embryos that were competent to develop to the blastocyst stage. Carryover of mtDNA was shown to be less than 2% and detailed characterisation of these blastocysts indicated no detectable increase in the incidence of aneuploidy or disruption to normal profiles of gene expression in isolated cells.

[18] Kang E, Wu J, Gutierrez NM, Koski A, Tippner-Hedges R, Agaronyan K, Platero-Luengo A, Martinez-Redondo P, Ma H, Lee Y, Hayama T, Van Dyken C, Wang X, Luo S, Ahmed R, Li Y, Ji D, Kayali R, Cinnioglu C, Olson S, Jensen J, Battaglia D, Lee D, Wu D, Huang T, Wolf DP, Temiakov D, Izpisua Belmonte JC, Amato P, Mitalipov S. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature 2016 DOI: 10.1038/nature20592

- The use of PNT to establish a pregnancy for a 30-year old nulligravid woman with unexplained infertility was published by Zhang et al. (2016a)[19]. After transfer of five embryos, a triplet pregnancy resulted that was surgically reduced to twins. The two remaining fetuses survived only to mid-gestation, probably due to the obstetric complications of the multiple pregnancy, rather than the PNT itself. Neither fetus had detectable levels of the maternal (karyoplast-derived) mtDNA haplotype.
- A recent abstract, entitled "First live birth using human oocytes reconstituted by spindle nuclear transfer for mitochondrial DNA mutation causing Leigh syndrome" by Zhang et al. was published online in the programme for the October 2016 American Society for Reproductive Medicine (ASRM) meeting. The baby is reported to be doing well and was found to have low levels of mutated mtDNA in several tissues. Some details of the MST methods used are given by the authors in another abstract in the same programme[20]. However, the full details of the methods and treatment cycle have not yet been published.

The fate of mtDNA carried over after MST and PNT

In previous reviews the panel recommended experiments on mtDNA behaviour in human embryonic stem (ES) cells (and their differentiated derivatives) derived from blastocysts generated by MST and PNT. Although such experiments do not accurately model the developing fetus, they do permit an analysis of the mtDNA carried over in the karyoplast in conditions where mtDNA replication occurs. There have been three studies[6,7,8], all of which report that in the majority of ES cell lines the karyoplast-derived mtDNA haplotype remained at a similarly low level as in the blastocysts from which the cells were derived, even after many passages, or was lost altogether.

However, each study also reported exceptions to this, in which the karyoplast-derived mtDNA haplotype increased in proportion to that of the cytoplast (one out of eight in Yamada et al., 2016; one out of five in Hyslop et al., 2016; and three out of 18 in Kang et al. (2016)). This "reversion"[21] was also seen in two out of 12 ES cell lines derived after SCNT by Yamada et al. (2016) and in one out of eight such lines described in Kang et al. (2016). Whilst the degree of reversion was variable and seemed stochastic when subclones of the ES cells were analysed, it could approach 100%. Data indicate that reversion may also occur in cells differentiating from ES cells[7,8], suggesting that it is not an issue specific to ES cells maintained in a pluripotent state.

Moreover, reversion can occur with normal or mutant mtDNA. Therefore, despite the findings of Zhang et al. (2016a and b), the panel could not rule out the possibility of reversion occurring in clinical application of these techniques. These experiments (Yamada et al., 2016; Hyslop et al., 2016; Kang et al., 2016), and their possible significance, are considered in detail in sections 3 and 4. Ideally, it would be possible to avoid any chance of reversion, an eventuality which may depend on understanding the underlying cause. Some possibilities are discussed in section seven.

MST or PNT: is there a preferred technique?

[19] Zhang J, Zhuang G, Zeng Y, Grifo J, Acosta C, Shu Y, Liu H. Pregnancy derived from human zygote pronuclear transfer in a patient who had arrested embryos after IVF. Reproductive BioMedicine Online. 2016a Oct 31;33(4):529-33.
[20] Zhang J, Liu H, Luo S, Chavez-Badiola A, Liu Z, Munne S, Konstantinidis M, Wells D, Huang T. First live birth using human oocytes reconstituted by spindle nuclear transfer for mitochondrial DNA mutation causing Leigh syndrome. Fertility and Sterility. 2016b Sep 1;106(3):e375-6.
Liu H, Lu Z, Luo S, Chavez-Badiola A, Blazek J, Munne S, Huang T, Zhang J. In vitro fertilization and development of human oocytes reconstituted by spindle nuclear transfer to replace mutated mitochondrial DNA. Fertility and Sterility. 2016 Sep 1;106(3):e21.
[21] Different authors have used different terms to describe this phenomenon. In Kang et al. (2016) this is described as "reversion" because the predominant mitochondrial DNA haplotype found is that of the karyoplast. In Yamada et al. (2016) this phenomenon is termed "genetic instability" and in Hyslop et al. (2016) "genetic drift".

The panel continues to note that available data do not indicate whether one technique, MST or PNT, is preferable to the other at this stage and recommends that both should be considered. However, it notes that PNT is currently more refined within the UK. The panel also reiterates its opinion that polar body transfer (PBT) techniques, discussed in the addendum to the 2014 report[4], showed great promise as a means to minimise mtDNA carryover and avoid mitochondrial disease, but notes that current regulations and UK legislation do not permit this technique.

Recommendations

The key recommendations are conditional on a number of considerations, including a requirement for appropriate levels of skill being demonstrated by named practitioners within a named clinic, and relevant key performance indicators being met, parameters that will be assessed by the HFEA.

From a medical point of view, all novel treatments pose essentially the same question: when is a treatment sufficiently safe to offer to patients? Research cannot answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time. It can only serve to reduce the risk; in this case of a child being born with symptomatic mitochondrial genetic disease, but with caveats concerning for whom this type of risk reduction strategy might be suitable and highlighting areas that need close attention. Patients must understand and accept the potential limitations of any proposed treatment, and possible risks, before proceeding. With this in mind, **the panel recommends that it is appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients.**

In coming to this decision, the panel makes some key recommendations for using these techniques in clinical practice.

Patient selection

The panel suggests that MST and PNT should in the first instance be offered to selected patients for whom preimplantation genetic diagnosis (PGD) would be inappropriate, or unlikely to succeed. Like PGD undertaken for mtDNA mutations, MST or PNT can be used as a risk reduction strategy[22], but initially only in those patients in whose germ line there are likely to be high levels of heteroplasmy or homoplasmy for the abnormal (pathogenic) mtDNA, and who are thus unlikely to have any suitable embryos for transfer.

Pre-treatment assessment would need to take into account the particular mutation involved, the inheritance pattern in the family, the likely clinical manifestations of disease, the efficacy of any previous treatments such as PGD, and the patient's understanding of the risks and limitations of what is being offered. If the techniques prove to be safe when used in these patients, including the absence of any significant reversion to the carried-over mtDNA haplotype, their application could be extended to other patients.

Prenatal testing and follow-up

The panel advises that (i) all patients should be offered prenatal testing if they become pregnant following MST or PNT treatment, and (ii) centres offering MST or PNT should encourage patients and their offspring to take part in long-term follow-up.

Haplogroup matching

[22] Bredenoord AL, Dondorp W, Pennings G, De Die-Smulders CE, De Wert G. PGD to reduce reproductive risk: the case of mitochondrial DNA disorders. Human reproduction. 2008 Nov 1;23(11):2392-401.

The panel continues to recommend that consideration is given to mtDNA haplogroup[23] matching as a precautionary step in the process of selecting donors. As highlighted in the 2014 report, this is a complex topic, with some potential risks or benefits associated with choosing a specific donor mtDNA haplogroup/haplotype donor. At present, the panel believes any risks associated with a mtDNA-nuclear DNA mismatch remain theoretical; the recent studies examining embryonic cells and stem cells generated from MST- and PNT-derived human embryos reported no evidence of any complications or compromise of mitochondrial function arising from unmatched mtDNA haplogroups (see section 4.14 – 4.20). However, the panel recommends that when these techniques are used clinically, the latest evidence regarding how mtDNA haplotypes affect mitochondrial-nuclear (mito-nuclear) interactions, including replicative behaviour of mtDNA, should be considered in order to inform the donor selection process. Such evidence might even indicate the selection of a specific, unmatched donor in any given case.

Whatever decision is made, the panel recommends that haplotype information on the recipient and the donor is recorded. The panel also noted that in assessing this risk the treating clinician should be mindful of parallels with potential mito-nuclear mismatch in natural reproduction. Evidence for any effects associated with particular combinations of mtDNA and specific nuclear alleles in natural reproduction, perhaps together with any influence of environment, may come from large-scale genome studies linking DNA sequence with health outcomes[24,25].

Further research

The panel also highlights some promising areas for continuing research, particularly the exploration of methods to further reduce or eliminate mtDNA carryover, through refinements of the techniques, and possible development of new techniques, as discussed above. Furthermore, the panel concludes that it will be important to decide whether reversion towards karyoplast-derived mtDNA in some ES cell lines derived from embryos following MST or PNT is clinically relevant and if so, what underlying mechanisms are responsible. Further research possibilities are discussed in section 7.

[23] A haplogroup is a term used to define a group of similar haplotypes. Mitochondria from separate human lineages can be classified according to similarities or differences in their DNA sequence into many different haplogroups. The more evolutionary distant the separation of two maternal lineages, the greater the differences between mitochondrial haplogroups.
[24] Horikoshi M, Beaumont RN, Day FR, Warrington NM, Kooijman MN, Fernandez-Tajes J, Feenstra B, van Zuydam NR, Gaulton KJ, Grarup N, Bradfield JP. Genome-wide associations for birth weight and correlations with adult disease. Nature. 2016 Oct 13;538(7624):248-52.
[25] Johnson SC, Gonzalez B, Zhang Q, Milholland B, Zhang Z, Suh Y. Network analysis of mitonuclear GWAS reveals functional networks and tissue expression profiles of disease-associated genes. Human Genetics. 2016 Oct 4:1-1.

Annex 2: Draft amended mitochondrial donation Code of Practice guidance note

33. Mitochondrial donation

Version 1.0

On this page:

Mandatory requirements

Human Fertilisation and Embryology (HFE) Act 1990 (as amended)

In cases where an egg or embryo has been created following mitochondrial donation, the following provisions of the HFE Act 1990 should be read so that they are modified as set out below:

Modification of section 31ZA: Request for information as to genetic parentage or mitochondrial donors etc,

(1) A person who has attained the age of 16 ("the applicant") may by notice to the Authority require the Authority to comply with a request under subsection (2) or (2A).

(2) The applicant may request the Authority to give the applicant notice stating whether or not the information contained in the register shows that a person (“the donor”) other than a parent of the applicant would or might, but for the relevant statutory provisions, be the parent of the applicant, and if it does show that—

(a) giving the applicant so much of that information as relates to the donor as the Authority is required by regulations to give (but no other information), or

(b) stating whether or not that information shows that there are other persons of whom the donor is not the parent but would or might, but for the relevant statutory provisions, be the parent and if so—

(i) the number of those other persons,

(ii) the sex of each of them, and

(iii) the year of birth of each of them.

(2A) The applicant may request the Authority to give the applicant notice stating whether or not the information contained in the register shows that a person is the applicant’s mitochondrial donor, and if it does show that, giving the applicant the following information contained in the register—

(a) the screening tests carried out on the mitochondrial donor and information on that donor’s personal and family medical history,

(b) matters contained in any description of the mitochondrial donor as a person which that donor has provided, and

(c) any additional matter which the mitochondrial donor has provided with the intention that it be made available to a person who requests information under this section, but not giving any information which may identify the mitochondrial donor or any person who was or may have been born in consequence of treatment services using genetic material from the applicant’s mitochondrial donor, by itself or in combination with any other information which is in, or is likely to come into, the possession of the applicant.

(3) The Authority shall comply with a request under subsection (2) if—

(a) the information contained in the register shows that the applicant is a relevant individual, and

(b) the applicant has been given a suitable opportunity to receive proper counselling about the implications of compliance with the request.

(3A) The Authority must comply with a request under subsection (2A) if—

(a) the information contained in the register shows that the applicant is a mitochondrial donor-conceived person, and

(b) the applicant has been given a suitable opportunity to receive proper counselling about the implications of compliance with the request.

(4) Where a request is made under subsection (2)(a) and the applicant has not attained the age of 18 when the applicant gives notice to the Authority under subsection (1), regulations cannot require the Authority to give the applicant any information which identifies the donor.

(5) Regulations under subsection (2)(a) cannot require the Authority to give any information as to the identity of a person whose gametes have been used or from whom an embryo has been taken if a person to whom a licence applied was provided with the information at a time when the Authority could not have been required to give information of the kind in question.

(6) The Authority need not comply with a request made under subsection (2)(b) by any applicant if it considers that special circumstances exist which increase the likelihood that compliance with the request would enable the applicant—

(a) to identify the donor, in a case where the Authority is not required by regulations under subsection (2)(a) to give the applicant information which identifies the donor, or

(b) to identify any person about whom information is given under subsection (2)(b).

(7) In this section—

"relevant individual" has the same meaning as in section 31;

"the relevant statutory provisions" means sections 27 to 29 of this Act and sections 33 to 47 of the Human Fertilisation and Embryology Act 2008.

(8) In this section and sections 31ZB to 31ZE—

"mitochondrial donor-conceived person" means a person who was or may have been born in consequence of treatment services using—

(a) an egg which is a permitted egg for the purposes of section 3(2) by virtue of regulations under section 3ZA(5), or

(b) an embryo which is a permitted embryo for those purposes by virtue of such regulations;

the "mitochondrial donor" in respect of a person who was or may have been born in consequence of treatment services using such a permitted egg or such a permitted embryo is the person whose mitochondrial DNA (but not nuclear DNA) was used to create that egg or embryo.

Modification of section 31ZD: Provision to donor of information about resulting children

(1) This section applies where a person ("the donor") has consented under Schedule 3 (whether before or after the coming into force of this section) to—

(a) the use of the donor's gametes, or an embryo the creation of which was brought about using the donor's gametes, for the purposes of treatment services provided under a licence, or

(b) the use of the donor's gametes for the purposes of non-medical fertility services provided under a licence.

(2) In subsection (1)—

(a) "treatment services" do not include treatment services provided to the donor, or to the donor and another person together, and

(b) "non-medical fertility services" do not include any services involving partner-donated sperm.

(3) The donor may by notice request the appropriate person to give the donor notice stating—

(a) the number of persons of whom the donor is not a parent but would or might, but for the relevant statutory provisions, be a parent by virtue of the use of the gametes or embryos to which the consent relates,

(ab) the number of persons in respect of whom the donor is a mitochondrial donor,

(b) the sex of each of those persons, and

(c) the year of birth of each of those persons.

(4) Subject to subsections (5) to (7), the appropriate person shall notify the donor whether the appropriate person holds the information mentioned in subsection (3) and, if the appropriate person does so, shall comply with the request.

(5) The appropriate person need not comply with a request under subsection (3) if the appropriate person considers that special circumstances exist which increase the likelihood that compliance with the request would enable the donor to identify the persons falling within paragraphs (a) to (c) of subsection (3).

(6) In the case of a donor who consented as described in subsection (1)(a), the Authority need not comply with a request made to it under subsection (3) where the person who held the licence referred to in subsection (1)(a) continues to hold a licence under paragraph 1 of Schedule 2, unless the donor has previously made a request under subsection (3) to the person responsible and the person responsible—

(a) has notified the donor that the information concerned is not held, or

(b) has failed to comply with the request within a reasonable period.

(7) In the case of a donor who consented as described in subsection (1)(b), the Authority need not comply with a request made to it under subsection (3) where the person who held the licence referred to in subsection (1)(b) continues to hold a licence under paragraph 1A of Schedule 2, unless the donor has previously made a request under subsection (3) to the person responsible and the person responsible—

(a) has notified the donor that the information concerned is not held, or

(b) has failed to comply with the request within a reasonable period.

(8) In this section “the appropriate person” means—

(a) in the case of a donor who consented as described in paragraph (a) of subsection (1)—

(i) where the person who held the licence referred to in that paragraph continues to hold a licence under paragraph 1 of Schedule 2, the person responsible, or

(ii) the Authority, and

(b) in the case of a donor who consented as described in paragraph (b) of subsection (1)—

(i) where the person who held the licence referred to in that paragraph continues to hold a licence under paragraph 1A of Schedule 2, the person responsible, or

(ii) the Authority.

(9) In this section "the relevant statutory provisions" has the same meaning as in section 31ZA.

Modification of paragraph 4 of Schedule 3

Variation and withdrawal of consent

(1) The terms of any consent under this Schedule may from time to time be varied, and the consent may be withdrawn, by notice given by the person who gave the consent to the person keeping the gametes, human cells, embryo or human admixed embryo to which the consent is relevant.

(1A) Sub-paragraph (1B) applies to a case where an egg is used in the process set out in regulation 4 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (and "egg A" and "egg B" have the same meanings in this paragraph as in that regulation).

(1B) The terms of the consent to that use of egg A or egg B cannot be varied, and such consent cannot be withdrawn, once all the nuclear DNA of egg B which is not polar body nuclear DNA is inserted into egg A.

(2) Subject to sub-paragraphs (3) to (3B), the terms of any consent to the use of any embryo cannot be varied, and such consent cannot be withdrawn, once the embryo has been used—

(a) in providing treatment services,

(aa) in training persons in embryo biopsy, embryo storage or other embryological techniques, or

(b) for the purposes of any project of research.

(3) Where the terms of any consent to the use of an embryo ("embryo A") include consent to the use of an embryo or human admixed embryo whose creation may be brought about in vitro using embryo A, that consent to the use of

that subsequent embryo or human admixed embryo cannot be varied or withdrawn once embryo A has been used for one or more of the purposes mentioned in sub-paragraph (2)(a) or (b).

(3A) Sub-paragraph (3B) applies to a case where an embryo is used in the process set out in regulation 7 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (and "embryo A" and "embryo B" have the same meanings in sub-paragraph (3B) as in that regulation).

(3B) The terms of the consent to that use of embryo A or embryo B cannot be varied, and such consent cannot be withdrawn, once all the nuclear DNA of embryo B which is not polar body nuclear DNA is inserted into embryo A.

(4) Subject to sub-paragraph (5), the terms of any consent to the use of any human admixed embryo cannot be varied, and such consent cannot be withdrawn, once the human admixed embryo has been used for the purposes of any project of research.

(5) Where the terms of any consent to the use of a human admixed embryo ("human admixed embryo A") include consent to the use of a human admixed embryo or embryo whose creation may be brought about in vitro using human admixed embryo A, that consent to the use of that subsequent human admixed embryo or embryo cannot be varied or withdrawn once human admixed embryo A has been used for the purposes of any project of research.

Modification of paragraph 22 of Schedule 3 (paragraphs which apply to mitochondrial donation)

Consent for use of eggs or embryos created following mitochondrial donation

(A1) For the purposes of this Schedule, neither of the following is to be treated as a person whose gametes were used to create an embryo ("embryo E")—

(a) where embryo E is a permitted embryo by virtue of regulations under section 3ZA(5), the person whose mitochondrial DNA (not nuclear DNA) was used to bring about the creation of embryo E;

(b) where embryo E has been created by the fertilisation of an egg which was a permitted egg by virtue of regulations under section 3ZA(5), the person whose mitochondrial DNA (not nuclear DNA) was used to bring about the creation of that permitted egg.

(3B) For the purposes of this Schedule, in a case where an egg is a permitted egg by virtue of regulations under section 3ZA(5) the egg is not to be treated as the egg of the person whose mitochondrial DNA (not nuclear DNA) was used to bring about the creation of that permitted egg.

Regulations

Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

Interpretation

2.— (1) In these Regulations "the Act" means the Human Fertilisation and Embryology Act 1990.

(2) In these Regulations "polar body nuclear DNA" means any nuclear DNA located in a polar body.

(3) In these Regulations a reference to the removal of any nuclear DNA (including polar body nuclear DNA) includes a reference to the removal of any material which is necessarily removed along with that DNA, and such material may include any associated organelles.

(4) For the purposes of these Regulations, the following are to be treated as removed from an egg—

(a) any polar body nuclear DNA which is destroyed while still located in the egg; and

(b) any material which is necessarily destroyed along with that DNA, and such material may include any associated organelles.

(5) In these Regulations a reference to the insertion of nuclear DNA includes a reference to the insertion of any material which is necessarily inserted along with that DNA, and such material may include any associated organelles.

Permitted eggs and permitted embryos

Permitted egg

3. An egg ("egg P") is a permitted egg for the purposes of section 3(2)(b) of the Act if—

(a) egg P results from the application of the process specified in regulation 4 to two eggs, each of which—

(i) is a permitted egg as defined in section 3ZA(2) of the Act (not an egg which is a permitted egg by virtue of these regulations), and

(ii) was extracted from the ovaries of a different woman;

(b) that process has been applied to those eggs in the circumstances specified in regulation 5; and

(c) there have been no alterations in the nuclear or mitochondrial DNA of egg P since egg P was created by means of the application of that process.

Permitted egg: process

4.— (1) The process referred to in regulation 3(a) consists of the following two steps.

(2) In step 1—

(a) either—

(i) all the nuclear DNA of an egg ("egg A") is removed, or

(ii) all the nuclear DNA of egg A other than polar body nuclear DNA is removed; and

(b) either—

(i) all the nuclear DNA of another egg ("egg B") is removed, or

(ii) all the nuclear DNA of egg B other than polar body nuclear DNA is removed.

(3) In step 2 all the nuclear DNA of egg B which is not polar body nuclear DNA is inserted into egg A.

Permitted egg: circumstances

5. The circumstances referred to in regulation 3(b) are that—

(a) the Authority has issued a determination that—

(i) there is a particular risk that any egg extracted from the ovaries of a woman named in the determination may have mitochondrial abnormalities caused by mitochondrial DNA; and

(ii) there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease; and

(b) egg B was extracted from the ovaries of the woman so named.

Permitted embryo

6. An embryo ("embryo P") is a permitted embryo for the purposes of section 3(2)(a) of the Act if—

(a) embryo P results from the application of the process specified in regulation 7 to two embryos, each of which—

(i) is a permitted embryo as defined in section 3ZA(4) of the Act (not an embryo which is a permitted embryo by virtue of these regulations), and

(ii) was created by the fertilisation of a permitted egg as defined in section 3ZA(2) of the Act (not an egg which was a permitted egg by virtue of these regulations) extracted from the ovaries of a different woman;

(b) that process has been applied to those embryos in the circumstances specified in regulation 8; and

(c) since embryo P was created by means of the application of that process—

(i) there have been no alterations in the nuclear or mitochondrial DNA of any cell of embryo P, and

(ii) no cell has been added to embryo P other than by the division of embryo P's own cells.

Permitted embryo: process

7.— (1) The process referred to in regulation 6(a) consists of the following two steps.

(2) In step 1—

(a) either—

(i) all the nuclear DNA of an embryo ("embryo A") is removed, or

(ii) all the nuclear DNA of embryo A other than polar body nuclear DNA is removed; and

(b) either—

(i) all the nuclear DNA of another embryo ("embryo B") is removed, or

(ii) all the nuclear DNA of embryo B other than polar body nuclear DNA is removed.

(3) In step 2 all the nuclear DNA of embryo B which is not polar body nuclear DNA is inserted into embryo A.

Permitted embryo: circumstances

8. The circumstances referred to in regulation 6(b) are that—

(a) the Authority has issued a determination that—

(i) there is a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of a woman named in the determination may have mitochondrial abnormalities caused by mitochondrial DNA; and

(ii) there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease; and

(b) embryo B was created by the fertilisation of an egg extracted from the ovaries of the woman so named.

Licence conditions

T124 a. No clinic may carry out either the process of pronuclear transfer* (PNT) or maternal spindle transfer* (MST) or part of either process, unless express provision has been made on the clinic's licence permitting it to undertake either or both processes.

b. Neither PNT nor MST may be carried out under third party, satellite or transport agreements.

c. No clinic may provide treatment using gametes or embryos which have been created using PNT or MST unless express provision has been made on the clinic's licence permitting the clinic to undertake either or both processes.

*Wherever reference is made in this licence to PNT or MST, or to the process of PNT or MST, it is to be treated as a reference to the process described in Regulation 4 or Regulation 7 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015.

T125 PNT and MST must only be carried out on premises of clinics that are licensed to undertake mitochondrial donation ('MD'). These processes must not be carried out on the premises of a clinic that is operating under a third party, satellite or transport agreement with a clinic that holds a licence to undertake MD.

T127 a. No alterations may be made to the nuclear or mitochondrial DNA of an egg created by means of the application of MST.

b. No alterations may be made to the nuclear or mitochondrial DNA of an embryo created by means of the application of PNT, and no cell may be added to an embryo created by means of the application of PNT other than by the division of the embryo's own cells.

T128 In the case of treatment involving mitochondrial donation, the clinic must ensure that it only carries out the process of PNT or MST for a particular, named patient once the Authority has issued a determination that:

- there is a particular risk that any egg extracted from the ovaries of the named woman, or any embryo created by the fertilisation of an egg extracted from the ovaries of the named woman, may have mitochondrial abnormalities cause by mitochondrial DNA, and
- there is a significant risk that a person with those abnormalities will have or develop a serious mitochondrial disease.

T129 Only those embryologists assessed as competent by the Authority to undertake PNT, MST or both, and named on the front of this licence, are permitted to undertake those processes or any part thereof.

Directions

0001 – Gametes and embryo donation

0005 – Collecting and recording information for the HFEA

0006 – Import and export of gametes and embryos

0007 – Consent

0008 – Information to be submitted to the HFEA as part of the licensing process

HFEA Guidance

Staff to be involved in mitochondrial donation

33.1 A senior clinical geneticist/mitochondrial disease specialist should be involved in deciding whether a particular patient should receive mitochondrial donation treatment.

33.2 The centre should ensure that a multidisciplinary team is involved in providing the treatment. The team should include mitochondrial disease specialists, reproductive specialists, embryologists, clinical geneticists, genetic counsellors and molecular geneticists. It should maintain close contact with the primary care physician, the referring clinician, or the mitochondrial disease centre.

33.3 Only embryologists who have been assessed as competent by the HFEA and named on the clinic's licence can perform maternal spindle transfer (MST) or pronuclear transfer (PNT) techniques as defined in Regulation 4 and 7 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. An application for an assessment of the competence of an embryologist must be submitted to the HFEA and will be considered by a Licence Committee. When submitting an application to the HFEA for a competency assessment, the person responsible (PR) and the relevant embryologist should provide:

a) evidence of the embryologist's experience of carrying out MST or PNT in treatment, training or research on human eggs or embryos (eg, embryo survival rates, blastocyst development, and rate of carryover of mitochondria, in line with key performance indicators (KPIs) determined by the HFEA)

b) references to support the embryologist's experience and knowledge, and

c) any other information that may demonstrate competence (such as the embryologist's experience of performing micro-manipulation on human or animal (eg, mice) eggs or embryos).

33.4 The PR should submit an application to the HFEA for an assessment of the competence of each embryologist who intends to perform MST or PNT or any part thereof. A PR wishing to make any changes to the authorised embryologists must submit an application to the HFEA for a variation of the clinic's licence, accompanied by the relevant evidence of competency for each proposed embryologist.

Mitochondrial donation for the avoidance of serious mitochondrial disease

Interpretation of mandatory requirements 33A

Maternal spindle transfer (MST) can only be carried out where the Authority has issued a determination that —

- there is a particular risk that any eggs collected from the patient named in the application form may have mitochondrial abnormalities caused by mitochondrial DNA; and
- there is a significant risk that a person with those abnormalities will have, or develop, serious mitochondrial disease.

Pronuclear transfer (PNT) can only be carried out where the Authority has issued a determination that—

• there is a particular risk that any embryos created with eggs collected from the patient named in the application form may have mitochondrial abnormalities caused by mitochondrial DNA; and

• there is a significant risk that a person with those abnormalities will have, or develop, serious mitochondrial disease.

Treatment involving mitochondrial donation can only be carried out by a clinic that is licensed to do so, as evidenced by express provision on the clinic's licence permitting it to undertake either MST, PNT or both.

The process of MST or PNT (as defined in Regulation 4 and 7 of the Human Fertilisation and Embryology Authority (Mitochondrial Donation) Regulations 2015) may only be carried out by embryologists who have been assessed by the HFEA as competent to undertake these processes and who are named on the clinic's licence.

MST or PNT may only be carried out on the premises of a clinic licensed to undertake mitochondrial donation and may not be done on third party premises or the premises of any satellite centre.

Clinics that are not licensed to undertake MST or PNT for treatment purposes may not use eggs or embryos created using these techniques in treatment services.

33.5 The centre should discuss with the patient the likely outcomes of the proposed treatment, the nature and potential risks of the treatment, and any other treatment options that may be suitable, such as preimplantation genetic diagnosis (PGD) or egg donation.

33.6 When deciding if it is appropriate to offer MST or PNT in particular cases, the seriousness of the disease in that case should be discussed between the patient seeking treatment and the clinical team. The level of risk for those seeking treatment and any child that may be born will also be an important factor for the centre to consider, and should be discussed with the patient.

The centre should only offer MST or PNT to patients for whom PGD is inappropriate and likely to be unsuccessful and who exhibit (or are predicted to exhibit) high levels of germ line heteroplasmy or homoplasmy. In making this assessment the centre should take into account:

- the particular mutation involved,
- the inheritance pattern in the family,
- the likely clinical manifestations of disease and the efficacy of any previous treatments such as PGD

For an overview of how the Statutory Approvals Committee will assess a case by case application download the Mitochondrial donation: explanatory note for Statutory Approvals Committee.

33.7 The centre should consider the following factors before deciding whether it is appropriate to offer MST or PNT in particular cases. Having considered these factors, if a decision is taken to offer MST or PNT, the clinic would need to submit an application for authorisation to the HFEA.

The Authority's assessment of the seriousness will be made, where possible, based on the most severe symptoms that could be expected for a particular patient's case. When submitting an application to the HFEA, the PR must, wherever possible, provide supporting evidence detailing:

a) the patient's medical history

b) the patient's family medical history of mitochondrial disease (to include previous cases of PGD treatment or details of affected family members)

c) the patient's mutant mitochondrial DNA (mtDNA) load and threshold associated with symptoms of disease (to include details about the level of heteroplasmy or whether the patient is homoplasmic for a mitochondrial mutation).

d) scientific literature relevant to the mtDNA mutation or disease, and

e) any additional information which the clinician may consider is relevant to the application, such as a statement from a genetic counsellor.

Embryo transfer using embryos following mitochondrial donation

33.8 Embryos that have undergone either MST or PNT (or any other technique) should not be transferred with any other embryos that have not undergone the same technique in the same treatment cycle.

33.9 A centre should not perform embryo biopsy (such as for the purpose of PGD or preimplantation genetic screening (PGS)) on embryos that have undergone MST or PNT.

33.10 A centre should use the same sperm provider for both steps of PNT unless there is a good reason for not doing so (ie, if the mitochondria donor is a close genetic relative of the intended father).

Genetic consultation and counselling

33.11 The centre should ensure that people seeking treatment have access to mitochondrial specialists, clinical geneticists, genetic counsellors and, where appropriate, infertility counsellors. Patients who have been referred by one clinic to another for the purposes of mitochondrial donation must be offered specific counselling about mitochondrial donation by the clinic licensed to do mitochondrial donation, regardless of whether the patient has previously been offered counselling by the referring centre.

33.12 The centre should work closely with the local genetics/mitochondrial disease centre of those seeking treatment.

Information for those seeking mitochondrial donation

33.13 The centre should ensure that people seeking MST or PNT are given appropriate information about the treatment. Where a patient has been referred by one clinic to another for the purposes of mitochondrial donation, the clinic licensed to provide mitochondrial donation must ensure that it provides the patient with appropriate information including:

a) information about the process, procedures and possible risks involved in mitochondrial donation, including the risks for any child that may be born following the mitochondrial donation, and the risks of IVF treatment, and

b) information about prenatal testing following treatment. In these circumstances the patients should be counselled about the specific additional risks associated with prenatal testing.

c) information about the experience of the centre and embryologist(s) carrying out the techniques.

33.14 The centre should also provide information to those seeking treatment to help them make decisions about their treatment, including:

a) genetic and clinical information about the mitochondrial disease

b) the possible impact (if known) of the mitochondrial disease on those affected and their families

c) the importance of telling any resulting children of the mitochondrial donation treatment

d) information about treatment and social support available, and

e) information from a relevant patient support group or the testimony of people living with the condition, if those seeking treatment have no direct experience of it themselves.

33.15 If the person seeking treatment has already been given information about the particular mitochondrial disease, for example from a regional mitochondrial disease centre with appropriate expertise, the centre does not need to provide this information again. However, the centre should ensure that the information which has been provided is accurate, sufficiently detailed and that the patient fully understands the information.

33.16 Before providing mitochondrial donation treatment, the centre should ensure that those seeking treatment have had sufficient opportunity to fully consider the possible outcomes and risks of these techniques and their implications.

33.17 The centre should provide information to people seeking mitochondrial donation treatment about the collection and provision of information, specifically:

a) information that centres must collect and register with the HFEA about the donors

b) what information may be disclosed to people born as a result of the mitochondrial donation and in what circumstances, and

c) that person's right to access anonymous information about the mitochondrial donor from the age of 16.

33.18 The centre should give people seeking mitochondrial donation treatment information about the screening of people providing mitochondria. This information should include details about:

a) the sensitivity and suitability of the tests, and

b) the possibility that a screened provider of mitochondria may be a carrier of a mitochondrial disease or infection.

33.19 The centre should provide information that explains the limitations of procedures and the risks of treatment to anyone seeking mitochondrial donation treatment. The centre should make available appropriate counselling.

Guidance note 20 applies to mitochondrial donation except guidance 20.1, 20.2 d)ii)-v) and 20.12.

See also:

Guidance note 20 – Donor assisted conception

Guidance note 3 – Counselling

Importance of informing children of their origins

33.20 The centre should tell people who seek mitochondrial donation treatment that it is best for any resulting child to be told about their origin early in childhood. Centres should refer to guidance set out in guidance note 20 on the importance of informing children of their donor origins.

33.21 Centres should inform patients of the potential risk of mitochondrial disease in future generations and the potential ways to avoid this (eg, that any female born following MST or PNT, should she wish to have children of her own, could have her eggs or early embryos analysed by PGD in order to select for embryos free of abnormal mitochondria).

See also:

Guidance note 20 – Donor assisted conception

Eligibility requirements for mitochondrial donors

Licence conditions

T52 Prior to the use and/or storage of donor gametes and/or embryos created with donor gametes the centre must comply with the selection criteria for donors and the requirements for laboratory tests and storage set out below, namely:

a. donors must be selected on the basis of their age, health and medical history, provided on a questionnaire and through a personal interview performed by a qualified and trained healthcare professional. This assessment must include relevant factors that may assist in identifying and screening out persons whose donations could present a health risk to others, such as the possibility of transmitting diseases, (such as sexually transmitted infections) or health risks to themselves (eg, superovulation, sedation or the risks associated with the egg collection procedure or the psychological consequences of being a donor)

b. the donors must be negative for HIV1 and 2, HCV, HBV and syphilis on a serum or plasma sample tested as follows, namely:

- HIV 1 and 2: Anti-HIV – 1, 2
- Hepatitis B: HBsAg and Anti-HBc

- Hepatitis C: Anti-HCV-Ab
- Syphilis: see (d) below

c. the centre must devise a system of storage which clearly separates:

- quarantined/unscreened gametes and embryos
- gametes and embryos which have tested negative, and
- gametes and embryos which have tested positive

d. a validated testing algorithm must be applied to exclude the presence of active infection with Treponema pallidum. The non-reactive test, specific or non-specific, can allow gametes to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. The donor whose specimen test reacted on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use

e. in addition to the requirements in (b) and (d) above, sperm donors must be negative for chlamydia on a urine sample tested by the nucleic acid amplification technique (NAT)

f. This requirement has been removed.

g. HTLV-1 antibody testing must be performed for donors living in or originating from high-prevalence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas

h. in certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the gametes donated (eg, RhD, Malaria, T.cruzi), and

i. genetic screening for autosomal recessive genes known to be prevalent, according to international scientific evidence, in the donor's ethnic background and an assessment of the risk of transmission of inherited conditions known to be present in the family must be carried out, after consent is obtained. Complete information on the associated risk and on the measures undertaken for its mitigation must be communicated and clearly explained to the recipient.

T126 Donors of gametes for use in MST and or PNT must be screened for pathogenic mitochondrial DNA mutations, and an assessment of the risk of transmission of any mitochondrial disease in the donor's family must be carried out, after consent is obtained. Complete information on the associated risk and on the measures undertaken for its mitigation must be clearly communicated and explained to the recipient.

Interpretation of mandatory requirements 33B

Sections (a) to (h) of Licence condition T52 on medical and laboratory tests should apply to mitochondrial donors and to men providing sperm used to fertilise eggs of the mitochondrial donor in the process of PNT.

33.22 As well as taking their medical history (in line with T52 and T126), the recruiting centre should take details of previous donations. If a prospective donor cannot give a full and accurate maternal family history, the centre should record this fact and take it into account in deciding whether or not to accept their eggs for treatment.

33.23 Centres should ensure that they keep up to date with relevant literature and professional guidance, such as on refinements to the techniques, to improve their efficacy in treatment. Centres should also keep up to date with emerging research relevant to mitochondria haplotype matching and consider matching the haplotypes of donors with recipients where possible.

33.24 Before accepting a mitochondrial donor, centres should follow the same requirements and guidance as set out in guidance note 11, except guidance 11.2, 11.3, 11.32 g) and j), 11.32 i)-l), 11.36, 11.37, 11.38, 11.39, 11.42, 11.46-11.52.

33.25 Guidance on the upper age limits for egg and embryo donors does not apply for mitochondrial donors. There is some evidence to suggest that mitochondria in a woman's eggs accumulate damage over time meaning the eggs of older donors may have reduced mitochondrial function. Age should therefore be taken into consideration when determining the suitability of a woman donating her eggs, in conjunction with an assessment of her reproductive health, such as an assessment of ovarian reserve.

33.26 The ten family limit guidance for those providing donor gametes (or embryos created using donated gametes) outlined at 11.46, does not apply to:

- egg donors who have donated their mitochondria only, or
- sperm donors who have donated for pronuclear transfer where they will not be genetically related to the child.

See also:

Guidance note 11 - Donor recruitment, assessment and screening

Information for prospective mitochondrial donors

33.27 Before any consents or samples are obtained from a prospective mitochondrial donor, the recruiting centre should provide information about:

a) the screening that will be done and why it is necessary

b) the possibility that the screening may reveal unsuspected conditions (eg, mitochondrial related anomalies or HIV infection) and the practical implications of this

c) the scope and limitations of the genetic testing that will be done and the implications for the mitochondria donor and their family

d) the importance of informing the recruiting centre of any medical information that may come to light after donation and that may have health implications for any woman who received treatment with their mitochondria, or for any child born as a result of such treatment

e) the procedure used to collect gametes, including any discomfort, pain and risk to the mitochondria donor (eg, from the use of superovulatory drugs)

f) the legal parenthood of any child born as a result of their mitochondrial donation

g) what information about the mitochondrial donor must be collected by the centre and held on the HFEA Register

h) that only non-identifying information will be disclosed when the applicant is aged over 16. No identifying information about the donor will be disclosed

i) the possibility that a child born as a result of their mitochondrial donation who is disabled as a result of an inherited condition that the donor knew about, or ought reasonably to have known about, but failed to disclose, may be able to sue the donor for damages, and

j) the ability of the mitochondrial donor to withdraw consent, the procedure for withdrawal of consent for the use of their mitochondria, and the point up until which the donor can withdraw consent.

Informing mitochondrial donors about information available to children born from the treatment

33.28 The centre should inform mitochondrial donors that anyone born as a result of their mitochondrial donation will have access to the following non-identifying information provided by them, from the age of 16:

a) the screening tests carried out on the mitochondrial donor and information on that donor's personal and family medical history

b) matters contained in any description of the mitochondrial donor as a person which that donor has provided, and

c) any additional matter which the mitochondrial donor has provided with the intention that it be made available to a person born from their donation.

Consent

33.29 The centre should obtain written informed consent from patients and their spouse or partner (if relevant), for mitochondrial donation treatment. Where a patient and their partner have been referred by one centre to another for the purposes of mitochondrial donation, the clinic that will be undertaking the mitochondrial donation must obtain consent specific to the treatment involving mitochondrial donation, regardless of what consent the patient and their partner may have provided to the referring centre. This is because the centre doing the mitochondrial treatment will have the necessary experience and expertise in mitochondrial donation and is best placed to provide the relevant information and obtain fully informed consent.

33.30 For mitochondrial donors, the centre should obtain the donor's written informed consent to the donation of her eggs or embryos for MST or PNT.

33.31 Any prospective women donating their eggs for mitochondrial donation, or men donating sperm for PNT where they will not be genetically related to the child, should be aware that they cannot withdraw or vary their consent

once the donated egg or embryo has undergone the process of MST or PNT (ie, all the nuclear material has been moved from one egg or embryo to another).

33.32 Centres should follow all other requirements and guidance on consent as outlined in guidance note 11 on donor recruitment, assessment and screening and in guidance note 5 on consent to treatment, storage, donation and disclosure of information.

Import of eggs or embryos which have undergone mitochondrial donation

Interpretation of mandatory requirements 33C

It is not lawful in the UK to provide treatment using gametes or embryos created abroad following the use of pronuclear transfer or maternal spindle transfer. Schedule 1(f) and 3 (i) of General Direction 0006 provides that the purpose of importing gametes or embryos must be to provide treatment services. However, as treatment using gametes or embryos created abroad following the use of pronuclear transfer or maternal spindle transfer is not lawful, it follows that the import of such gametes or embryos should not take place.

See also:

Guidance note16 – Imports and exports

Guidance note 5 – Consent to treatment, storage, donation and disclosure of information

Guidance note 11 – Donor recruitment, assessment and screening

Follow-up arrangements

33.33 Centres offering mitochondrial donation should have a documented process setting out how children born from mitochondrial donation will be followed up, where patients have consented to follow-up. These should include long-term medical follow-up of children born as a result. Centres should establish links with mitochondrial disease centres to facilitate follow-up. If the patient is not a UK resident but nevertheless wishes to participate in follow-up, the centre and patient should discuss whether the patient wishes to be followed up at a mitochondrial disease centre based in the UK or a relevant centre overseas, in a location more convenient for the patient.

33.34 Centres should explain to patients the benefits of participating in follow-up, both immediate follow-up and long term follow-up.

33.35 If a centre becomes aware that a child born following mitochondrial donation has been born with a mitochondrial disease, birth defect, or genetic abnormality, or if there has been some other adverse outcome (including but not limited to failed or no embryo development, miscarriage or premature birth) following treatment involving mitochondrial donation, the centre must regard this as an adverse incident and report this to the HFEA in line

with the requirements on adverse incidents set out in guidance note 27. This is to capture information about any abnormalities that may occur as a result of carrying out the MST or PNT treatment, to inform any regulatory or licensing action that the HFEA may wish to take and to inform the scientific sector.

See also:

Guidance note 27 – Adverse incidents

Annex 3: Mitochondrial donation: Explanatory note for statutory approvals committee

1. Overview

1.1. The Statutory Approvals Committee of the Human Fertilisation and Embryology Authority will utilise this explanatory note to set outline their approach to the statutory criteria of 'risk' and 'seriousness' which it is required to assess when considering applications to undertake mitochondrial donation. This explanatory note should be read in conjunction with the mitochondrial donation decision tree.

1.2. The approach set out in this explanatory note was approved by the Authority on [DD Month].

1.3. This explanatory note is effective for the Statutory Approvals Committee from [DD Month].

2. Introduction

2.1. Following the introduction of The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (the Regulations) on 29 October 2015 the Authority has delegated the function of considering mitochondrial donation applications to the Statutory Approvals Committee. The Regulations require the Authority to adopt a case by case based approach to the approval of applications which means that the Statutory Approvals Committee will consider applications to perform mitochondrial donation with reference to the particular circumstances of the patient.

2.2. Only clinics that have express provision on their licence to undertake mitochondrial donation can apply to undertake the process on behalf of a particular patient, and only those embryologist(s) approved by the HFEA are permitted to carry out the procedure.

2.3. When making applications to carry out mitochondrial donation, centres will need to assess, on an individual patient basis, whether the particular request for mitochondrial donation is appropriate. The Code of Practice provides guidance on how such decisions should be made.

2.4. When considering mitochondrial donation applications, the Statutory Approvals Committee will take into account material provided with the application, including evidence from the applicant, and any evidence from independent clinical experts and patient groups.

2.5. **The Committee should ensure that the patient identified for treatment is (or is predicted to be) highly heteroplasmic or homoplasmic for a particular mtDNA mutation in their germ line and has undergone an assessment that deems PGD inappropriate or likely to be unsuccessful.**

3. Statutory requirements

3.1. Paragraphs 5(a) and (b) and 8(a) and (b) of the Regulations (Annex A) prescribe the criteria that must be met before the Statutory Approvals Committee can issue a determination permitting the application of two mitochondrial donation techniques, pronuclear transfer (PNT) or maternal spindle transfer (MST).

3.2. These criteria include the requirements that:

- there should be a particular risk that an egg or embryo may have mitochondrial abnormalities caused by mitochondrial DNA, and
- there should be a significant risk that the person with the abnormalities will have or develop serious mitochondrial disease.

4. Particular risk

4.1. When considering whether or not there is a particular risk that an embryo may have mitochondrial abnormalities caused by mitochondrial DNA (mtDNA), the Statutory Approvals Committee will take into account evidence of the genetic basis of the inherited disorder.

4.2. This is an objectively measurable criterion. Only a woman with an identified, pathogenic genetic alteration to her mtDNA can be determined to have a particular risk of transmitting this to her embryos.

4.3. Due to the intrinsic variability in the inheritance of those mitochondrial diseases caused by mutations to the mtDNA, the HFEA has determined that any woman harbouring such a genetic alteration is at particular risk of transmitting abnormal mitochondria to her eggs and embryos.

5. Seriousness: general information

5.1. Before the Statutory Approvals Committee can authorise mitochondrial donation treatment for a particular patient it must consider the risk to the patient's child, conceived in the absence of mitochondrial donation, of developing a serious mitochondrial disease.

5.2. In order to frame its assessment of this seriousness the Statutory Approvals Committee will first consider information from the scientific literature relating to the following factors:

a. Symptoms of the disease

It is important for the committee to recognise that the symptoms associated with the same genetic alteration to the mtDNA, can vary from family to family, and person to person, and can range from mild to severe.

The committee should therefore take into account the range of symptoms associated with the mitochondrial disease/genetic alteration, ensuring that they understand the symptoms that manifest when the disease is in its most severe form.

If the symptoms in this worst case scenario are not judged to be sufficiently serious, the Committee will not authorise mitochondrial donation for this patient.

b. Age of onset

As part of its consideration of the seriousness the committee should consider whether symptoms usually manifest at birth or later in life. If the symptoms do manifest later, at which stage (childhood, early adulthood, later)? If the disease is degenerative, how quickly does it progress?

c. Effect of the disease on quality of life of the patient

This will include any evidence about the speed of degeneration in progressive disorders and the extent of any physical and/or intellectual impairment.

d. Are treatments available for the disease or any of its symptoms?

If so, what is the type and extent of the treatments available? How invasive is the treatment or likely treatment?

6. Significant risk: general information

6.1. Mutations to the mtDNA can be present in all mitochondria or in only a proportion. Where all the mitochondria are affected this is known as homoplasmy. While if only a subset are affected this is known as heteroplasmy.

6.2. Where the mutation is heteroplasmic, the proportion of affected mitochondria versus unaffected mitochondria (known as the mutant mitochondrial load) often correlates with the symptoms, with higher loads associated with more severe symptoms. However this is not always the case.

6.3. Before the Statutory Approvals Committee can authorise mitochondrial donation treatment for a particular patient it must consider how significant the risk of developing a serious mitochondrial disease to is to the patient's child, if conceived in the absence of mitochondrial donation.

6.4. This risk will be influenced by the mutant mitochondrial load a child might inherit from its mother as well as the threshold beyond which the mutant mitochondrial load needs to pass in order to cause clinical symptoms.

6.5. In order to understand this risk the Statutory Approvals Committee will first consider information from the scientific literature, which provides information on:

- The usual threshold mutant mitochondrial load necessary to cause clinical manifestation of the mitochondrial disease.
- The degree to which mutant mitochondrial load usually correlates with severity of symptoms of the mitochondrial disease.
- Any cases indicating what the mutant mitochondrial loads were in women who have had children affected by the mitochondrial disease.

6.6. Due to the rare nature of some mitochondrial diseases and the paucity of publications characterising them, information on the threshold level of mtDNA harbouring a pathogenic genetic alteration required to result in the development of a mitochondrial disease may not be available.

6.7. This information is intended to provide a foundation upon which a judgement, based on the patient's individual circumstances, can be made.

6.8. The committee should bear in mind that the mutant mitochondrial load of the patient may not be the same as the load present in her eggs and embryos. This is because the inheritance of mitochondria between a woman and the eggs she produces is unpredictable. This results in women with heteroplasmic mutations producing eggs with a wide range of mutant mitochondrial loads, some of which would be sufficiently high to cause disease while some of which would not.

7. Significant risk and seriousness: patient information

7.1. The centre should only offer MST or PNT to patients for whom PGD is inappropriate and likely to be unsuccessful and who exhibit (or are predicted to exhibit) high levels of germ line heteroplasmy or homoplasmy. In making this assessment the centre should take into account:

- the particular mutation involved,
- the inheritance pattern in the family,
- the likely clinical manifestations of disease and the efficacy of any previous treatments such as PGD

7.2. Based on the information from the scientific literature the Committee should hopefully have an understanding of the possible symptoms a particular mitochondrial disease/alteration to the mtDNA can cause, as well as the mutant mitochondrial load usually necessary to cause a clinical manifestation of disease.

7.3. However, in its assessment of 'significant risk' and 'seriousness', the Statutory Approvals Committee must take into account the circumstances of the individual patients.

7.4. The Committee should consider the following questions:

a. Does the patient's medical history provide evidence of risk and seriousness?

- Does the patient have any symptoms? If so, how severe are they?
  - A patient with symptoms herself may be at significant risk of transmitting a mitochondrial disease with comparable or more serious symptoms to her children.
- Has the patient previously had any children affected by mitochondrial disease? If so, what were their symptoms? What was the age of onset? What was the effect on quality of life? Were any treatments available and what effect did they have? Would this manifestation of mitochondrial disease pass the seriousness test?
  - A patient who has had a child/children affected by a serious mitochondrial disease may be at significant risk of having another child affected by a mitochondrial disease of similar severity.
- Has the patient previously been treated with preimplantation genetic diagnosis (PGD) to avoid transmission of mitochondrial disease? Was the PGD successful? What was the mutant mitochondrial load of the embryos tested? Did any of the embryos have a mutant mitochondrial load above the threshold level usually necessary for clinical manifestation of serious mitochondrial disease?
  - A patient who has had an unsuccessful PGD cycle because no embryos with sufficiently low mutant mitochondrial loads were found may be at significant risk of having eggs with mutant mitochondrial loads sufficiently high to cause a serious mitochondrial disease.
- Likewise a patient who has had a successful PGD cycle in which embryos were found to have mutant mitochondrial loads sufficiently high to cause a serious mitochondrial disease may be at significant risk of transmitting a serious mitochondrial disease to any children conceived in the absence of mitochondrial donation.

b. Does the patient's mutant mtDNA load provide evidence of risk and seriousness?

- Is the patient homoplasmic or heteroplasmic for the mutation? What is the patient's mutant mitochondrial load?
  - A patient who is homoplasmic for the mutation will only have eggs that are homoplasmic for the mutations. Therefore all her children are at risk of developing mitochondrial disease. Her children may have mitochondrial disease similar in severity to her own or that of her relatives.
  - A patient who is heteroplasmic for the mutation is likely to have eggs which are also heteroplasmic. However, the mutant mitochondrial load of the patient may not be the same as the load present in her eggs and embryos, which are likely to have considerable variability in mutant mitochondrial load. The committee should consider whether there is evidence from the scientific literature and/or family

medical history showing that women with comparable mutant mitochondrial load have had a severely affected child.

c. Does the patient's family history provide evidence of risk and seriousness?

- Does the patient have a family history of mitochondrial disease? How prevalent is mitochondrial disease in the family ie, which family members are/have been affected by mitochondrial disease? For each affected family member, how serious was their disease: what were the symptoms, what was the age of onset, what was the effect on quality of life, were any treatments available and effect did they had?
- What were the mutant mitochondrial loads of affected family members with severe mitochondrial disease and what were the mutant mitochondrial loads of their mothers? Are the mutant mitochondrial loads of female family members who have had severely affected children comparable to the patient?
  - A patient with a family history of serious mitochondrial disease may be at significant risk of having a child with a similar severity of symptoms. This is especially the case if she has a comparable mutant mitochondrial load to that of her female relatives who have had an affected child.
- For each family member, their symptoms, age of onset, effect on quality of life, their mutant mitochondrial load, if any treatment was available, what it was and what effect it had.

8. Decision-making

8.1. The Statutory Approvals Committee will give reasons for the decisions it makes. The reasons will set out clearly the matters that the Statutory Approvals Committee took into account in deciding whether or not to grant approval to perform mitochondrial donation.

9. Publication of minutes

9.1. It is important for transparency that wherever possible documentation of the committee's decision-making process is published and available for public scrutiny. However it is vital that patient confidentiality is upheld.

9.2. Some mitochondrial disease and genetic alterations to the mtDNA are very rare and as such it may be possible to identify a patient by some of the details recorded in the Statutory Approvals Committee minutes.

9.3. The committee should weigh up these two competing principals when deciding whether or not its minutes should be made publicly available, and consider publishing redacted minutes to preserve patient confidentiality where necessary, stating this as the reason.

Annex A: Regulations

5. Permitted egg: circumstances

The circumstances referred to in regulation 5(b) are that

a) The Authority has issued a determination that

1. there is a particular risk that any egg extracted from the ovaries of a woman named in the determination may have mitochondrial abnormalities caused by mitochondrial DNA and
2. there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease; and

b) Egg B was extracted from the ovaries of the woman so named.

8. Permitted embryo: circumstances

The circumstances referred to in regulation 8(b) are that

a) The Authority has issued a determination that

i. there is a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of a woman named in the determination may have mitochondrial abnormalities caused by mitochondrial DNA,

3. and

ii. there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease,

4. and

b) Embryo B was created by the fertilisation of an egg extracted from the ovaries of the woman so named.

Annex 4: Amended General Direction 0008 - Information to be submitted to the HFEA as part of the licensing process

Information to be submitted to the Human Fertilisation and Embryology Authority as part of the licensing process

Ref: 0008

Version: 4

These Directions are:	GENERAL DIRECTIONS
Sections of the Act providing for these Directions:	Sections 12 (1) (g) and 19B (1)
These Directions come into force on:	1 October 2009
These Directions remain in force:	Until revoked
This version issued on:	29 October 2015

General requirement relating to all applications to the Authority

1. Applications to the Authority relating to categories A-M must be made by completing and submitting the relevant on-line application, together with relevant supporting information detailed below, via the 'electronic portal' located on the Authority's website (www.hfea.gov.uk). An application fee (details of current fees payable are available on the Authority's website) must also be submitted.

2. Failure to submit a fully completed application form, pay the application fee or provide all the necessary information set out below will, in normal circumstances, result in the application not being considered until such times as these requirements have been satisfied.

3. Persons Responsible for centres which are licensed by the Authority to carry out licensed activities (treatment, storage, non-medical fertility services or research) must at all times have available the information set out in iv-xiv of paragraph 4 of this Direction and submit this information to the Authority when requested no later than 10 working days after the date of any written request.

Information to be supplied with applications

A. Applications for a new (initial) treatment, storage and non-medical fertility services licence

4. An application for a new licence authorising:

(a) activities in the course of providing treatment services; and/or
(b) the storage of gametes, embryos or human admixed embryos; or
(c) activities in the course of providing non-medical fertility services,
must be accompanied by the information specified below:

i. where the proposed Person Responsible is not the applicant, a written confirmation from the proposed Person Responsible that the application is made with his or her consent;
ii. a current CV of the proposed Person Responsible listing academic and professional qualifications; work experience and registration details with the relevant professional body;
iii. a current CV of the proposed Licence Holder listing academic and professional qualifications; work experience and registration details with the relevant professional body;
iv. the Person Responsible Entry Programme ("PREP") certificate number confirming satisfactory completion of the PREP by the proposed Person Responsible;
v. a floor plan of the premises to be referenced on the licence;
vi. a suite of information documents to be provided to patients undergoing treatment at the centre once licensed;
vii. a completed self-assessment questionnaire submitted via the electronic portal;
viii. a copy of the centre's organisational chart clearly defining accountability and reporting relationships for named individuals;
ix. evidence that staff are registered with a professional or statutory body and are appropriately qualified and trained in techniques relevant to their work, or are in a programme of supervised training;
x. a copy of the centre's induction and training programme that ensures that staff have adequate knowledge of the scientific and ethical principles, together with the regulatory context, relevant to their work;
xi. evidence that a robust quality management system is in place;
xii. a statement that all the equipment and processes to be used in activities authorised by a licence, and in other activities carried out in the course of providing treatment services that do not require a licence, have been validated;
xiii. a detailed list of the quality indicators, a schedule of the audit programme and the reporting arrangements established for all activities authorised by a licence, and other activities carried out in the course of providing treatment services that do not require a licence; and
xiv. a copy of the centre's multiple birth minimisation strategy (where applicable).

B. Applications to renew a treatment, storage or non-medical fertility services licence

5. An application for the renewal of a licence authorising:

(a) activities in the course of providing treatment services; and/or
(b) the storage of gametes, embryos or human admixed embryos; or
(c) activities in the course of providing non-medical fertility services,
must be accompanied by the information specified below:

i. where the Person Responsible is not the applicant, a written confirmation from the Person Responsible that the application is made with his or her consent;
ii. a completed self-assessment questionnaire; and
iii. a suite of information documents to be provided to patients undergoing treatment at the centre (if different to those submitted with the original or previous renewal application).

C. Applications to vary the activities authorised by a current treatment, storage or non-medical services licence

6. An application to vary the activities authorised by a current licence in the course of providing treatment services or non-medial fertility services must be accompanied by the information specified below:

i. copies of information provided to patients relating to the new activity;
ii. evidence that the process(es) and, where applicable, the equipment used in carrying out the new activity have been validated; and
iii. a schedule of the quality indicators, and reporting arrangements, established for this activity.

7. An application to vary a licence to allow mitochondrial donation through maternal spindle transfer (MST) or pronuclear transfer (PNT) must be accompanied by the information specified below:

i. copies of information provided to patients and donors relating to treatment involving mitochondrial donation and the benefits of participating in follow-up;
ii. information to demonstrate the competence of the embryologist(s) proposed to conduct the technique(s) being applied for, as follows:

a) a CV and references of the embryologist(s), to support their experience and knowledge
b) key performance indicator data relating to the proposed embryologist's/embryologists' experience in carrying out the technique(s) on human eggs or embryos as follows:
    i) whether they have carried out the techniques in treatment, training or research
    ii) **Embryo survival rates** - must exceed 70%.
    iii) **Blastocyst development rates** - which must be no less than 50% of that observed in the control embryos at day 5. Where possible, controls should be age-matched to the karyoplast donor.
    iv) **Rates of carryover of mtDNA** - should not on average exceed 2% and no greater than 10% per embryo.

c) any other information that may demonstrate competence (such as their experience of performing micro-manipulation on human or animal (eg, mice) eggs or embryos)

iii. evidence that the equipment, and process(es) where applicable, used in carrying out the new technique(s) has been validated;
iv. a schedule of the quality indicators, and reporting arrangements, established for the new treatments; and
v. procedures for the follow-up of children born as result of mitochondrial donation, including the arrangements the centre has in place with a mitochondrial disease expert centre.

An application to add or vary the name of the embryologist(s) practising MST or PNT need only include section 7ii) (a-c).

D. Application to carry out a licensed activity using a 'novel' process

8. Where centres want to carry out a licensed activity using a process that has not been authorised by the Authority, an application must be accompanied by the information specified below:

i. copies of information provided to patients relating to the new activity;
ii. evidence that the process and, where applicable, the equipment used in carrying out the new activity have been validated; and
iii. a schedule of the quality indicators, and reporting arrangements, established for this process.

E. Applications for a new (initial) research licence

9. An application for a new licence authorising activities for a research project must be accompanied by the information specified below:

i. where the proposed Person Responsible is not the applicant, a written confirmation from the proposed Person Responsible that the application is made with his or her consent;
ii. the PR Entry Programme ("PREP") certificate number confirming satisfactory completion of the PREP (for Person Responsible appointed after 1 October 2009);
iii. a floor plan of the premises to be specified on the licence;
iv. copies of all information provided to patients and/or donors relating to the proposed research project;
v. copies of the consent forms to be used to authorise the use of gametes, embryos or human cells in the research project;
vi. evidence of ethics approval of the research project from a properly constituted research ethics committee; and
vii. a completed self-assessment questionnaire.

10. For applications for a new licence authorising activities in connection with the derivation from embryos of stem cells that are intended for human application, the following additional information must be submitted with the application:

    i. evidence that the proposed Person Responsible possesses a diploma, certificate or other evidence of formal qualifications in the field of medical or biological sciences, awarded on completion of a university course of study, or other course of study recognised in the United Kingdom as equivalent and has at least two years' practical experience which is directly relevant to the activity to be authorised by the licence; and
    ii. evidence that the centre has, or is obtaining, a licence from the Human Tissue Authority.

F. Applications to renew a research licence

11. An application for the renewal of a licence authorising activities for a research project must be accompanied by the information specified below:

    i. a completed self-assessment questionnaire;
    ii. evidence of ethics approval of the research project from a properly constituted research ethics committee;
    iii. copies of all information provided to patients and/or donors relating to the proposed research project (if different to those submitted with the original or previous renewal application); and
    iv. copies of the consent forms to be used to authorise use of gametes, embryos or human cells in the research project (if different to those submitted with the original or previous renewal application).

12. For applications to renew a licence authorising activities in connection with the derivation from embryos of stem cells that are intended for human application, the following additional information must be submitted with the application:

    i. evidence that the centre has a licence from the Human Tissue Authority.

G. Applications to vary a research licence to vary the purposes for which the research is licensed

13. An application to vary a research licence to vary the purposes for which the current research is licensed must be accompanied by the information specified below:

    i. evidence of ethics approval of the research project from a properly constituted research ethics committee;
    ii. copies of all information provided to patients and/or donors relating to the proposed research project (if different to those submitted with the original or previous renewal application); and
    iii. copies of the consent forms to be used to authorise use of gametes, embryos or human cells in the research project (if different to those submitted with the original or previous renewal application).

H. Applications to vary a licence to either relocate to new premises or change existing premises

14. An application to vary a licence to either relocate to new premises not authorised by a current licence for the conduct of licensed activities (treatment, storage, research and non-medical fertility services) or to alter premises authorised by a current licence for the conduct of licensed activities (treatment, storage, research and non-medical fertility services) must be accompanied by the information specified below:

    i. where the Person Responsible is not the applicant, a written confirmation from the Person Responsible that the application is made with his or her consent;
    ii. a floor plan of the premises to be referenced on the licence, and;
    iii. confirmation that any re-commissioned equipment has been tested and validated.

I. Applications to change the Person Responsible or the Licence Holder

15. An application to change the Person Responsible or the Licence Holder of a licence authorising licensed activities (treatment, storage, research and non-medical fertility services) must be accompanied by the information specified below:

    i. a current CV of the proposed Person Responsible listing academic and professional qualifications; work experience and registration details with the relevant professional body;
    ii. a current CV of the proposed Licence Holder listing academic and professional qualifications; work experience and registration details with the relevant professional body; and
    iii. the PR Entry Programme ("PREP") certificate number confirming satisfactory completion of the PREP (applications for a change of PR only).

J. Applications to authorise pre-implantation genetic diagnosis

16. An application to authorise pre-implantation genetic diagnosis (PGD) for a condition which has not previously been authorised by the Authority is subject to an application as per paragraph 1.

K. Applications to authorise human leukocyte antigen tissue typing

17. An application to authorise human leukocyte antigen (HLA) tissue typing, in isolation or in conjunction with PGD must be accompanied by the information specified below:

    i. a copy of a signed letter of support from a clinician responsible for the care of the sibling child providing information on the:

        (a) degree of suffering associated with the disease of the affected sibling,
        (b) speed of degeneration in progressive disorders,
        (c) prognosis for the affected sibling in relation to all treatment options available,
        (d) availability of alternative sources of tissue for the treatment of the affected sibling, now and in the future, and
        (e) availability of effective therapy for the affected sibling now and in the future.

L. Applications to authorise mitochondrial donation for a specific patient

18. Applications for authorisation of mitochondrial donation for a specific patient must be made by completing the relevant application and submitting this to the HFEA.

19. A documented rationale of why PGD may be deemed inappropriate and likely to be unsuccessful.

M. Applications for Special Directions to export gametes or embryos

20. An application for a Special Direction to export gametes or embryos must be accompanied by the information specified below:

    i. a letter from the intended export destination centre/clinic confirming that it is willing to accept the gametes or embryos for the purpose specified in the application form.

Notifying the Authority of information relating to licensed activities

21. Persons Responsible must notify the Authority, through the electronic portal located on the Authority's website, of all processes undertaken in the licensed centre in carrying out a licensed activity.

Additional information to be submitted to the Authority as part of on-going compliance

22. Persons Responsible for centres licensed by the Authority must complete and submit to the Authority the self-assessment questionnaire (SAQ) published on the Authority's website no later than six weeks prior to the date on which the Authority has confirmed it will carry out an inspection visit. Before submitting the SAQ, Persons Responsible must confirm that the information they have provided on that document is true and accurate.

23. Where a member of the Authority's Compliance Department requests the Person Responsible to submit a further SAQ in addition to that required by paragraph 21 above, the Person Responsible must submit this to the Authority no later than 15 working days after the date of the written request.

24. Where a member of the Authority's Compliance Department requests the Person Responsible to submit a further PREP, the Person Responsible must submit this to the Authority no later than 21 working days after the date of the written request.