HFEA Licence Committee Meeting

15 January 2015

Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF

Minutes – Item 1

Centre 0035 (Oxford Fertility Unit) – Initial Research Licence application

Members of the Committee: Andy Greenfield (lay) (Chair) Kate Brian (lay) Jane Dibblin (lay) Committee Secretary: Trent Fisher	Legal Adviser: Shelley Edwards, Fieldfisher Also in Attendance: Sam Hartley, Head of Governance and Licensing

Declarations of Interest: members of the Committee declared that they had no conflicts of interest in relation to this item.

The following papers were considered by the Committee:

- Inspection report
- Application form
- Two redacted peer reviews
- Patient information sheet and consent form for the project
- Email from Person Responsible in response to the peer reviewer's request to clarify the justification for the egg and embryo usage data
- Email from Person Responsible clarifying the nature of the eggs and embryos to be used in the project
- Evidence of ethics approval
- Three publications associated with the application
- Previous committee minutes for the centre
    - ELP minutes 12 December 2014: Change of LH for project R0111 at centres 0035 and 0311
    - ELP minutes 8 August 2014: Research interim inspection report for project R0111 at centre 0035 and 0311
    - RLC minutes 13 September 2012: Research renewal inspection report for project R0111 at centre 0035 and 0311
- Tabled confirmation from the centre’s inspector that the licence application fee had been paid

The Committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings

- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree); and
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Directions 0000 – 0012
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Background

1. Oxford Fertility Unit (centre 0035) is currently licensed to undertake research project R0111, 'Development of a model to study implantation in the human' and has applied for an additional research licence for the project 'Studying mitochondrial DNA quality control in human oocytes and pre-implantation embryos'.

Discussion

2. The Committee noted that at the time initial inspection took place, 23 December 2014, there were no areas of concern that required improvement.

3. The Committee had regard to its Decision Tree. The Committee was satisfied that the application was submitted in the form required, and contained the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fee had been paid. The Committee noted that the application was made by the proposed Person Responsible ("PR") for Research.

4. The Committee was satisfied that the proposed PR possesses the required qualifications and experience and that the character of the PR is such as is required for supervision of the licensed activities. It was further satisfied that the PR will discharge her duties under section 17 of the Act. The Committee noted that the Inspector was satisfied the PR had satisfactorily completed the PR entry programme and is suitably qualified and experienced to undertake the role. The PR is also the current PR for research for project R0111 at centre 0035.

5. The Committee was satisfied that the premises to be licensed are suitable for the conduct of licensed activities as the Inspector confirmed that the premises were suitable and secure.

6. The Committee was satisfied that the licence application involved the authorisation of activities for the purpose of research.

Discussion

7. The Committee was satisfied that the licence for centre 0035 would not apply to more than one project and that the activities of the licence, permitted under the Act, is for 'use of embryos'.

8. The Committee was satisfied that the use of human embryos is necessary because, although the segregation of mitochondrial genomes can be studied in animals such as mice, only by studying the process in human embryos will information directly relevant to human development and PGD be obtained.

9. The Committee was further satisfied that the activities to be licensed are necessary or desirable for the following purposes, specified in Schedule 2 paragraph 3A(1) and 3A(2) to the Act, for the following reasons according to the peer reviewer:

    - *Developing methods for detecting the presences of gene, chromosome or mitochondrion abnormalities in embryos before implantation*: The research addresses the question of how different mitochondrial genomes segregate into the cells of the developing embryo – is it by differential expansion of different genomic clones or by differential attrition? The aim of the research is to improve the predictive ability of preimplantation genetic diagnoses (PGD), making it easier for mothers whose offspring may suffer from mitochondrial diseases of the mitochondrial genome to make reproductive choices;
    - *Increasing knowledge about the development of embryos:* The research aims to understand certain aspects of the behaviour of mitochondria during embryo development, which may help in understanding the mitochondrial genome's contribution to embryo viability.

10. The Committee was satisfied that the proposed project does not involve mixing sperm with the egg of an animal.

11. The Committee was satisfied that the inspector had previously seen the patient information and consent forms, and that these met the statutory requirements.

12. The Committee was satisfied that the research project had received the necessary level of research ethics approval required for this project.

13. The Committee noted the recommendation from the Executive to grant the new research licence for a period of three years without additional conditions.

14. The Committee noted that the three-year licence recommended by the inspector is longer than usual for an initial research licence; however, it agreed that this was justified due to the PR already undertaking a HFEA-licensed research project (R0111).

Decision

15. The Committee agreed to grant the research licence for centre 0035 for project (R0196) for a period of three years with no additional conditions.

16. Any future renewal applications for this licence should be considered by the Licence Committee.

17. The Licensed activity is:
    - Use of embryos

Signed: Date: 29 January 2015

Andy Greenfield (Chair)

New research application: Inspection report

Purpose of this inspection report

The HFEA licenses and monitors establishments undertaking human embryo research. This is a report of an inspection, carried out to assess whether this centre will comply with essential requirements when carrying out such research. Licences for individual research projects can be granted for up to three years and this report provides information on the centre's initial application for a research licence. The Authority's Licence Committee uses the application and this report to decide whether to grant a licence and, if so, whether any additional conditions should be applied to the licence.

Date of inspection: 23 December 2014

Purpose of inspection: This inspection was performed in response to the centre's application for a new research licence.

Inspection details:
The report covers the findings from the initial licensing inspection, communications received from the centre and consideration of the application by the peer reviewers.

Date of Licence Committee: 15 January 2015

Centre Details:

Project title	Studying mitochondrial DNA quality control in human oocytes and pre-implantation embryos
Centre name	Oxford Fertility Unit
Centre number	0035
Research project number	New project application, number not yet allocated
Centre address	Institute for Reproductive Sciences, Oxford Business Park North, Oxford, OX4 2HW
Proposed Person Responsible (PR)	Dr Karen Turner
Proposed Licence Holder (LH)	Dr Ingrid Granne
Treatment centres donating to this research project	Centre 0035 only

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Section 1: Summary report

Brief description of the centre and the background to the application:

The Oxford Fertility Unit is situated within the Institute for Reproductive Sciences, Oxford University. The centre holds a treatment (including embryo testing) and storage licence. The centre has also held a research licence for project R0111 (Development of a model to study implantation in the human) since 1998 (since 2009 at the current centre premises) and previously held research licences for projects R0143 (Deriviation of human embryonic stem cell lines) and R0149 (Preimplantation genetic diagnosis for mitochondrial DNA disease). Project R0111 is also licensed at the Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford (centre 0311). The licence for project R0111 was last renewed in June 2012 and an interim inspection was performed in May 2014.

The Person Responsible (PR) of research project R0111 (Dr Karen Turner) has applied for a further research licence to undertake another project at centre 0035 entitled: 'Studying mitochondrial DNA quality control in human oocytes and pre-implantation embryos'. Dr Turner is the proposed PR. Dr Turner has considerable experience of embryological sciences, being the Lead Embryologist for the treatment and storage activities at centre 0035, and has completed the PR entry programme (R/1021/7). The proposed Licence Holder of the new research project (Dr Ingrid Granne) was recently approved as the LH of project R0111.

Summary for licensing decision:

Taking into account the essential requirements set out in the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended), the HF&E Act 2008 and the HFEA Code of Practice (CoP), the inspection team considers that it has sufficient information regarding this licence application to conclude that:

Administrative requirements:

- the centre has submitted an appropriately completed licence renewal application form;
- the centre has submitted the supporting information required by General Direction 0008 including evidence of ethics approval, patient information and a consent form;
- the application has designated a suitable individual to act as the PR;
- the proposed licence applies to one project of research;
- the centre has paid licensing fees to the HFEA in accordance with requirements;
- the project application has been reviewed positively by two peer reviewers.

Research activities applied for:

The new licence application form requests the following activities are included on the licence for the purpose of research at the centre:

- The use of embryos in research.

The PR has also indicated in the application form that she wishes to apply for a licence for the following additional activities:

- Use of immature oocytes in research
- Fixing of eggs or embryos for research
- Genetic testing of cells removed from embryos
- 'Other activities' (In vitro culture of immature eggs and abnormally fertilised embryos (for no longer than 5 days)

The inspector notes that a HFEA licence is not required for using gametes in research in the manner proposed in this application, and that the additional activities in relation to embryos fall within the scope of a licence to use embryos in research.

The application does not include ‘storage of embryos for research’ or ‘keeping embryos for research’ as activities to be licensed. The PR has confirmed that these activities are not required, because embryos and eggs will be transferred to and used in the project very soon after they are judged to be not clinically useful. No stored embryos will be used in the project and no eggs or embryos used in the project will be subsequently frozen.

The proposed research project does not involve the derivation of human embryonic stem cell lines for human application or the genetic modification of embryos.

Purposes for which research activities may be licensed:

The application for the proposed research licence indicates that the PR considers that the research project will meet the following purposes defined in Schedule 2 3A (1) and (2) to the HF&E Act 1990 (as amended). Comments on whether the project will meet these purposes were also provided by two peer reviewers:

A) Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation (HF&E Act 1990 (as amended), Sch. 2 3A (2) g).

> The reason for this, as stated by the PR, is: ‘We aim to increase understanding of mitochondrial DNA (mtDNA) transmission in order to improve strategies for preventing transmission of severe MtDNA disease. In particular, we will investigate alternative strategies to replacing defective mitochondria using "nuclear transfer" which remains controversial. Instead our investigations will be based on the established option, pre-implantation genetic diagnosis (PGD). We will investigate whether "purifying selection" of mtDNA can be enhanced by increasing mtDNA turnover. Combining this with PGD may be more robust and sustainable way of reducing the recurrence of mtDNA disease, without the uncertainties surrounding nuclear transfer.’
>
> Both peer reviewers agreed that this purpose would be addressed by the project.
>
> Peer reviewer 1 stated: ‘The research addresses the question of how different mitochondrial genomes segregate into the cells of the developing embryo – is it by differential expansion of different genomic clones or by differential attrition? The aim of the research is to improve the predictive ability of pre-implantation genetic diagnoses (PGD), making it easier for mothers whose offspring may suffer from mitochondrial diseases of the mitochondrial genome to make reproductive choices.’
>
> Peer reviewer 2 stated: ‘see above’ referring to comments previously made, these being ‘by examining mitochondrial turnover rates in human eggs/embryos’ and ‘may make pgd a possible route to avoid genetic disease’. These comments had been made in support of defined purposes not indicated by the PR, specifically a) Increasing knowledge about serious disease or other serious medical conditions; and b) Developing treatments for serious disease or other serious medical conditions.

B) Increasing knowledge about the development of embryos (HF&E Act 1990 (as amended), Sch. 2 3A (2) h).

The reason for this, as stated by the PR, is: ‘At the blastocyst stage, a proportion of undifferentiated cells become the inner cell mass which eventually gives rise to the body of the embryo, the remainder differentiating into the placenta and membranes. A tiny minority of cells become the precursors of primordial germ cells that transmit mtDNA to future generations. Yet little is known about mtDNA replication or mitophagy in the human germline, and no timing or measurement of it has been made, to inform HFEA decisions on therapeutic nuclear transfer for mtDNA disease.’

Neither peer reviewer acknowledged that the proposed project would address this defined purpose.

In the absence of a comment from either peer reviewer it is recommended that should the Licence Committee consider granting this licence, the purposes for which the research is licensed should be restricted to ‘Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation (HF&E Act 1990 (as amended), Sch. 2 3A (2) g)’.

Prohibited research activities:
The activities to be licensed are not prohibited by the HF&E Act 1990 (as amended).

The creation of embryos:
No embryos are to be created specifically for the proposed research project and embryo creation is not requested as an activity on the research licence.

Use of human embryos:
Both peer reviewers agreed that the use of human embryos in the proposed research project is necessary.

Peer reviewer 2 did not state why however peer reviewer 1 stated: ‘Although the segregation of mitochondrial genomes can be studies in animals such as mice, only by studying the process in human embryos will information relevant to human PGD be obtained.’

PR considerations:
The proposed PR is suitable and is expected to discharge her duty under Section 17 of the HF&E Act 1990 (as amended). This conclusion is based on the proposed PR’s qualifications, previous experience and activities as PR of research project R0111 at the centre.

Premises:
The premises at centre 0035 were reviewed on inspection and were considered suitable.

Recommendation:
The Licence Committee is asked to note that at the time of the inspection, no recommendations for improvement were made.

The inspector considers that there is sufficient information and evidence available to recommend that a research licence is granted to centre 0035 for the proposed research project for a period of three years without additional conditions. The inspector notes that this period of licence is longer than usual for an initial research licence but considers that this is justified because the PR already undertakes another HFEA-licensed research project.

The inspection team recommends that the licence issued should include the following activity:

- Use of embryos

For the following purposes:

- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation (HF&E Act 1990 (as amended), Sch. 2 3A (2) g).

The PR has requested that the licence for the project is issued at the earliest opportunity so that the work can progress.

Section 2: Summary of the research project

This section summarises information submitted by the proposed PR in the research licence application.

Lay summary of the research project:

'Mitochondria are cell components, essential for life. However, one in 400 people has a maternally inherited mutation in mitochondrial DNA (mtDNA), the 'blue print' for mitochondrial components. MtDNA mutations can cause a range of illnesses, which may be extremely severe, and there are no curative treatments. There are centres developing techniques for replacing disabled mitochondria with healthy ones using a radical technique called "nuclear transfer", but this remains controversial. Alternative techniques are hampered by poor understanding of the underlying mechanisms around the inheritance of mtDNA. We know that MtDNA is inherited via the female line only and the severity of the disease depends on the proportion of abnormal mtDNAs in particular cells of the body. However, this proportion varies from one generation to the next and cannot be predicted. The variability in the number of abnormal mtDNAs inherited is caused by an event known as the 'mitochondrial bottleneck' which takes place in the female germline. We aim to study the biological processes that occur at this point (the mitochondrial bottleneck) as the effectiveness of medical interventions to reduce the load of mutant mtDNA will depend critically upon the timing and impact of it. Our work seeks to provide greater understanding of the biological process underlying the timing and impact of the mitochondrial bottleneck, with our overall aim to provide strategies for reducing mutant mtDNA load in embryos prior to implantation, which will translate into reduced risk of affected mothers having offspring with severe disease. To do our investigations we plan to use eggs and very early stage embryos donated from patients having In Vitro Fertilisation (IVF) at the Oxford Fertility Unit. They are eggs/embryos which are not suitable for clinical procedures and would otherwise be discarded.'

Objectives of the research:

'We wish to seek evidence for the presence of a mitochondrial DNA (mtDNA) bottleneck in human oocytes and preimplantation embryos. This could arise as a result either of clonal mtDNA proliferation, or as a result of mtDNA turnover of damaged mtDNA. (A third possibility that is beyond the scope of the current investigation is that the bottleneck arises through partitioning of subpopulations of mtDNA into specific cells that are destined to become the inner cells mass). Specifically:

- To investigate mtDNA synthesis in immature oocytes and preimplantation embryos (Identify newly synthesized mtDNA by pulse labelling);
- To investigate mitochondrial autophagy (self-degradation)(Compare levels of autophagy with the mtDNA synthesis at different stages of development);
- To investigate mtDNA damage in oocytes and pre-implantation embryos (Identify differences in mtDNA sequence data that suggest mtDNA turnover).'

Donation and use of embryos:

The new licence application proposes the use in the research project of 16 fresh eggs, 16 failed to fertilise embryos and 16 fresh embryos in year 1, and 17 fresh eggs, 17 failed to fertilise embryos and 17 fresh embryos in years 2 and 3.

The PR has clarified in an email subsequent to the application that the licensed material to be used in the proposed project comprises:

‘Fresh (immature) Eggs: These are immature oocytes which are rejected for ICSI purposes (injection with a single sperm) as they have not reached the correct maturation (Metaphase II of meiosis) stage where they can be fertilised within the required time (6 hours post oocyte retrieval, 40-42h post hCG). i.e. oocytes at Germinal vesicle and Metaphase I stages of meiosis. These eggs will be available for research use following fertilization checks (16-18 hours post insemination).
‘Failed Fertilised Eggs: Oocytes which have been inseminated/injected with sperm (IVF/ICSI) and which fail to fertilise after the fertilisation checks 16-18 and 25 hours post insemination, i.e. no sign of pronuclear formation (0PN). These eggs will be available after the 25 hour checks.
‘Fresh (non-clinical) Embryos: Eggs which are fertilised, but have an abnormal number of pronuclei (either 1 or 3 or more). These eggs will be available after the 25 hour checks.’

The inspector notes that the fresh (immature) eggs will not have been exposed to sperm and can be considered to remain gametes. The research activities to be undertaken using these gametes, as detailed in the licence application, are not licensable by the HFEA.

The ‘failed to fertilise’ eggs will have been exposed to sperm but not shown signs of fertilisation 16-18 and 25 hours post insemination; they will thus be considered abnormal and unsuitable for use in treatment. The possibility remains that they may be abnormally fertilised and thus should be considered to be embryos according to the definition in the HF&E Act 1990 (as amended), Section 1.1 (b). The fresh (non-clinical) embryos will also be unsuitable for use in treatment but will be live embryos. Research on such ‘failed to fertilise’ eggs and fresh (non-clinical) embryos requires a HFEA licence (HF&E Act 1990 (as amended) Section 3.1A.a).

The peer reviewers both considered that the proposed number of embryos to be used is justified.

Section 3: Details of the inspection findings

Principle:

3. Have respect for the special status of the embryo when conducting licensed activities.

What we inspected against:

RLCs R23, R24, R26, R27, R28, R29, CoP Guidance Note 22.

What the centre does well.

Observations and discussions during the inspection, provided assurance that the special status of the human embryo will be respected at centre 0035 in the proposed research project:

- the centre has processes to ensure that embryos obtained for the purposes of the research project, will not be kept or used for any other purposes (RLC R23).
- research staff have been advised regarding the restrictions of the HF&E Act 1990 (as amended) and effective supervision of the project by the PR will prevent the use of donated embryos in unlicensed activities.
- each embryo used in the research project will be uniquely labelled (RLC R26).
- clinical and research roles will be separated (RLC R27).
- procedures will ensure that embryos do not develop after 14 days or the primitive streak has appeared (if earlier) (RLC R28). The manipulation of each egg and embryo will be recorded in the laboratory records.

What they could do better.

No recommendations for improvement were made relating to this principle.

Principles:

5. Provide prospective and current patients and donors with sufficient, accessible and up-to-date information in order to allow them to make informed decisions.

6. Ensure that patients and donors have provided all relevant consents, before any licensed activity is undertaken.

What we inspected against:

Information, counselling and consent; CoP Guidance Note 22, RLCs R18, R19, R20, R21, R22. Consent for storage; CoP Guidance Note 22, RLCs R31, R32, R33, R34, R35, R36, R37, R38, R39.

What the centre does well.

Provision of information and counselling to those consenting to donate to research

All embryos to be used in the proposed project will be donated to the project at the Oxford Fertility Unit (centre 0035) using the same process as is currently used for project R0111. The centre has a dedicated research nurse who co-ordinates the research donation pathway. Trained nursing staff will give suitable information regarding the research project and offer

counselling to gamete providers considering consenting to donation to the research project (RLCs R18, R19 and R21). Research consents will be verified to be in place before material is moved from the embryology laboratories to the research laboratory. This donation process was considered during the renewal of the licence for project R0111 in 2012 and was found to be compliant with HFEA requirements. The donation process was discussed with the PR and the research nurse at this inspection and was considered to remain compliant.

The combined patient information and consent form document for the proposed new project was reviewed by the inspector and was considered to be compliant with HFEA requirements (RLCs R19 and R22).

Consent for storage

The PR confirmed that no embryo storage for research purposes will be undertaken for this project.

What they could do better.

No recommendations for improvement relating to this principle were made.

Principle:

8. Ensure that all premises, equipment, processes and procedures used in the conduct of licensed activities are safe, secure and suitable for the purpose.

What we inspected against:

Premises and facilities; RLC R10

What the centre does well.

Premises and facilities

The premises where research will be carried out were reviewed and were considered to be secure, clean, well maintained and suitable for carrying out the proposed licensed activities (RLC R10). The equipment within the research laboratory is maintained, cleaned and suitable for the activities to be undertaken (RLC R10). It is noted that the research laboratory is also already licensed to undertake project R0111.

What they could do better.

No recommendations for improvement relating to this principle were made.

Principle:

10. Maintain proper and accurate records and information about all licensed activities

What we inspected against:

Information and record keeping; RLCs R13, R14, R15, R16, R17, General Direction 0002.

What the centre does well.

Discussions with the proposed PR and the research nurse, and review of the existing embryo donation log for research project R0111, indicated that proper records of embryo usage in the proposed project will be maintained (RLC R15).

The proposed PR has, in previous years in her role as the PR of project R0111, submitted annual research information and data sheets to the HFEA (RLC R14 & General Direction 0002).

What they could do better.

No recommendations for improvement were made relating to this principle.

Principle:

11. Report all adverse incidents (including serious adverse events and reactions) to the HFEA, investigate all complaints properly, and share lessons learned appropriately

What we inspected against:

Incidents; RLC R40

What the centre does well.

Processes are in place to detect, report and investigate adverse incidents (RLC R40).

What they could do better.

No recommendations for improvement were made relating to this principle.

Principle:

12. Ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos.

What we inspected against:

HF&E Act 1990 (as amended), Schedule 2 (3(5) and 3A).

What the centre does well.

The research project has been approved by the National Research Ethics Service (NRES) Committee South Central – Oxford B. Evidence was provided by the proposed PR that approval by this committee remains active and covers the activities described in this licence application.

The research project does not include any activities that are prohibited by the HF&E Act 1990 (as amended).

Two peer reviews of the application for the proposed research project were obtained; both are supportive of the project and recommended it be provided with a HFEA research licence.

What they could do better.
No recommendations for improvement were made relating to this principle.

Principle:

13. Conduct all licensed activities with regard for the regulatory framework governing treatment and research involving gametes or embryos within the UK, including:

- maintaining up-to-date awareness and understanding of legal obligations;
- responding promptly to requests for information and documents;
- co-operating fully with inspections and investigations by the HFEA or other agencies responsible for law enforcement or regulation of healthcare.

What we inspected against:

Licensing; RLCs R1, R2, R3, R5, R6. The Person Responsible; HF&E Act 1990 (as amended) Section 16 & 17, RLCs R8, R9.

What the centre does well.

Licensing

Inspection of the proposed licensed premises indicated that the proposed research activities can be performed within the premises specified in the application, which are also already licensed for project R0111. These activities will be carried under the supervision of the PR and LH (RLC R1, R2).

The Person Responsible

The PR has a key role to play in implementing the requirements of the HF&E Act 1990 (as amended) and is the person under whose supervision the licensed activities are authorised. The PR has the primary legal responsibility under Section 17 of the HF&E Act 1990 (as amended) to secure:

- that suitable practices are used in undertaking the licensed activities;
- that other persons working under the licence are suitable and;
- that the conditions of the licence are complied with.

The proposed PR has suitable qualifications and experience for the activity authorised by the licence (HF&E Act 1990 (as amended), Section 16 2 ca). The PR has successfully completed the HFEA PR Entry Programme (R/1021/7) and is currently the PR of project R0111 at centre 0035.

Discussions with the PR and research nurse on inspection indicated that they are aware of the conditions of the research licence applied for.

What they could do better.
No recommendations for improvement were made relating to this principle.

Section 4: Areas of practice that require the attention of the Person Responsible

The section sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been classified into critical, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Standard Licence Conditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well as the timescales in which these improvements should be carried out.

Critical areas of non compliance

A critical area of non compliance is an area of practice which poses a significant direct risk of causing harm to a patient, donor or to an embryo. A critical area of non compliance requires immediate action to be taken by the Person Responsible

Area of practice and reference	Action required and timescale for action	PR Response	Executive Review
None.			

Major areas of non compliance

A major area of non compliance is a non critical area of non compliance:

- which poses an indirect risk to the safety of a patient, donor or to an embryo through the procurement, use, storage or distribution of gametes and embryos, which do not comply with the centre's licence;
- which indicates a major shortcoming from the statutory requirements;
- which indicates a failure of the Person Responsible to carry out his/her legal duties
- a combination of several "other" area of non compliance, none of which on their own may be major but which together may represent a major area of non compliance.

Area of practice and reference	Action required and timescale for action	PR Response*	Executive Review
None			

‘Other’ areas of practice that requires improvement

Other areas of practice that require improvement is any area of practice, which cannot be classified as either a critical or major area of non compliance, but which indicates a departure from good practice.

Area of practice and reference	Action required and timescale	PR Response	Executive Review
None			

Additional information from the Person Responsible