Executive Licensing Panel Minutes

Centre 0067 (St Mary's Hospital)

Renewal Inspection Report – Research Project R0026

Date:	13 July 2021	
Venue:	HFEA Teleconference Meeting	
Attendees:	Clare Ettinghausen (Chair) Kathleen Sarsfield-Watson Niamh Marren	Director of Strategy and Corporate Affairs Communications Manager Regulatory Policy Manager
Executive:	Bernice Ash	Secretary
Observers:	Catherine Burwood	Licensing Manager

Declarations of interest

- Members of the panel declared that they had no conflicts of interest in relation to this item.

The panel had before it:

- 9th edition of the HFEA Code of Practice.
- Standard licensing and approvals pack for committee members.

The following papers were considered by the panel:

Papers enclosed:

- Research Renewal Report
- Application form
- Document provided by PR: 'Supporting information for applications and PR response to peer review comments'.
- Sperm, Egg and Embryo research – Patient Information Sheet (the consent form is contained within the document)
- Frozen Egg and Embryo Research – Patient Information
- Frozen Embryo Research Consent Form
- Email from the current PR authorising application

  [Note: the patient information and consent forms include tracked changes reflecting the amendments made by the PR immediately after the inspection.]
- Email from PR confirming project title R0026
- Email from PR confirming licenced activities applied for
- Publications;
  - Muller 2019.
  - Smith et al 2019
  - Ruane 2020
- Peer Review
- Previous licensing minutes:
  - 2018-11-08 Licence Committee Minutes Research Renewal R0026 Centre 0067

1. Background

1.1. The panel noted that St Mary's Hospital is a treatment and storage and research centre located in St Mary's Hospital, Manchester.

1.2. The panel noted that the research project entitled 'In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos', project R0026, was first licensed in June 1996.

1.3. The panel noted that the centre's current licence was granted by the Licence Committee (LC) in November 2018 and is due to expire on 31 December 2021.

1.4. The panel noted that in March 2020, the World Health Organisation declared a world-wide pandemic of Coronavirus (Covid-19). In response to UK measures to contain and mitigate the spread of the virus, new inspection methodologies were developed and implemented. These methods enable compliance to be reviewed through desk based assessment (DBA) and the use of virtual technology where available and appropriate. A risk based approach (RBA) can then be applied, balancing the risks of on-site inspection during the Covid-19 pandemic against those resulting from potential non-compliances, identified during DBA, if not adequately investigated

1.5. The panel noted that HFEA licensed premises must be inspected on site every two years in accordance with Schedule 3B paragraph (4)(1) of the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended). Whilst the current restrictions of the pandemic do not prohibit on-site inspection, the risks of doing so must be balanced against the need for the Authority to fulfil its legal duties.

1.6. The panel noted that the centre was last inspected in July 2017. An on-site inspection should usually have been conducted by July 2019; due to an oversight in the inspection scheduling process, this did not occur.

1.7. The panel noted that the centre was due to be inspected in 2020, but this was cancelled owing to the Covid-19 pandemic. Due to the length of time since the last on-site inspection visit, the executive requested that the Person Responsible (PR) submit an application to renew the licence, earlier than usual, so that a site visit could be conducted as soon as practicable, taking into account government guidance relating to the pandemic.

1.8. The panel noted that PR also carries out licensed activities for research project R0026 at two other research only licensed premises; University of Manchester (centre 0175) and the Maternal and Fetal Health Research Centre, St Mary's Hospital (centre 0360). Activities, in relation to the research project being undertaken at all three centres, were also reviewed during the DBA, videoconference meeting and on-site inspection visit.

1.9. The panel noted that the research licences for centres 0175 and 0360 are also due to expire on 31 December 2021; the PR's applications to renew those licences are also for consideration at the meeting.

1.10. The panel noted that a slight amendment to the project title has been requested; the word 'pre-embryos' is to be replaced by 'embryos'. This is to make the project title accurately reflect the research activity, there is no change to research purposes.

1.11. The panel noted that, following the DBA/RBA for this centre, items of concern identified were of relatively low risk and could be reviewed effectively using virtual technology via a videoconference meeting with key members of staff. In order to meet the HFEA's statutory

requirements, a short on-site inspection visit was also conducted with one inspector only to minimise risks of travel and social contact, and in accordance with the centre's Covid-19 safety measures.

1.12. The panel noted that a videoconference meeting occurred on 30 March 2021, followed by an on-site visit on 19 April 2021.

1.13. The panel noted that the research project does not involve the derivation of human embryonic stem cell lines for human application. Research licence conditions R41-89 are therefore not applicable to this research project.

2. Consideration of Application

2.1. The panel noted that the application was submitted, by the PR, to renew the research licence for project R0026, for a period of three years.

2.2. The panel noted that the centre has applied for the following activities:

- Creation of embryo's in vitro
- Keeping embryos
- Using of embryos
- Storage of gametes
- Storage of embryos

2.3. The panel noted that the activities licensed had previously been for the following purposes:

- Promoting advances in the treatment of infertility
- Increasing knowledge about the causes of miscarriage
- Increasing knowledge about the development of embryos

2.4. The panel noted that, at the time of the centre's renewal inspection, one 'other' area of non-compliance was identified regarding patient information and consent. Since the inspection, the PR has provided evidence, confirming that all the recommendations have been fully implemented.

2.5. The panel noted the PR's proposed number of eggs and embryos to be used across all three centres involved in the project (centres 0067, 0175 and 360). The Peer Reviewer stated, 'The proposed annual usage of fresh and frozen eggs and embryos appears to be based on the numbers of each cells type /stage of development as defined in the previous licence application. Unfortunately, this aspect of the application is very vague and no details or justification are provided of how the eggs or embryos will be partitioned and used to address and progress the 5 different research objectives as detailed in the application.' Further to this statement, the PR provided additional information on the allocation of proposed usage of donated material for each of the project aims.

2.6. The panel noted that the Peer Reviewer was supportive of project R0026.

2.7. The panel noted that the inspection team recommends that the project title is changed from 'In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos' to 'In vitro development and implantation of normal human preimplantation embryos and comparison with uni or poly pronucleate embryos.'

2.8. The panel noted that the inspectorate recommends the renewal of the licence for project R0026, with the new project title, for a period of three years, without additional conditions.

3. Decision

3.1. The panel had regard to its decision tree. It was satisfied that the appropriate application and fee had been submitted and that the application contained the supporting information required by General Directions 0008.

3.2. The panel noted that the premises to be licensed are suitable for the conduct of licensed activity.

3.3. The panel was satisfied that the qualifications and character of the PR are such as is required for the supervision of licensed activities and the PR will discharge his duty under section 17 of the HFE Act 1990 (as amended).

3.4. The panel was satisfied that the research project has been approved by the South Central Berkshire B Research Ethics Committee. Evidence was provided by the PR that this approval remains active and covers the research activity described in the licence application.

3.5. The panel was satisfied that the research licence would not apply to more than one research project.

3.6. The panel was satisfied with the suitability of the activities applied for:

- Creation of embryos in vitro
- Keeping embryos
- Using embryos
- Storage of gametes
- Storage of embryos

3.7. The panel was satisfied that the activities to be licensed are necessary or desirable for the following purposes, specified in paragraphs 3A(1) and 3A(2) of Schedule 2 of the HF&E Act 1990 (as amended):

- Promoting advances in the treatment of infertility
- Increasing knowledge about the causes of miscarriage
- Increasing knowledge about the development of embryos

Prohibited Research Activities

3.8. The panel was satisfied that none of the proposed activities are prohibited by the HF&E Act 1990 (as amended).

3.9. The panel was satisfied that this is a research project and that no embryos used in the project would be implanted into a woman.

3.10. The panel was satisfied that the proposed research project does not involve the mixing of sperm with the egg of an animal.

Use of Human Embryos

3.11. The panel was satisfied the use of human embryos is necessary for the purposes of the research.

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

3.13. The panel was satisfied that no embryos would be used without obtaining proper consent for the use of embryos in research from patients.

3.14. The panel noted that the current research is approved by the South Central – Berkshire B Research Ethics Committee and remains active, covering the research activity applied for in the application.

3.15. The panel agreed that the title of project R0026 should be changed from 'In vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly pronucleate pre-embryos' to 'In vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly pronucleate embryos'.

3.16. The panel agreed to renew the research licence for project R0026 at St Mary's Hospital (centre 0067) now entitled 'In vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly pronucleate embryos', for three years, with no additional conditions. The panel agreed that if no representations or any other information is received within 28 days, the final renewal licence should be issued.

3.17. The panel agreed to the following activities and purposes:

Activities:

- Creation of embryos in vitro
- Keeping embryos
- Using embryos
- Storage of gametes
- Storage of embryos

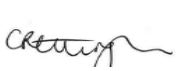
for the following purposes:

- Promoting advances in the treatment of infertility
- Increasing knowledge about the causes of miscarriage
- Increasing knowledge about the development of embryos

4. Chair's signature

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

Signature



Name

Clare Ettinghausen

Date

19 July 2021

Research Renewal 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 complies 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 application for a renewal of its existing licence. The Authority's Executive Licensing Panel (ELP) uses the application and this report to decide whether to grant a new licence and, if so, whether any additional conditions should be applied to the licence.

Date of inspection: 30 March 2021 (videoconference meeting) and 19 April 2021 (on-site visit).

Purpose of inspection: Renewal of a licence to carry out research.

Inspection details: The report covers the performance of the centre since the last inspection, findings from the desk based evaluation, communications received from the centre and the on-site visit.

In March 2020, the World Health Organisation declared a world-wide pandemic of Coronavirus (Covid-19). In response to UK measures to contain and mitigate the spread of the virus, new inspection methodologies were developed and implemented.

These methods enable compliance to be reviewed through desk based assessment (DBA) and the use of virtual technology where available and appropriate. A risk based approach (RBA) can then be applied, balancing the risks of on-site inspection during the Covid-19 pandemic against those resulting from potential non compliances, identified during DBA, if not adequately investigated.

HFEA licensed premises must be inspected on site every two years in accordance with Schedule 3B paragraph (4)(1) of the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended). Whilst the current restrictions of the pandemic do not prohibit on-site inspection, the risks of doing so must be balanced against the need for the Authority to fulfil its legal duties. This centre was last inspected in July 2017 therefore an on-site inspection should usually be conducted by July 2019. However, this did not take place due to an oversight in the inspection scheduling process. An on-site visit was planned for 2020 but this was cancelled due to the Covid-19 pandemic.

Following the DBA/RBA for this centre items of concern identified were of relatively low risk and could be reviewed effectively using virtual technology via a videoconference meeting with key members of staff. In order to meet the HFEA's statutory requirements a short on-site inspection visit was also carried out with one inspector only to minimise risks of travel and social contact, and in accordance with the centre's Covid-19 safety measures.

Inspectors: Karen Conyers (lead videoconference meeting and on-site visit) and Karen Campbell (HFEA observer videoconference meeting).

Date of Executive Licensing Panel: 13 July 2021

Centre Details:

Current project title	In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos
Centre name	St Mary's Hospital
Centre number	0067
Centre address	The Department of Reproductive Medicine, Old Saint Mary's Hospital, Oxford Road, Manchester, M13 9WL
Research project number	R0026
Person Responsible	Professor Daniel Brison
Licence Holder	Professor Sue Kimber
Treatment centres donating to this research project	0005 Fertility Exeter 0006 The Lister Fertility Clinic 0007 Hewitt Fertility Centre 0008 CARE Tamworth 0033 Manchester Fertility 0035 Oxford Fertility 0067 St Mary's Hospital 0144 CARE Woking 0197 Salisbury Fertility Centre 0316 Centre for Reproduction & Gynaecology Wales (CRGW)
Date licence issued	01 January 2019
Licence expiry date	31 December 2021
Additional conditions applied to this licence	None

Contents

Section 1: Summary report

Brief description of the centre and its licensing history:

Centre 0067 is a treatment and storage and research centre located in St Mary's Hospital, Manchester. The research project entitled 'In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos' was first licensed in June 1996. The current research licence is due to expire on 31 December 2021, having been renewed for three years by a Licence Committee on 8 November 2018. There are no additional conditions on the licence.

The centre was last inspected on 11 July 2017. A desk-based renewal of the licence was carried out in August 2018, at that time there were no areas of practice that required improvement. The centre was due to be inspected in 2020 but this was cancelled due to the Covid-19 pandemic. In view of the length of time since the last on-site inspection visit, the executive requested that the Person Responsible (PR) submit an application to renew the licence earlier than usual so that a site visit could be conducted as soon as practicable taking into account government guidance relating to the pandemic. The site visit took place on 19 April 2021.

The PR also carries out licensed activities for the research project R0026 at two other research only licensed premises; University of Manchester (centre 0175), and Maternal and Fetal Health Research Centre (centre 0360). Activities in relation to the research project being undertaken at all three centres were reviewed during the DBA, videoconference meeting and on-site inspection visit. The research licences for centres 0175 and 0360 are also due to expire on 31 December 2021 and the PR's applications to renew those licences are also being considered by ELP at this meeting. ELP is asked to note that there is a slight amendment to the project title where the word 'pre-embryos' is to be replaced by 'embryos'. This is to make the project title accurately reflect the research activity, there is no change to research purposes.

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, Research Licence Conditions (RLCs) and the HFEA Code of Practice (CoP), the inspection team considers that it has sufficient information to conclude the following.

Administrative requirements:

- The centre has submitted an appropriately completed application form.
- The centre has submitted the supporting information required by General Direction 0008, including evidence of ethics approval and patient information and consent forms.
- The application has designated an individual to act as the PR.
- The proposed licence applies to one project of research carried out at three sites separately licensed.
- The centre has submitted fees to the HFEA in accordance with requirements.

Following discussions with the PR, the inspection team notes that the project title no longer accurately reflects the accepted definition of an embryo in the context of this research project. Therefore, the title of the project should be amended from the current title

‘In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos’
to
‘In vitro development and implantation of normal human preimplantation embryos and comparison with uni or poly pronucleate embryos’.

Research activities applied for:
The PR has confirmed by email that he wishes to apply for the following activities for the purpose of research:

- Creation of embryos in vitro
- Keeping embryos
- Use of embryos
- Storage of gametes
- Storage of embryos

The proposed research project does not involve the derivation of human embryonic stem cell lines for human application. Research licence conditions R41-89 are therefore not applicable to this research project.

Purposes for which research activities may be licensed:
The activities specified above are required by the PR for the following purposes, as defined in Schedule 2 3A (1) and (2) of the HF&E Act 1990 (as amended):

- Promoting advances in the treatment of infertility
- Increasing knowledge about the causes of miscarriage
- Increasing knowledge about the development of embryos

The PR and peer reviewer consider that the research project will meet the purposes defined in Schedule 2 3A (1) and (2) to the HF&E Act 1990 (as amended) as follows.

- Promoting advances in the treatment of infertility.
  The PR has stated:
  ‘The aim of this project is to understand the way in which human embryos develop normally and abnormally in culture. In particular, we study the regulation of cell fate in embryos, in terms of survival, maintenance of pluripotency, and differentiation/cell lineage specification, and expression of molecules involved in embryo development, and the implantation process. We have a particular interest in how the in vitro environment and IVF manipulations impact on this, for example the way in which growth factors regulate cell fate, the influence of DNA damage in sperm on embryonic development, or the impact of cryopreservation on embryonic development, gene expression and implantation. This work has lead to an assessment of the role of growth factors in embryo culture medium, the influence of DNA damage in sperm on fertility treatment, the possible role of oocyte activation in fertility treatment, and increasing understanding of implantation failure.’

- Increasing knowledge about the causes of miscarriage.
  The PR has stated:

‘Understanding early human embryo development and the regulation of cell fate and pluripotency and the interaction with maternal cells at implantation may be relevant to understanding why embryos do not develop to term, i.e. miscarry.’

- Increasing knowledge about the development of embryos.
  The PR has stated:
  ‘Understanding gene expression in early human embryo development and the regulation of cell fate and pluripotency may be relevant to understanding why embryos do not develop in human ART.’

  The peer reviewer agrees that the research project will meet these three purposes, as described above, and has stated:
  ‘Human preimplantation embryo developmental competence and implantation potential (i.e. quality) is ultimately dependent on the quality of the eggs and sperm from which the embryo is derived and is influenced by a series of parameters including: (i) aetiology of infertility in the couple from which the gametes and embryos are derived ; (ii) the nature of the infertility treatment and ovarian stimulation protocol(s) used to generate the gametes; (iii) the efficacy of assisted reproduction technologies such as cryopreservation of gametes and embryos; (iv) the in vitro environment and culture conditions used to grow embryos in the laboratory; and (v) the endometrial environment in vivo at the time of embryo transfer and hence implantation environment. The conduct of fundamental research into some/all of these parameters, as is proposed in the current project, will help to increase understanding of how normal vs. abnormal embryo development and implantation are regulated and the information so derived will help to advance infertility treatment and improve understanding of the causes of implantation failure and early miscarriage.’

Prohibited research activities:
The activities to be licensed are not prohibited by the HF&E Act 1990 (as amended) including those activities specifically prohibited by Sections 3, 3ZA, 4 or 4A, or by Schedule 2, paragraph 3 of the Act.

Use of embryos:
The use of human embryos is considered necessary. This is based on the application and comments by the peer reviewer who has stated ‘While useful research into preimplantation embryo development can be conducted using animal species, there is no doubt that the best and most valuable model for studying human embryo development and for advancing understanding of human embryo competence in health and infertility is to study human embryos directly.’

PR considerations:
The PR is suitable and has discharged their duty under Section 17 of the HF&E Act 1990 (as amended).

Premises:
The premises are suitable. This is based on information submitted with this application, and the on-site inspection visit on 19 April 2021.

Recommendation:
ELP is asked to note that at the time of the inspection recommendations were made in relation to one 'other' area of non compliance or poor practice that required improvement.

Since the inspection the PR has provided evidence confirming that all of the recommendations have been fully implemented.

'Other' area of non-compliance:

- The PR should ensure that information for patients donating their embryos to the research project includes all requirements of HFEA research licence conditions and that consent from both gamete providers is obtained.

The inspection team considers that, overall, there is sufficient information and evidence available to recommend the renewal of the centre's licence for a period of three years without additional conditions.

The inspection team recommends that the licence issued should include the following activities that the centre has applied for:

- Creation of embryos in vitro
- Keeping embryos
- Use of embryos
- Storage of gametes
- Storage of embryos

For the following purposes:

- Promoting advances in the treatment of infertility
- Increasing knowledge about the causes of miscarriage
- Increasing knowledge about the development of embryos

The inspection team recommends that the project title is changed from 'In-vitro development and implantation of normal human pre-implantation embryos and comparison with uni- or poly-pronucleate pre-embryos' to 'In vitro development and implantation of normal human preimplantation embryos and comparison with uni or poly pronucleate embryos'.

Section 2: Summary of the research project

This section summarises information submitted in the research licence application and from the Peer Reviewer.

Lay summary of the research project:

The PR has provided the following information in the application form.
'We plan to continue our current project to understand early human embryo development by studying sperm, eggs and embryos donated by IVF patients at our participating centres. For this we use some sperm eggs and embryos which have been frozen as in IVF procedures. We analyse sperm for damage to their DNA and culture the embryos up to day 8 after fertilisation, well before the limit of 14 days post-fertilisation. We are looking at the effect of culture conditions and freezing on how the embryos develop using molecules which tell us about their health and normality and their ability to implant in the wall of the womb and develop. We are looking at how the different cells in the embryo vary from one another and how molecules added to the culture medium affect the developmental decisions that the embryos make, and their ability to implant. These studies will help us to be able to identify what the normal time course of molecular changes are in early human development and what goes wrong. This work will ultimately benefit IVF treatments by increasing our understanding of human embryo development and implantation.'

Objectives of the research:

The PR has provided the following information in the application form.
'We aim to continue and extend our current licence aims to include:

1) studies of gene expression in order to understand normal and abnormal embryonic development and in particular the regulation of cell fate and lineage allocation, including analysis of individual embryonic cells, and genes involved in implantation.

2) the impact of cryopreservation, including vitrification, on oocyte and embryo development.

3) the impact of sperm DNA damage on embryonic development, including the influence of the environment e.g. lifestyle factors and environmental exposures.

4) the impact of the environment on oocyte and embryonic development, including maternal health and embryo culture conditions including medium components such as nutrients, small molecules which alter metabolic pathways, oxygen, growth factors, bacteria, and the extracellular matrix molecular hyaluronate.

5) derivation of trophoblast stem cells from blastocysts for experimental evaluation of Implantation and placental development and function. (Okae H et al. Derivation of Human Trophoblast Stem Cells. Cell Stem Cell. 2018 Jan 4;22(1):50-63.e6. doi: 10.1016/j.stem.2017.11.004. PMID: 29249463).

In some studies human embryos may be created by chemical activation of failed to fertilise oocytes, these studies are important and have proved very revealing in the past as a model of abnormal human embryo development.'

Summary of the research undertaken to date:

The PR has provided the following information in the application form.
'In the 2 years of the current licence period we have continued our studies of gene expression profiles of early human embryos using QPCR and whole genome RNAsequencing and DNA methylation studies, supplemented with immunofluorescence detection of proteins in embryos and assays of the ability of embryos to attach to cells in vitro and form outgrowths. These projects combine to address our project aims to characterize normal and abnormal human embryonic development from fertilization onwards.

In this licence period we have found that:

1) Vitrified and warmed human oocytes show altered gene expression profiles compared to fresh oocytes. We have used PCR assays and single oocyte RNA seq for these studies. Manuscript in preparation.

2) We have extended our work on the impact on embryo development and implantation of molecules found naturally in development such as bacterial contaminants which we show stimulate the embryo's innate immunity (Toll like receptor) system. Manuscript submitted to a journal.

3) We also showed that embryo attachment to uterine epithelial cells in vitro correlates with morphological grading and that hyaluronate (EmbryoGlue) does not enhance embryo attachment (Ruane et al 2020a).

4) ICM and TE cells show distinct global gene expression profiles to each other and to comparable samples of pluripotent embryonic stem cell lines, measured by whole genome microarray. Manuscript in preparation.

5) We have also analysed whole blastocyst gene expression profiles in relation to embryo development parameters measured by time lapse incubation using state of the art gene network analysis approaches, in collaboration with University of Cambridge. Manuscript in preparation.

6) Embryos breach the uterine epithelium with multinuclear trophoblast derived from the trophectoderm (Ruane et al 2020b)

The above work forms the basis of a number of manuscripts, 4 of which have been published in the last 2 years and several more which are currently in submission or in the final stages of preparation for submission. It meets the original project objectives by comparing normal with abnormal embryo development and seeking to understand more about the process of human embryo development and implantation.'

Donation and use of embryos:

In the period from 1 January 2020 to 31 December 2020, the PR reported the following embryo usage across this project.

- The donation of 14 fresh embryos, all of which were used in this project.
- The donation of 279 frozen embryos to this project.
- 38 frozen embryos were used in this project.
- 17 frozen embryos were allowed perish before being used in this project.

- A total of 476 embryos are in storage for use in this project, including 252 embryos donated prior to 1 January 2020.

No embryos have been created for use in this project.

The Covid-19 pandemic and suspension of fertility treatments across the United Kingdom has had an impact on the research centre's activity in 2020. The inspection team notes that in the period from 1 January 2019 to 31 December 2019, the PR reported the use of 206 fresh embryos and 107 frozen embryos.

From the renewal application, the PR proposes to use the following numbers of eggs and embryos across all three centres involved in the project (centres 0067, 0175 and 0360):

100 fresh eggs
50 frozen eggs
100 'failed to fertilise' embryos
200 fresh embryos
200 frozen embryos

Peer review comments:

The peer reviewer stated:
'The proposed annual usage of fresh and frozen eggs and embryos appears to be based on the numbers of each cells type /stage of development as defined in the previous licence application. Unfortunately, this aspect of the application is very vague and no details or justification are provided of how the eggs or embryos will be partitioned and used to address and progress the 5 different research objectives as detailed in the application.'

The PR was asked to comment on this and provided additional information on the allocation of proposed usage of donated material for each of the project aims. This is included as track changes on pages 6 and 7 of the document 'Supporting information for applications and PR response to peer reviewer comment' included in the paper set.

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 during the DBA, an audit of records of embryos usage completed by the PR as part of the DBA, videoconference meeting and on-site inspection provided assurance that the special status of the human embryo is respected.

- Processes, documented in standard operating procedures (SOPs), are in place to ensure that no embryo obtained for the purposes of any research project is kept or used for any purpose other than the purposes of that research project (RLC R23). Staff training and their close supervision ensure procedures are adhered to, preventing the use of donated embryos in unlicensed activities.
- Recruitment practices ensure that no money or other benefit is given to those donating embryos to research unless authorised by directions (RLC R24).
- Each embryo used in the research project is uniquely labelled (RLC R26).
- Documented procedures have been established, implemented and complied with to ensure that clinical and research roles are separated (RLC R27).
- Procedures ensure that embryos do not develop after 14 days or the primitive streak has appeared (if earlier) (RLC R28). The culture and manipulation of each embryo is recorded in the laboratory records, which are regularly reviewed.
- Steps are taken to ensure that if embryos have been created using human cells stored before 1 October 2009, then the embryos cannot subsequently be attributed to the person whose cells were so used (RLC R29).

What they could do better.

Nothing noted.

Principle:

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, R21, R22.
Consent for storage; CoP Guidance Note 22, RLCs R31, R32, R33, R35, R36, R38, R39.

What the centre does well.

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

Prior to giving consent, those donating to research should be provided with relevant information and given a suitable opportunity to receive counselling about the implications of their donation. Observations and discussion during the DBA, an audit of records of embryos usage completed by the PR as part of the DBA, videoconference meeting and on-site inspection provided assurance of the following with the exceptions noted below.

- Prior to giving consent, those donating to research are given a suitable opportunity to receive proper counselling about the implications of their donation (RLC R18).
- Necessary information is provided to patients prior to giving their consent with the exceptions noted below (RLC R19 and R20).
- Information is provided to patients by trained personnel in a manner and using terms that are easily understood (RLC R21). The competence of staff at the recruiting centres to provide information in this way, and to seek consent, has been assessed.
- A designated individual, who is not directly involved in the patient's treatment, is available to discuss with the patient the project of research and the possibility of donating material to the project (RLC R22). Contact details for this designated individual are provided in the patient information.

Consent for storage

The centre is licensed for the storage of gametes, but none are currently in storage at the centre.

Stored embryos are obtained only from centres to which a HFEA licence or third party agreement applies (RLCs R31, R32, R33).

No embryos are kept in storage for longer than the statutory storage period (RLCs R35, R36, R38 and R39), or the period specified in a patients' consent if less than the statutory storage period. This was assessed by reviewing the centre's audit of records of stored embryos recently used in the project.

A bring-forward system is maintained, ensuring that embryos are stored within the statutory storage period or the patients' consent.

What they could do better.

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

During the DBA the following were noted in the patient information and consent forms (recommendation 1).

- The patient information sheet 'Frozen Egg and Embryo Research – Patient Information' did not state whether the embryos or human admixed embryos will be reversibly or irreversibly anonymised, and the implications of this (RLC R19d). In addition, the inspection team noted that the patient information sheet 'Sperm, Egg and Embryo Research – Patient Information Sheet' stated 'Any sperm, eggs or embryos used in research will be anonymised to protect your confidentiality' but did fully explain

this as required in RLC R19d.

- The inspection team also noted that whilst the patient information explained how the research was funded, it did not clarify whether or not any benefit may accrue to the researchers and/or their departments (RLC R19f). The PR explained that no benefits accrue to researchers and therefore it was not stated in the patient information but agreed to amend the documents to make this clearer to patients.

The inspection team also identified the following areas for improvement in the patient information and consent forms.

- The consent form 'Sperm, Egg and Embryo research consent form' for patients to agree to the use of failed to fertilise eggs only required the consent of the egg provider, not the sperm provider. During discussion in the videoconference meeting, the PR agreed that to minimise any potential risk that failed to fertilise eggs are donated and used in the research project less than 48 hours after insemination (falling under the HFEA's definition of an 'embryo' Code of Practice (CoP) guidance note 22, section 22.5), the consent forms should be amended to ensure consent is obtained from both gamete providers.

- In addition, the PR agreed with a suggestion by the inspection team to add a section to each consent form so that the patient can confirm they have been offered an opportunity for counselling prior to providing their consent. The inspection team is assured that patients are being offered an opportunity for counselling about their donation to research, and this change to the consent form will provide a robust process of documenting this offer.

- The PR also agreed that any reference to 'sperm' should be removed from the patient information sheet 'Frozen Egg and Embryo Research – Patient Information' as the centre does not receive frozen sperm for use in the research project.

- The inspection team also suggested that the information regarding creation of embryos for use of research could include some additional information to make this clearer for patients.

The inspection team notes that all patients considering donating their gametes, or embryos, to this project are contacted by the research nurses at centre 0067. Therefore, the inspection team is assured that patients are provide with relevant information verbally before providing consent for their gametes or embryos to be used in the project. RLC R19 does not require that information about the research project is given specifically in writing: compliance can be achieved by giving information verbally. However, the inspection team considers that such detailed information is best given in a written format to ensure patients can consider it fully.

Immediately after the inspection the PR provided revised copies of the patient information and consent forms addressing all of the points noted by the inspection team and confirmed that the changes have been reviewed and approved by the 'Trust Research Sponsorship team'. The PR has also confirmed that these changes are considered to be minor and non-notifiable, therefore do not need to be reviewed by the Health Research Authority (HRA) or the Research Ethics Committee (REC).

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; RLCs R10,

What the centre does well.

Premises and facilities

The premises and facilities are secure, clean, well maintained and are suitable for carrying out the licensed activities (RLC R10). This conclusion is based on the centre's self-assessment questionnaire (SAQ), DBA, videoconference meeting and on-site inspection visit on 19 April 2021.

What they could do better.

Nothing noted.

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.

The centre's audit of records indicates that proper records are maintained (RLCs R13 and R15). These records are in a form that prevents the removal of data (RLC R16). If embryos are to be transferred to another centre, the required information is also sent with them (RLC R17).

Since the last inspection, the centre has submitted the annual research information and data sheet to the HFEA within the required timeframes (RLC R14 & General Direction 0002).

What they could do better.

Nothing noted.

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 to the HFEA and investigate adverse incidents (RLC R40).

What they could do better.

Nothing noted.

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 South Central Berkshire B Research Ethics Committee. Evidence was provided by the PR that this approval remains active and covers the research activity described in the licence application.

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

A peer review was obtained for this renewal application and it is supportive of the licence renewal. Justifications that the activities to be licensed are necessary or desirable to meet the statutory purposes, have been provided by the PR and the peer reviewer, as discussed in detail in the 'Summary for Licensing Decision'. The PR has provided a response for the peer reviewer to address reasons why the use of human embryos is necessary and the proposed number of embryos to be used is justified.

What they could do better.

Nothing noted.

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

The DBA, videoconference meeting and inspection of the licensed premises indicated that all licensed research activities are performed only on the premises specified on the licence and under the supervision of the PR (RLCs R1 and 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 PR has suitable qualifications and experience for the activities authorised by the licence (HF&E Act 1990 (as amended), Section 16 (2)(ca)). The PR has successfully completed the HFEA PR entry programme. The inspection team considered that the PR has fulfilled his responsibilities under Section 17 of the HF&E Act 1990 (as amended).

What they could do better.

Nothing noted.

Section 4: Monitoring of the centre's performance

Following a renewal inspection DBA in 2018 there were no areas of practice that required improvement.

Section 5: 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 'other'. Each area of non-compliance is referenced to the relevant sections of the Act, Regulations, Research 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 identified.			

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 identified.			

‘Other’ areas of practice that require 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
1. Patient information and consent During the DBA the following were noted in the patient information and consent forms and are described in detail in the body of the report. • The documents did not clearly explain whether the embryos or human admixed embryos will be reversibly or irreversibly anonymised, and the implications of this (RLC R19d). • The information did not clarify whether or not any benefit may accrue to the researchers and/or their departments (RLC R19f). • The consent form ‘Sperm, Egg and Embryo research consent form’ for patients to agree to the	The PR should ensure that information for patients donating their embryos to the research project includes all requirements of HFEA research licence conditions and that consent from both gamete providers is obtained. Immediately after the inspection the PR provided revised copies of the patient information and consent forms addressing all of the issues noted.	The PR provided his responses via email on 26 May 2021: ‘On the patient information, we have now been told that the changes are minor and non-notifiable, so won’t require HRA or REC review.’	The executive acknowledges the PR’s response and immediate actions to address the issues identified. No further action is required.

use of failed to fertilise eggs only required the consent of the egg provider, not the sperm provider. (CoP 22.5). The inspection team also recommended three further changes and improvements that could be made to the patient information and consent forms as described in the body of the report. RLCs R19d, R19f and CoP 22.5. It is noted that the HFEA's assessment framework recommends classification as a 'major' non-compliance but the inspection team is assured that all patients are provided with relevant information verbally before providing consent for this gametes or embryos to be used in the project, therefore this has been graded as an 'other' non-compliance.			

Additional information from the Person Responsible