Licence Committee - minutes

Centre 0035 (Oxford Fertility)

Renewal Research Licence – Research Project R0198

Thursday, 6 September 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Kate Brian (Chair) Ruth Wilde Anita Bharucha	
Members of the Executive	Dee Knoyle	Committee Secretary
Legal Adviser	Ros Foster	Browne Jacobson LLP
Specialist Adviser		
Observers	Jonathan Herring (New Authority Member Induction)	

Declarations of interest:

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

The committee had before it:

- 8th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members

The following papers were considered by the committee:

- Renewal Inspection Report
- Renewal application form
- Email from centre providing additional information for application
- Further information provided by centre for peer reviewer
- Email from proposed Licence Holder
- Patient information and consent form
- Publications
- Peer review
- Previous licensing minutes for the last three years:
    - 23 September 2016 – interim research inspection
    - 10 September 2015 - Initial research licence application

1. Background

1.1. Oxford Fertility, centre 0035 is a large treatment and storage centre and provides a full range of fertility services. The centre also has a research unit which currently has two research licences for the following projects:

- R0198 - entitled 'Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality'. This research licence is due to expire in September 2018.

  This research programme was initially undertaken as part of project R0111, after the licence for that project was varied in 2014 to allow it. When considering the application for licence renewal in 2015, the PR decided that the scope of the research work more accurately related to two separate projects. Therefore, project R0111 reverted to its original scope and objectives prior to the variation in June 2014 and a new research licence for the artificial egg activation research was applied for and approved as project R0198 in September 2015.

- R0111 - entitled 'Development of a model to study implantation in the human'. This licence is due to expire in September 2018 and will not be renewed.

1.2. An interim inspection was carried out in July 2016, prior to this recent renewal inspection, and there were no areas of practice that required improvement.

2. Consideration of application

Application

2.1. The committee noted that an application was submitted to renew the research licence for project R0198.

2.2. The committee noted that the application to renew the research licence was made by the Person Responsible (PR) for a period of three years.

2.3. The committee noted that the centre has applied for the following activities:

- creation of embryos in vitro
- keeping embryos
- use of embryos.

2.4. The committee noted that the proposed activities are to be licensed for the following purposes:

- promoting advances in the treatment of infertility
- developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- increasing knowledge about the development of embryos.

2.5. The committee noted that the treatment centre donating to this research project is:

- Oxford Fertility, centre 0035.

Inspection Process

2.6. The committee noted that the renewal inspection took place on 20 June 2018 and the renewal inspection report dealt with the performance of the centre since the last inspection, findings from the inspection, and communications received from the centre. The committee noted that the centre has one critical area of practice that requires improvement.

- Critical area of non-compliance - the PR should ensure that appropriate consent is in place prior to the use of embryos in research.

2.7. A patient couple attended a nurse consultation in July 2016, when consent for a number of research projects at the centre was given by both gamete providers. This included consent for the use of embryos in research for project R0111. However, on the consent form for research project R0198 the male partner's signature was missing. The centre's standard procedure is for two members of staff to review consent at two separate time points prior to use in research, both at the nurse consultation and then prior to laboratory set up for the treatment cycle. Both checks failed to notice that the male partner's consent to this research project was missing.

2.8. The committee noted that immediately after the inspection, the PR performed a sample audit of 21 sets of records to ensure appropriate consent was in place for research project R0198. The audit found one other case where a 1PN egg had been used in this research project without the consent of the male gamete provider. The committee noted that the PR considers that one contributory factor is a misunderstanding amongst patients and staff that only female consent is required for this project because of its focus on eggs. The PR provided evidence immediately after the inspection that actions had already been taken to implement the recommendation for this critical non-compliance.

2.9. The committee noted that the peer reviewer was supportive of the project.

Recommendation

2.10. The committee noted that the inspectorate recommends the renewal of the licence for research project R0198 for a period of three years, without additional conditions, with the above activities and purposes applied for by the PR.

2.11. The committee noted that there was a delay in renewing the research licence for project R0198 due to various administrative issues, resulting in this application being considered late and close to the expiry date of the licence. The inspectorate recommended the issue of Special Directions under Section 24 (5A)(b) of the HF&E Act 1990 (as amended) to permit the continuation of the licensed research project R0198, to be in force from 24 September 2018 to 24 December 2018, or earlier if a new licence is granted.

3. Decision

3.1. The committee had regard to its decision tree.

Administrative Requirements

Supporting Information under General Direction 0008

Application

3.2. The committee was satisfied that the application was submitted in the form required and contained all the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fees had been paid.

Ethics Approval

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

Proposed Person responsible (PR) – Dr Karen Turner

3.4. The committee noted that the proposed PR, Dr Karen Turner is willing to assume the responsibility of the role of PR.

Proposed Licence Holder (LH) – Anne Francis

3.5. The committee noted that the proposed Licence Holder (LH), Anne Francis is willing to assume the responsibility of the role of LH.

Research Project

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

Activities

3.7. The committee was satisfied with the suitability of the activities applied for:

- creation of embryos in vitro
- keeping embryos
- use of embryos.

Permitted Research Purposes

3.8. The committee 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**

  This research objective is relevant in terms of exploring the possibility of developing new treatments where egg activation fails using current techniques, and in refining existing treatments, in improving techniques for distinguishing between abnormal embryos that do not have the potential to develop into successful pregnancies resulting in healthy offspring and “normal” embryos that do have that potential.

- **Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation**

  The studies using high frequency time lapse imaging around the time of fertilisation, and during early embryogenesis will increase the knowledge and understanding of fertilisation, and may lead to the development of techniques for the better identification of embryos most likely to develop into blastocysts and lead to a healthy pregnancy; it is possible that exploration of any anomalies identified using high frequency time lapse imaging may reveal associations with gene, chromosome or mitochondrion abnormalities.

- **Increasing knowledge about the development of embryos**

  For over 30 years the appearance of the human zygote has been studied, but observations have been made at relatively long time intervals. The proposal is to describe these changes by taking digital photographs every 10 seconds. At this interval it will be possible to observe cytoplasmic movements that occur over 10-20 seconds. This is the speed at which cytoplasmic movements in the human and mouse eggs have been observed. The PLCzeta work aims to provide a novel therapeutic option to rescue the activation ability of oocytes that have previously failed to activate and develop into an embryo.

Prohibited Research Activities

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

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

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

Use of Human Embryos

3.12. The committee was satisfied that the use of human embryos is necessary for the purposes of the research.

3.13. The research questions relate specifically to human fertilisation and human reproduction; where possible and appropriately, the research team are carrying out preliminary studies using mouse oocytes and embryos, and only when appropriate and necessary, transfer the studies to human material.

3.14. The committee 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.

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

Person Responsible (PR) – Dr Karen Turner

3.16. The committee was satisfied that the proposed PR possesses the required qualifications and experience and that the character of the proposed PR is such as is required for supervision of the licensed activities. It was further satisfied that the proposed PR will discharge her duties under section 17 of the HF&E Act 1990 (as amended). The committee noted that the inspectorate was satisfied that the proposed PR had satisfactorily completed the PR entry programme. The committee agreed to the appointment of the proposed PR.

Licence Holder (LH) – Anne Francis

3.17. The committee was satisfied that the proposed LH is suitable. The committee agreed to the appointment of the proposed LH in accordance with Section 18A of the HFE Act 1990 (as amended).

Premises – Institute of Reproductive Sciences, Oxford Business Park North Oxford, Oxfordshire OX4 2HW

3.18. The committee was satisfied that the premises and facilities are suitable for the conduct of the licensed activity applied for.

Licence

3.19. The committee agreed to renew the research licence for project R0198 at centre 0035, entitled ‘Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality’, with no additional conditions for a period of three years with the following:

Activities:

- creation of embryos in vitro
- keeping embryos
- use of embryos

for the following purposes:

- promoting advances in the treatment of infertility
- developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- increasing knowledge about the development of embryos.

3.20. The committee agreed that the centre's future renewal inspection report should be submitted to it for consideration.

3.21. The committee endorsed the inspectorate's recommendation to issue Special Directions under Section 24 (5A)(b) of the HF&E Act 1990 (as amended), to permit the continuation of the licence for research project R0198, to be in force from 24 September 2018 to 24 December 2018, or earlier if a new licence is granted.

4. Chair's signature

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

Signature

Name

Kate Brian

Date

21 September 2018

Research Renewal Inspection Report

Purpose of this inspection report

We license and monitor 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. Our Licence Committee (LC) 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: 20 June 2018

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 inspection, and communications received from the centre.

Inspectors: Sara Parlett

Date of Licence Committee: 6 September 2018

Centre Details:

Project title	Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality
Centre name	Oxford Fertility
Centre number	0035
Research project number	R0198
Centre address	Institute of Reproductive Sciences Oxford Business Park North Oxford, Oxfordshire OX4 2HW
Person Responsible (PR)	Dr Karen Turner
Licence Holder (LH)	Dr Ingrid Granne
Treatment centres donating to this research project	Oxford Fertility (0035)
Date licence issued	24 September 2015
Licence expiry date	23 September 2018
Additional conditions applied to this licence	None

Contents

Section 1: Summary report

Brief description of the centre and its licensing history:

Oxford Fertility is a large treatment, storage and research centre which provides a full range of treatment services. It currently has two research licences, one of which (R0111) will not be renewed when its licence expires in September 2018.

This report is specific to research project R0198: Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality.

This research programme was initially undertaken as part of project R0111, after the licence for that project was varied in 2014 to allow it. When considering the application for licence renewal in 2015, the PR decided that the scope of the research work more accurately related to two separate projects. Therefore project R0111 reverted to its original scope and objectives prior to the variation in June 2014 and a new research licence for the artificial egg activation research was applied for and approved as project R0198 in September 2015.

The project was subjected to an interim inspection on 27 July 2016. There were no areas of practice that required improvement.

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 to conclude that:

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. Patient information and consent forms have not changed since those submitted with the previous renewal application.
- the application has designated an individual to act as the PR.
- the proposed licence applies to one project of research.
- the centre has submitted fees to the HFEA in accordance with requirements.

Change of Licence Holder:

The Person Responsible (PR) has applied for a change of Licence Holder (LH) from Ingrid Granne to Anne Francis as part of this renewal application. Anne Francis has been LH for Oxford Fertility's Treatment (including embryo testing) and Storage licence since March 2017. An email confirming that Anne Francis is willing to additionally take on the responsibilities of LH for this research licence is included in the papers. The application and supporting documentation provide evidence of compliance with General Direction 0008.

Research activities applied for:

An application has been made for the following activities for the purpose of research:

- Creation of embryos in vitro
- Keeping embryos

- Use of embryos

The renewal application states that one of the aims of the project is to: 'determine how clinical procedures (such as cryopreservation and in vitro maturation) can influence oocyte proteins involved in the PLCzeta pathway that initiates oocyte activation'. However, the application form describes only the use of fresh material in this research project. The PR has provided clarification that they originally added this section in case they were going to look at eggs that had been cryopreserved following treatment and then later donated to research towards the end of their storage period. However, the PR has confirmed that this is not a proposed focus of the project.

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
- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- Increasing knowledge about the development of embryos

The PR considers these purposes will be met for the following reasons.

> 'Promoting advances in the treatment of infertility: Failure of eggs to activate occurs in an estimated 1 - 5% of ICSI cases (Amdani et al., 2013; Adv Biol Regul. 53(3):292-308). Using HFEA (2018) data, this equates to approximately 1250 cases per year in the UK alone. The only available treatment at present is the use of artificial oocyte activation agents such as calcium ionophores or strontium chloride - which cause calcium release within the egg in a very abnormal manner. The sperm protein PLCzeta represents a much safer, endogenous, alternative. In the proposed study, different concentrations of recombinant human PLCzeta protein will be applied (via injection or culture media) to fresh eggs or failed to fertilise embryos in order to assess the ability of the protein to initiate egg activation. We will determine how clinical procedures (such as cryopreservation and in vitro maturation) can influence oocyte proteins involved in the PLCzeta pathway that initiates oocyte activation. In addition, cytoplasmic movements of the human egg and embryo may indicate its vitality, as has been found in mouse eggs. Observations of movement may improve the chance of recognizing eggs and embryos that have the best chance of developing into healthy offspring.'
>
> 'Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation: Aneuploidy may influence cell cycle kinetics and some cases may change movements at the 1 and 2-cell stage. We will be observing these movements and thus may be able to recognise if any are associated with aneuploidy (so can aid its detection).'
>
> 'Increasing knowledge about the development of embryos: For 30+ years the appearance of the human zygote has been studied, but observations have been made at relatively long time intervals. The proposal is to describe these changes by taking digital photographs every 10 sees. At this interval it will be possible to

observe cytoplasmic movements that occur over 10-20 secs. This is the speed at which cytoplasmic movements in the human and mouse eggs have been observed. The PLCzeta work aims to provide a novel therapeutic option to rescue the activation ability of oocytes that have previously failed to activate and develop into an embryo.'

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 peer reviewer states that the use of human embryos is necessary for this research project because: 'The research questions relate specifically to human fertilisation and human reproduction; where possible and appropriately, the research team are carrying out preliminary studies using mouse oocytes and embryos, and only when appropriate and necessary, transfer the studies to human material.'

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

Premises:
The premises are suitable.

Peer review:
The peer reviewer initially considered that the application form did not provide sufficient information to allow for a full review. Further information was requested from the PR and provided to the peer reviewer. This 'additional information for peer review' is included in the paper set. The peer reviewer subsequently revised the peer review form, which is also included in the paper set.

The peer reviewer agreed that the purposes defined by the PR are relevant.

The peer reviewer commented regarding the importance of the research objectives:

> 'The research objectives are relevant in terms of exploring the possibility of developing new treatments, where egg activation fails using current techniques, and in refining existing treatments, in improving techniques for distinguishing between abnormal embryos that do not have the potential to develop into successful pregnancies and healthy offspring, and "normal" embryos that do have that potential.'

The peer reviewer considered that the research objectives could not be addressed without the use of human embryos and that the type of embryos to be used in the project were justified. The peer reviewer commented regarding the number of embryos to be used in the project:

> 'It was not possible to assess whether or not the number of embryos utilised to date is justified from the information provided in the original application, which was insufficient to enable this judgement to be made. Full details of the nature, number and specific use of each of the different categories of human oocytes and embryos (see comments in the answer to questions in Section 2 above) are required to justify "sufficiently" the use of "*around 450 unfertilised eggs and 200 embryos …….*

over the past three years". However, after evaluation of the additional information that was submitted to supplement the original application, there is no reason to suggest that the numbers used to date are inordinately high, or that their use may have been inappropriate.'

The peer reviewer goes on to comment:

'The general summaries of experiments and findings that were provided in the original application did not allow a detailed, critical evaluation of the progress of the research so far. However, after evaluation of additional, more detailed information that was submitted later, concerning the material used (how many oocytes and embryos, from what source and of what nature) for each series of experiments, and their outcomes, and on the basis of the reputation of the research group, I am confident that renewal of the Research License is justified.'

Recommendation:
The Licence Committee is asked to note the one critical area of practice that requires improvement.

The PR provided evidence immediately after the inspection that actions have already been taken to implement the following recommendation:

Critical non compliance:

- **The PR should ensure that appropriate consent is in place prior to the use of embryos in research.**

The inspection team notes the engagement of the PR and the immediate action taken to address the critical area of non compliance. It is considered 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 subject to the recommendation made in this report being implemented in full within the prescribed timescales.

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

For the following purposes:

- Promoting advances in the treatment of infertility
- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- Increasing knowledge about the development of embryos

It is recommended that the committee approves the application for a change of LH from Ingrid Granne to Anne Francis.

Finally, it is noted that the centre name changed by licence variation from Oxford Fertility Unit to Oxford Fertility in December 2015, but this change was not reflected in the centre's research licences. The research licence issued should use the correct centre name, i.e. Oxford Fertility.

There has been a delay in renewing this research licence due to various administrative issues. As a result, this application is being considered late and close to the expiry date of the licence. It is recommended that Special Directions are issued to the PR under Section 24 (5A)(b) of the HF&E Act 1990 (as amended) to permit the continuation of the licensed research project R0198 at centre 0035 from 24 September 2018 to 24 December 2018 (or earlier, if a licence has been granted).

Section 2: Summary of the research project

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

Lay summary of the research project:

At fertilisation, the sperm activates the egg to begin development. This is called 'egg activation' and PLCzeta is a protein found in sperm which regulates these processes. If sperm do not have adequate PLCzeta protein then the egg may not be activated and fertilised. Men without adequate PLCzeta may therefore be infertile. However, we believe that we can rescue these cases of egg activation deficiency by using an artificially synthesised version of PLCzeta, called recombinant PLCzeta that we have created in our labs. We now need to make sure that this protein can restore fertility in these patients. To test that our PLCzeta protein can activate human eggs in this way we will, in a laboratory, inject it into fresh human eggs, or those which have previously failed to fertilise, and record what happens. We may also simply expose the protein to the egg by adding it to the surrounding culture media, so we can find out the best way of administering the protein to the egg. In a second part of the study, we will use high frequency time lapse filming to observe the tiny movements that take place in an egg during the first few hours after activation. These, and other experiments on eggs and very early stage embryos, will increase our knowledge of the processes that occur around fertilisation. In the future we may be able to use our PLCzeta to help in cases where there are egg activation problems, and use the time lapse technique to predict which embryos are healthier for transfer in IVF treatments.

Objectives of the research:

To continue existing approved research: To determine the appropriate way to administer PLCzeta protein to an egg. To identify the oocyte-borne protein factor that interacts with sperm PLCzeta following fertilisation. To determine how clinical procedures (such as cryopreservation and in vitro maturation) can influence oocyte proteins involved in the PLCzeta pathway that initiates oocyte activation. To find out if cytoplasmic movements in the early embryo can be used to predict subsequent blastocyst development and chromosomal health of embryos.

Summary of the research undertaken to date:

Thus far, we have not identified any specific association between cytoplasmic movements and the successful development of human embryos to the blastocyst stage in culture. Analysis with a powerful microscope found that the appearance and localisation of specific markers of embryo health in the human embryo are similar to those of the mouse and therefore represent useful tools for future studies. For this work we have used around 450 unfertilised eggs and 200 embryos over the past three years.

Donation and use of embryos:

In total, 41 fresh embryos were used in 2017.

The renewal application project proposes the use of 100 fresh eggs, 100 failed to fertilise embryos, 100 fresh embryos and the creation of 100 embryos in each year of the three year term of the licence.

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:

Research Licence Conditions (RLC) R23, R24, R26, R27, R28, R29, CoP Guidance Note 22.

What the centre does well.

Observations during the 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 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.

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, RLC R18, R19, R20, R21, R22. Consent for storage; CoP Guidance Note 22, RLC 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

Before 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 inspection provided assurance that:

- before 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 (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 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.

What they could do better.

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

Consent from both gamete providers is required where embryos, whether normally or abnormally fertilised, or unfertilised eggs which have been exposed to sperm, are used in research.

An audit of five sets of records was performed on inspection. In one case, two failed to fertilise eggs and one abnormally fertilised (3PN) embryo were used in this research project in May 2018. The male partner had not however consented to the use of failed to fertilise eggs or embryos in this research project (RLC R18).

The patient couple had attended a nurse consultation in July 2016, where consent for a number of research projects at the centre was given by both gamete providers. This included consent for the use of embryos in a research project that is no longer active (R0111): 'development of a model to study implantation in the human'. The inspector considers it likely that the male partner intended to give consent for research project R0198 as well but missed signing the particular consent form. The centre's standard procedure is for two members of staff to review consent at two separate time points prior to use in research, both at the nurse consultation and then prior to laboratory set up for the treatment cycle. Both checks failed to detect the male partner's consent to this research project was not present.

Immediately following the inspection, the PR performed a sample audit of 21 sets of records to ensure appropriate consent was in place for this research project. The audit found one other case where a 1PN egg had been used in this research project without the consent of the male gamete provider. The PR considers that one contributory factor is a misunderstanding amongst patients and staff that only female consent is required for this project because of its focus on eggs.

The following corrective actions are in the process of being implemented:

- the consent form has been revised to highlight that for consent to be valid, both male and female patients must complete the consent form.
- a presentation will be given to all centre staff by the principal investigator of the project to provide an update on the project and to remind staff that both patient and partner signatures are required.
- laboratory staff have been reminded of the requirement for consent from both

gamete providers for this project. An additional check step has been introduced to the research pathway: the witness step for the transfer of eggs/embryos from treatment to research now includes a review of the original consent form.
- the PR for the treatment centre is currently on leave, but upon his return will consider the appropriate follow up in terms of informing the male patients where embryos were used without consent.
- a further audit is scheduled for December 2018 to ensure that the corrective actions implemented above are effective.

See recommendation 1.

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 and facilities are secure, clean, well maintained and are suitable for carrying out the licensed activities (RLC R10).

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; RLC R13, R14, R15, R16, R17, General Direction 0002.

What the centre does well.

A review of embryo storage and use records indicate that proper records are maintained (RLC R13 and R15). These records are in a form that prevents the removal of data (RLC R16).

Since the last renewal inspection, the centre has submitted the annual research information and data sheets 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 National Research Ethics Service Committee South Central – Berkshire B. 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 and Peer Reviewer have also provided reasons why the use of human embryos is necessary.

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

What the centre does well.

Licensing

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 (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 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. The inspection team considers that the PR has fulfilled her 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 an interim inspection in 2016, no recommendations for improvement were made.

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 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
1. Consent An audit of five sets of records demonstrated that in one case two failed to fertilise eggs and one abnormally fertilised (3PN) embryo had been used in the research project without the male gamete provider's consent. Immediately following the inspection, the PR performed a further audit of 21 sets of records. This found one other case where a 1PN egg had been used in the research project without the male gamete provider's consent.	The PR should ensure that appropriate consent is in place prior to the use of embryos in research. The PR has taken immediate and thorough corrective action to resolve this non compliance, as detailed in the main body of the report. When responding to the report, the PR should provide an update as to whether they have informed the two male partners where abnormally fertilised eggs/embryos were used without their consent. Centres have a duty of candour and the	As documented in the Report, we have responded to this non-compliance to prevent its reoccurance by making our checking processes more robust. All laboratory members of staff have been informed and this is documented in the Minutes of our Daily Lab Meeting. Kevin Coward (PI) has arranged to speak to staff at our Unit meeting on 2nd October and we will reiterate to all staff that the consent of both partners is required for this project.	The executive acknowledges the PR's response and the considered approach taken to address this non compliance. The PR is committed to meeting with the PR of Oxford Fertility's treatment licence on his return from leave to determine appropriate follow up for the male patients who did not provide consent to use of failed to fertilise eggs/embryos. The PR is asked to update the centre's inspector on actions taken by 20 October 2018.

RLC R18.	HFEA expects all clinics to be open and honest with patients when dealing with such incidents and to provide appropriate support, as necessary. As the further audit performed by the PR found an additional case where consent to research was not in place, the PR is asked to perform a full audit of all abnormally fertilised eggs/embryos that have been used in this research project since the licence was granted on 24 September 2015 to the time of this inspection. The findings of the audit should be provided to the centre's inspector by 20 October 2018. If further instances of use in research without consent are found, the gamete provider should be informed. The PR is also asked to share the findings of the re-audit scheduled for December 2018 with the centre's inspector.	We will perform the additional audits requested. A discussion with the PR for the treatment centre on those consent discrepancies found to date will not be able to take place until end of August/early sept due to conferences and planned leave	

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 noted.			

‘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
None noted.			

Additional information from the Person Responsible
I would like to say that we always find Sara a very fair and knowledgeable inspector. Despite best intentions, where humans are involved, sometimes processes can fail and we appreciate Sara working with us in a calm, proportionate way to resolve and improve those areas. We hope we have put appropriate practices in place to prevent this from happening again and will audit our processes to ensure this is the case.