Licence Committee - minutes

Centre 0035 (Oxford Fertility Unit) – application for initial research licence

Thursday, 10 September 2015

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

Committee members	Bishop Lee Rayfield (Chair) Kate Brian Anita Bharucha	
Members of the Executive	Sam Hartley Trent Fisher	Head of Governance and Licensing Secretary
Legal Adviser	Graham Miles	Blake Morgan
Observers	None	

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:

- new licence inspection report
- application form
- peer review
- previous licensing minutes for the last three years

1. Background

1.1. In 2014 the Person Responsible (PR) for centre 0035 made an application for a new research project to study artificial egg activation. After discussions between the PR and the Executive it was agreed that the application should be a variation of the centre's existing research project R0111.

1.2. When considering the renewal of the licence, the PR decided that the scope of the research work performed under R0111 more accurately relates to two separate projects.

1.3. The PR has consequently submitted two applications, one a renewal of R0111 reverting the project scope to the scope prior to the 2014 variation and an initial research application to cover the additional scope of artificial egg activation.

1.4. This application before the committee is dealing with the initial research application.

2. Consideration of application

2.1. The committee noted that the centre is applying for an initial research licence under the title of 'Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality'.

2.2. The committee noted that at the time of inspection, which took place on 3 August 2015, there were no areas of practice requiring improvement.

2.3. The committee had regard to its decision tree. The committee was satisfied that the application was submitted in the form required and contained the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fees had been paid. The committee noted that the application was made by the Person Responsible (PR) for the research project.

2.4. The committee was satisfied that the PR possesses the required qualifications and experience and that the character of the PR is such as is required for supervision of the licensed activities. It was further satisfied that the PR will discharge their duties under section 17 of the Act. The committee noted that the inspectorate was satisfied that the PR had satisfactorily completed the PR entry programme.

2.5. The committee was satisfied that the premises to be licenced are suitable for the conduct of licensed activities as stated by the inspectorate.

2.6. The committee was satisfied that the renewed research licence would not apply to more than one research project and that the activities applied for, permitted under the Act, are creation of embryos in vitro, keeping embryos and use of embryos.

2.7. The committee found that the use of human embryos is necessary because the proposed research will examine activation of human oocytes and therefore, when activation is successful, embryos will develop; these will not be created for the purpose of the research, but rather, will result from the research.

2.8. The committee was further 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 to the Act, for the following reasons:

- Promoting advances in the treatment of fertility:
  The research will use recombinant PLC zeta protein to explore the possibility of its application in artificial oocyte activation for the treatment of infertility where oocytes fail to become activated after ICSI, as an alternative to the use of potentially toxic agents such as calcium ionophores or strontium chloride. As a secondary outcome of these studies,

examination of cytoplasmic movements in embryos that develop from activated oocytes may lead to the identification of associations between movement patterns and the ploidy of the embryo; any associations identified may be useful in the refinement of techniques for embryo selection for transfer during assisted conception treatment.

- 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-cell stage. The research involves observing these movements and may be able to recognise if any are associated with aneuploidy (and so aid its detection).
- Increasing knowledge about the development of embryos:
  Examination of cytoplasmic movements in blastomeres of embryos that develop following oocyte activation will be carried out using time lapse imaging at 10 second intervals; such imaging may lead to increased knowledge concerning the development of embryos.

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

2.10. The committee was satisfied that the research project had received the necessary level of research ethics approval required by the project.

2.11. The committee noted that the recommendation from the inspectorate was that the centre's application for an initial research licence be granted for a period for three years without any additional conditions.

3. Decision

3.1. The committee agreed to renew the research licence for project R0198 at centre 0035 for a period of three years with no additional conditions.

3.2. The committee noted that an initial research licence would generally be granted for one year period; however, due to the background circumstances, the committee found it justified to grant a three year licence.

3.3. The licensed activities are:

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

4. Chair's signature

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

Signature

Name

Lee Rayfield

Date

25 September 2015

New research application: Desk based assessment report

Purpose of this inspection report:
The HFEA licenses and monitors establishments undertaking human embryo research. This is a report of an evaluation of 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 new research licence. The Authority's Licence Committee 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 that licence.

Date of assessment: 3 August 2015

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

Inspector: Sara Parlett

Assessment details:
The report covers the performance of the centre since the last inspection, findings from the desk based evaluation, and communications received from the centre. For this assessment, an inspector completed a desk-based evaluation of appropriate documentation. There was no site visit.

Date of Licence Committee: 10 September 2015

Centre Details:

Project title	Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality, and development of a model to study implantation in the human
Centre name	Oxford Fertility Unit
Centre number	0035
Research project number	R0111
Centre address	Oxford Business Park North Institute of Reproductive Sciences Oxford Oxfordshire OX4 2HW
Person Responsible (PR)	Dr Karen Turner
Licence Holder	Dr Ingrid Granne
Treatment centres donating to this research project	Oxford Fertility Unit (0035)
Date licence issued	1 October 2012
Licence expiry date	30 August 2015
Additional conditions applied to this licence	None

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Section 1: Summary report

Brief description of the centre and its licensing history:

Centre 0035 is a treatment and storage with research centre. Research project R0111 was first licensed in 1998.

In February 2014 the Person Responsible (PR) made an application for a new research licence at centre 0035 to permit the study of artificial egg activation. Following discussions with the PR, it was agreed that the application should be treated as a variation of the centre's existing licence for research project R0111. In June 2014, a Licence Committee considered this variation application and agreed to:

- change the title of the project;
- add an additional objective;
- add the additional activity of 'creation of embryos'.

When considering the renewal of the licence, the PR decided that the scope of the research work performed under R0111 more accurately relates to two separate projects. The centre has consequently submitted two renewal application forms and has requested that:

- research project R0111 reverts to its original scope (prior to the variation in June 2014). This is the subject of a second inspection report being considered by this committee.
- a new research licence is created for the additional scope (artificial egg activation) that was added as a variation to R0111 in June 2014. This is the subject of this inspection report.

The centre requested a delay to the submission of their application to renew the research project to allow for an amendment to their ethics committee approval to be processed. This was to enable the centre to submit the latest ethics committee approval and related documents with the renewal application. This request was agreed by the executive. Once received, the centre's application was considered by a peer reviewer. The peer reviewer requested some additional information before they made their recommendation as to whether it was appropriate to carry out the proposed research, which delayed processing the application further. As a result, this application could only be considered by a Licence Committee after the expiry of the centre's licence. On 24 July 2015, an executive licensing panel issued Special Directions to the PR under Section 24 (5A)(b) of the HF&E Act 1990 (as amended) to permit the continuation of the research project from 1 September 2015 to 30 November 2015.

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. Although the centre submitted a renewal application form rather than an initial application form, the executive is satisfied that the renewal form captures all relevant information;
- the centre has submitted the supporting information required by General Directions 0008 for a renewal of a research licence. Although the centre has not submitted all of the information required by General Directions 0008 for an initial research licence (the floor plan of the premises to be licensed), the centre has provided this previously;

- 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.

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 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 research project is currently licensed for the following purposes:

- promoting advances in the treatment of infertility;
- increasing knowledge about the development of embryos.

The project is also currently licensed for the following purpose:

- increasing knowledge about the causes of miscarriage.

  The PR does not consider that this is an appropriate purpose for this aspect of the project if it is separated from the broader project R0111 and she does not wish this purpose to be included on a new licence.

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

- promoting advances in the treatment of infertility;

  The PR has stated that: ‘Failure of eggs to activate occurs in an estimated 1-5% of ICSI cases (Amdani et al., 2013; Advances in Biological Regulation, In Press). Using HFEA (2010) data, this equates to approximately 1200 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. PLC zeta 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 PLC zeta 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 recognising eggs and embryos that have the best chance of developing into healthy offspring’.

  The peer reviewer agrees and has stated:
  ‘The research will use recombinant PLC zeta protein to explore the possibility of its application in artificial oocyte activation for the treatment of infertility where oocytes fail to become activated after ICSI, as an alternative to the use of potentially toxic agents such as calcium ionophores or strontium chloride.

As a secondary outcome of these studies, examination of cytoplasmic movements in embryos that develop from activated oocytes may lead to the identification of associations between movement patterns and the ploidy of the embryo; any associations identified may be useful in the refinement of techniques for embryo selection for transfer during assisted conception treatment'.

- Increasing knowledge about the development of embryos

  The PR has stated: '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 secs. 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 PLC zeta 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'.

  The peer reviewer agrees and has stated:
  'Examination of cytoplasmic movements in blastomeres of embryos that develop following oocyte activation will be carried out using time lapse imaging at 10 second intervals; such imaging may lead to increased knowledge concerning the development of embryos'.

The PR has applied for the following purpose to be included on the new licence:

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

  The PR has stated that the proposed research addresses the purpose by:
  'Aneuploidy may influence cell cycle kinetics and some cases may change movements at the 1-cell stage. We will be observing these movement and thus may be able to recognise if any are associated with aneuploidy (so can aid its detection)'.

  The peer reviewer agrees and has stated:
  'Ooctyes that are activated during the studies exploring the use of recombinant PLC zeta protein will be used to examine cytoplasmic movements in the blastomeres of the developing embryos, in an attempt to determine whether or not there are any identifiable associations between movement patterns and the ploidy of the embryo; any associations identified may be useful in the refinement of techniques for embryo selection for transfer during assisted conception treatment'.

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 the following comments made by the peer reviewer:
'Investigations using human oocytes and embryos that develop from their artificial activation follow those that have already been carried out extensively in the mouse and other mammalian models, examining changes in intracellular calcium levels and cytoplasmic movements during

the first cell cycle of embryogenesis. These have revealed a series of characteristic oscillations in Ca^{2+} levels, and spasms of cytoplasmic movement that are associated with peaks of free calcium in the cytoplasm. It is appropriate to use human oocytes and embryos that develop following their artificial activation, in order to examine whether or not, and how these changes occur during human development, in order to derive greater knowledge and understanding of oocyte activation following fertilisation in the human'.

This research project will involve the creation of human embryos. The peer reviewer supports this activity, stating:
'The proposed research will examine activation of human oocytes and therefore, when activation is successful, embryos will develop; these will not be created for the purpose of the research, but rather, will result from the research'.

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 considered suitable. This is based on information submitted with this application and the previous inspection visit in May 2014.

Recommendation:
The Licence Committee is asked to note that at the time of the assessment there were no areas of practice that required improvement.

The inspector recommends that a new research licence 'Artificial oocyte activation and egg/embryo movements as early indicators of embryo quality' is granted to centre 0035 for this part of current research project R0111 for a period of three years without additional conditions. A new research project number will be required for this. The inspector notes that this period of licence is longer than usual for an initial research licence but considers this is justified because of the unusual circumstances.

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

Section 2: Summary of the research project

This section summarises information submitted in the research licence application.

Lay summary of the research project:

At fertilisation, the sperm activates the egg to being 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 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 filing 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.

Objective of the 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 1-cell and 2-cell zygotes can be used to predict subsequent blastocyst and chromosomal health of embryos.

Summary of the research undertaken to date:

Work on this project only started in late 2014 (previously under research licence R0111) and has therefore involved small numbers of oocytes/embryos only. In total 36 oocytes (eggs) have been used by the researchers. Many of the failed to fertilise and immature eggs (m1 stage) spontaneously divided to the 2-cell stage without artificial activation. The eggs were kept in a culture media, illuminated and photographed every 2 minutes, for 2 or 3 days, and so movements previously unreported in human eggs were revealed. The movements seen and recorded were similar to those previously observed in mice during similar stages of development. However, many more observations will be needed before any significant conclusions can be made. So far no PLCzeta injections have been carried out as protein expression work is still progressing.

Donation and use of embryos:

The centre has used 36 oocytes in total to date. The PR estimates that 200 fresh eggs, 300 failed to fertilise embryos and 100 fresh embryos will be used in each year. For the second and third year of the licence they also estimate 200 embryos will be created.

Section 3: Details of the assessment 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 last inspection in May 2014 provided assurance that the special status of the human embryo would be respected:

- the researchers have a documented procedure for ensuring that embryos do not develop beyond 14 days post-fertilisation or the appearance of the primitive streak, whichever is earlier (SLC R28). An audit of records confirmed compliance with this requirement.
- discussions with the team provided assurance that all embryos donated to the project were only used for the objectives authorised by the licence to meet the defined statutory purposes (RLC R5 and R23).
- All frozen embryos used in the research project were used within their consented storage period and embryos still in store were also within their consented storage period (RLC R39).

An on-site renewal inspection was last performed at the centre in June 2012 and the following was demonstrated:

- processes, documented in standard operating procedures (SOPs), were in place to ensure that no embryo obtained for the purposes of the research project would be kept or used for any purpose other than the purposes of the research project (RLC R23).
- recruitment practices ensured that no money or other benefit would be given to those donating embryos to research unless authorised by directions (RLC R24).
- each embryo used in the research project was uniquely labelled (RLC R26)
- documented procedures had been established to ensure that clinical and research roles are separated (RLC R27).

Centre staff have confirmed that no changes have been made to their procedures since this renewal inspection.

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 assessed against:

Information, counselling and consent; CoP Guidance Note 22, RLCs R18, R19, R20, R22.

What the centre does well.

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

Patient information and consent forms are compliant with requirements that:

- 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 (RLC R19);
- 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.

Nothing noted.

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 assessed against:

Premises and facilities; RLC R10

What the centre does well.

Premises and facilities

The premises are suitable for carrying out the licensed activities (RLC R10). This conclusion is based on the centre's SAQ and the last research inspection visit in May 2014.

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 R14, General Directions 0002.

What the centre does well.
Fully completed research information and data sheets have been submitted to the HFEA within the prescribed timescales (RLC R14 and General Directions 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 assessed 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 new application and it is supportive of the project and recommended it be provided with a HFEA research licence. 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. Overall, the peer reviewer has agreed that it would be appropriate to carry out the proposed research.

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

What the centre does well.

Licensing

Information obtained at the last inspection, a review of the SAQ and discussions with the PR confirm that all licensed research activities will be performed only at the licensed premises under the supervision of the PR (RLC R1). The PR provided all information requested in support of this inspection within the required timescales (RLC R3).

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 is suitable and has discharged her duty under Section 17 of the HF&E Act 1990 (as amended) and RLC R8. This conclusion is based on the centre's SAQ and on-going monitoring by the inspectorate that indicates that there are no outstanding non-compliances associated with the research project.

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 (PREP number R/0121/7).

What they could do better.
Nothing noted.

Section 4: Monitoring of the centre's performance

Following an interim inspection in May 2014 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
None			

Major areas of non compliance

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

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

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

‘Other’ areas of practice that requires improvement

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

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

Additional information from the Person Responsible