HFEA Executive Licensing Panel Meeting

8 August 2014

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

Minutes – Item 2

Centre 0035 – (Oxford Fertility Unit) &
Centre 0311 – (University of Oxford, Department of Obstetrics and Gynaecology)
- Interim Inspection Report for Research Project R0111

Members of the Panel:	Committee Secretary:
Rachel Hopkins – Head of Human Resources (Chair) Joanne Anton – Policy Manager Matthew Watts – Regulatory Policy Manager	Dee Knoyle

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:

- HFEA Protocol for the Conduct of Meetings of Executive Licensing Panel
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Direction 0008 (where relevant), and any other relevant Directions issued by the Authority
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Consideration of Application

1. The Panel noted that research project R0111 is carried out at Oxford Fertility Unit (centre 0035), a treatment and storage with research centre and University of Oxford, Department of Obstetrics and Gynaecology (centre 0311), a research only centre.

2. The Panel noted that the current research project entitled 'Development of a model to study implantation in the human' was first licensed at centre 0035 in 1998. Centre 0035 relocated to new premises in October 2009 and when this move occurred, research project R0111 moved to the new premises but also continued at the original premises, which were re-designated as a research-only centre (centre 0311).

3. The Panel noted that the Research Licence Committee renewed both research licences to start from 1 October 2012.

4. The Panel noted that all licensed material used in the project had been obtained from Oxford Fertility Unit (centre 0035).

5. The Panel noted that the current licence is due to expire on 30 August 2015.

6. The Panel noted that at the time of the inspection on 28 May 2014, there were no areas of non-compliance identified at centre 0035. One 'other' area of non-compliance was identified at centre 0311, although there is currently no research work being performed. The Panel noted the Inspectorate's recommendation that prior to research activity recommencing at centre 0311, the Person Responsible (PR) must provide the following evidence to the Inspectorate:

    - research embryos will be kept securely, inaccessible to unlicensed persons
    - research laboratory equipment is suitable for use, including evidence of servicing and electrical safety testing.

7. The Panel noted that the PR is committed to fully implementing the recommendations within the prescribed timescales and this will be subject to on-going monitoring by the Inspectorate.

8. The Panel noted that the Inspectorate recommends the continuation of the licences for research project R0111 at centres 0035 and 0311.

Decision

9. The Panel endorsed the Inspectorate's recommendation to continue the licences for research project R0111 at centres 0035 and 0311.

Signed: Date: 18 August 2014

Rachel Hopkins (Chair)

Research Interim Inspection Report

Date of inspection: 28 May 2014
Purpose of inspection: Interim inspection of the research licences for project R0111 at centres 0035 and 0311
Inspector: Sara Parlett

Inspection details:
The report covers the pre-inspection analysis, the visits to centres 0035 and 0311 and information received from the centres since the last inspection.

Date of Executive Licensing Panel: 8 August 2014

Centre details

Project Title	Development of a model to study implantation in the human
Centre name and number	Centre 0035: Oxford Fertility Unit Centre 0311: University of Oxford, Department of Obstetrics and Gynaecology
Research licence number	Both centres: R/0111/2/a
Centre address	Centre 0035: Oxford Business Park North, Institute of Reproductive Sciences, Oxford, Oxfordshire, OX4 2HW Centre 0311: Women's Centre, Level 4, Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford, OX3 9DU
Person Responsible	Dr Karen Turner
Licence Holder	Professor Ian Sargent
Treatment centres donating to this research project	Oxford Fertility Unit (centre 0035)
Date licence issued	Both centres: 1 October 2012
Licence expiry date	Both centres: 30 August 2015
Additional conditions applied to this licence	None

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Purpose of the Inspection report

The purpose of the inspection is to assess whether research using human embryos is carried out in compliance with the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended) and the Code of Practice (CoP) and that progress is made towards achieving the stated aims of the project. The report summarises the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the Authority's Executive Licensing Panel (ELP) which makes the decision about the centre's licence.

Report to Executive Licensing Panel

Brief description of the centres and the licensing history:

Research project R0111 is undertaken at centres 0035 and 0311. Centre 0035 is a treatment and storage with research centre. Research project R0111 was first licensed at centre 0035 in 1998. Centre 0035 relocated to new premises in October 2009. When this move occurred, research project R0111 moved to the new premises but also continued at the original premises, which were re-designated as a research-only centre (centre 0311).

The last renewal reports for project R0111 at centres 0035 and 0311 were originally presented for consideration by the ELP in July 2012. The Chair of the ELP judged that the reports were best considered by the Research Licence Committee (RLC) in September 2012. The previous licences at both centres were however due to expire in August 2012, therefore the ELP issued Special Directions to allow the research project to continue at both centres while the renewal applications were considered by the RLC. The RLC in September 2012 then renewed both research licences from 1 October 2012.

Summary for licensing decision

In considering overall compliance, the inspector considers that she has sufficient information drawn from documentation submitted by the centres prior to inspection and from observations and interviews conducted during the inspection visits to draw a conclusion on the continuation of the centres' licences.

The ELP is asked to note that there are no areas of non-compliance that require improvement in relation to the research project at centre 0035.

At the time of the inspection, there was one area of non-compliance that required improvement in relation to the research project at centre 0311. The Person Responsible (PR) has provided a commitment to fully implement the following recommendation:

'Other' area of non compliance – centre 0311:

- The PR must ensure that research laboratory equipment is suitable for use.

Recommendation to the Executive Licensing Panel

The inspector recommends the continuation of the licences for research project R0111 at centres 0035 and 0311.

Summary of project

Lay summary of the research project (centre 0035 and 0311):

Despite significant advances in assisted reproduction technology over the last decade, pregnancy rates remain disappointingly low. While fertilisation is now achievable in most cycles, embryos which appear morphologically normal still fail to implant. The purpose of this project is to investigate the development of embryos before and during the implantation process and the factors which control these crucial events. To do this we are developing in vitro systems to specifically model how human embryos develop prior to implantation, how they initially attach to the endometrium and how they invade and interact with the different cell populations of the endometrium during implantation. In these models human embryos donated for research will be cultured to the blastocyst stage. Blastocyst invasion is studied by co-culturing blastocysts with endometrial stromal or epithelial cells or on microbiopsies of endometrial tissue. Trophoblast invasion is monitored by time lapse photography and immunofluorescence microscopy. By adding factors which either stimulate or suppress the actions of a range of molecules, we will determine their role in these processes. The ultimate aim is to develop new treatments which will improve blastocyst implantation and hence pregnancy rates in assisted reproduction.

Objectives of the research (centre 0035 and 0311):

1) Detection of molecules involved in the implantation process in pre-, peri- and post implantation embryos.
2) The implantation models will be used to investigate aspects of human embryo implantation: Fresh embryos donated for research will be obtained from the Oxford Fertility Unit (0035). For some experiments (preimplantation development) embryos will be cultured to the blastocyst stage in the embryo research laboratory in the Oxford Institute for Reproductive Sciences (IRS) facility. However, for other experiments (implantation model) embryos will be transported at the cleavage or blastocyst stages to the existing facility in the Nuffield Department of Obstetrics and Gynaecology (NDOG), John Radcliffe Hospital, and cultured. The reason for this is that the endometrial cells are cultured in the NDOG and the image analysis system used for these studies is also located there. Given the space limitations and the cost it is not possible to duplicate these facilities in the IRS.

Future Developments
The role of IL-33 and ST2 in the maternal immune response to the implanting embryo: One of the causes of implantation failure could be an abnormal maternal immune response against the embryo. We are studying the role of the cytokine IL-33 and its receptor ST2 in this process. We have recently published work showing that levels of ST2 are significantly altered in pre-eclampsia [1] and that its source may be the placenta. We are now looking at IL-33 and ST2 in early pregnancy and our preliminary data suggest that both molecules are expressed by pre-implantation embryos. One aim of this study will be to map the expression of IL-33 and ST2 at different stages of embryo development and at the time of implantation. A second aim is to investigate the effect of adding IL-33 or ST2 to embryo culture to determine whether either affects embryo development and invasion, using our implantation model. [1] Granne, I.,

Southcombe, J.H., Snider, J.V.,Tannetta, D.S., Child, T., Redman, C.W.G. and Sargent, I.L. (2011) ST2 and IL-33 in pregnancy and pre-eclampsia. PLoS One Vol. 6 (9), e24463'

Objectives of the research (centre 0035 only – additional to above):

Novel molecular markers for human gametes and embryos competence. The purpose of this project is to develop new methods for determining embryo viability to enable the selection of those with the highest implantation potential for transfer back to the mother. By doing this we hope to improve the pregnancy rate per cycle and thereby the cost effectiveness of the treatment. This study will utilize a new way to sample the blastocyst proteome by collecting fluid from the blastocoel during the vitrification process. The fluid will then be analysed by mass spectrometry and the levels of expression of molecules detected will be correlated with blastocyst morphology and subsequent development post thawing. Genetic assessment of the blastocysts will also be carried out using comparative genomic hybridization. Molecules identified in this initial study will then be analysed in the blastocoel fluid of blastocysts used for clinical treatment to determine whether there is any correlation with pregnancy success.

Lay summary of research undertaken (centre 0035):

Analysis of biomarkers of embryo quality in blastocoel fluid

This project investigates a novel way of selecting the best embryos for transfer in IVF by looking at the repertoire of proteins and DNA in the fluid from inside the blastocyst. The fluid is obtained from the blastocoel by microsuction and the collapsed blastocyst is then frozen by vitrification. The success of this process has been assessed by thawing the blastocysts and measuring their survival. Analysis of DNA (by PCR and aCGH) and protein (by Mass Spectrometry) content of the blastocoel samples has been carried out and validated. Gene expression by the Inner Cell Mass (ICM) and Trophectoderm (TEs) from blastocysts has also been carried out in parallel, using microarrays.

Future work will involve the collection and analysis of more blastocoel fluid samples. Fresh and frozen embryos will be biopsied to determine their chromosomal status to determine whether it correlates with the blastocoel secretion profile and/or transcription analysis. We will seek to validate the findings of the ICM/TE study using RealTime PCR.

Lay summary of research undertaken (centre 0311):

The role of IL-33 and ST2 in embryo development

We have evidence that a chemical messenger (cytokine) called IL-33 and its receptor (called ST2) may play a role in preventing the rejection of the baby by the mother's immune system. This is important as in some IVF cycles apparently good quality embryos are transferred to the mother but fail to implant. This may be due to immune rejection of the embryo. We have therefore looked to see whether the early human embryo is a source of IL-33 and ST2 which may regulate the mother's immune response. We have found that day 5 blastocysts express ST2 but not IL-33. The significance of this finding is under investigation.

Donation and use of embryos:

Centre 0035

In the period from 1 January – 31 December 2013, the centre reported the use of 98 fresh and 38 frozen embryos. This is less than the 500 predicted in the renewal application form. Centre staff explained that they are making good progress with the research project and have sufficient numbers of patients donating embryos to the project. However, there is only one researcher dedicated to the work which is the reason why fewer embryos are currently being used.

Centre 0311

In the period from 1 January – 31 December 2013, the centre reported the use of 15 frozen embryos. This is less than the 500 predicted in the renewal application form; refer to page 9 of the report for further details.

Details of inspection findings

Inspection findings

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 (Guidance note 29, 30, 31)

What the centre does well.

Centres 0035 and 0311 were granted a renewal of their research licences by a RLC on 11 September 2012 for the following activities: storage of embryos, keeping embryos and use of embryos. None of these activities are prohibited by the HF&E Act 1990 (as amended). The renewal of the licences was approved to allow research for the following designated purposes:

- promoting advances in the treatment of infertility
  HF&E Act 1990 (as amended) Schedule 2 3A(2)(d)
- increasing knowledge about the causes of miscarriage
  HF&E 1990 (as amended) Schedule 2 3A(2)(e)
- increasing knowledge about the development of embryos
  HF&E Act 1990 (as amended) Schedule 2 3A(2)(h)

At the last licence renewal for both centres, a peer reviewer agreed that the use of human embryos was necessary and justified for the proposed research project.

Evidence that the research project had received approval by an ethics committee was also provided at the last renewal of the licence and continued approval for the research was confirmed on this inspection.

What they could do better.

Nothing identified at this inspection.

Have respect for the special status of the embryo when conducting licensed activities (Guidance note 15, 18, 22, 25, 26)

What the centre does well.

On inspection, a review of centre documentation and an audit of records of the use in project R0111 of five sets of embryos from centre 0035 and two sets of embryos from centre 0311 demonstrated that:

- comprehensive records of embryo use are maintained and annual use is reported to the HFEA (General Directions 0002 and standard licence conditions (SLC) R13, R14 and R15).

- evidence was provided to demonstrate that effective consent had been given by the gamete providers for the use of the embryos in the research project (SLC R18).
- 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). The 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 have been used within their consented storage period and embryos still in store are also within their consented storage period (RLC R39).

What they could do better.

Nothing identified at this inspection.

Compliance with HFEA research licence conditions

From the information submitted in the centres' self assessment questionnaire and from observations during the visit to the centres, the inspector noted no additional non-compliances.

Changes & improvements since the last inspection

Following the renewal inspection at centre 0035 in 2012, recommendations for improvement were made in relation to two major and one 'other' areas of non-compliance. Since the inspection, evidence has been provided showing that all of the recommendations have been implemented.

Following the renewal inspection at centre 0311 in 2012, recommendations for improvement were made in relation to four major and two 'other' areas of non-compliance. The PR provided evidence that all of the recommendations were fully implemented, with the following exception:

- the PR should ensure that all research embryos are kept securely and are inaccessible to unlicensed persons. The PR should review the situation and take appropriate actions to prevent any potential breach of Section 33A or Section 15(4) of the HF&E Act 1990 (as amended).

Centre 0311 reported the use of 15 embryos in 2013, less than the 500 predicted in the last renewal application form. The PR explained that the implantation model part of the project has been put on hold since the main researcher left two years ago. A small number of embryos have been used in the project at centre 0311 since then (e.g. 15 embryos were used in 2013), but none have been cultured at the centre since May 2012. Because no embryo culture is being performed, some of the research laboratory equipment is not currently suitable for use; for example, the incubator hasn't been serviced in the last year. The research laboratory is also shared with other research staff who are not named on the research licence and they would have access to any research embryos being cultured in the incubator. After the last inspection, the PR committed to fit the incubator with a lock to ensure research embryos are not accessible to unlicensed persons. A padlock was purchased for this purpose but has not yet been fitted to the incubator. Although the PR has not implemented the recommendation, no risk to embryos has resulted because no embryo culture has been performed at the centre since the last inspection (see recommendation 1).

Provision of information to the HFEA

Licensed research centres are required by law to provide an annual research information and data sheet.

The centres are compliant with register submission related requirements.

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 area 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 noted.			

Major area 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 requires improvement

Areas of practice that requires 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 for action	PR Response	Executive Review
Centre 0311 Some of the research laboratory equipment is not currently suitable for use, for example the incubator hasn't been serviced in the last year and cannot be locked to prevent unlicensed persons having access to research embryos. HF&E Act 1990 (as amended), Section 33A and Section 15(4) and Section 17 (1)(b). It is acknowledged that no embryos have been cultured at the centre since 2012 and therefore this non-compliance has not resulted in any risk to embryos.	No research work is currently being performed at the centre. Prior to research activity re-commencing, the PR must provide evidence to the inspector that: • research embryos will be kept securely, inaccessible to unlicensed persons. • research laboratory equipment is suitable for use, including evidence of servicing and electrical safety testing.	The PR provided the following response by e-mail: "If there is a plan to resurrect embryo work over at the university, we will ensure the equipment is serviced and lock fitted before any is done".	The lead inspector acknowledges the PR's response and this will be subject to on-going monitoring.

Additional information from the Person Responsible