Research Interim Inspection Report

Date of Inspection: 11 August 2011
Purpose of inspection: Interim Inspection of Research Licence
Length of inspection: 4 hours
Inspectors: Dr Andrew Leonard

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 18 August 2009 and the submission of papers to the Executive Licensing Panel on the 9 September 2011.

Date of Executive Licensing Panel: 25 September 2011

Centre details

Project Title	Biochemistry of Early Human Embryos
Centre Name	Hull IVF Unit
Centre Number	0021
Research licence Number	R0067/8/b
Centre Address	Reproductive Medicine Research, Hull York Medical School, Hull IVF Unit, Women's and Children's Hospital, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ
Person Responsible (PR)	Professor Henry Leese
Licence Holder (LH)	Dr Roger Sturmey
Treatment centres donating to this research project	The Hull IVF Unit
Date Licence Issued	01/02/2010
Licence expiry date	31/1/2013
Additional conditions applied to this licence	NONE

Contents

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), Standard Research Licence Conditions (SRLCs) and the 8th edition of the HFEA 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 which makes the decision about the centre's licence.

Report to Executive Licensing Panel

Brief description of the centre and its licensing history:

The project, 'Biochemistry of Early Human Embryos' (R0067), was first licensed in 1995 and the current licence is active from 1 February 2010 to 31 January 2013. The project was last renewed by a Licence Committee on 18 November 2009, the project having been inspected in August 2009. The licence was approved for the use of embryos in research and the storage of embryos for the following defined purposes:

- Promoting advances in the treatment of infertility
  HF&E Act (1990) as amended, Sch 2 3 A (2)(d)
- Increasing knowledge about the development of embryos
  HF&E Act (1990) as amended, Sch 2 3 A (2)(h)
- Increasing knowledge about serious disease
  HF&E Act (1990) as amended, Sch 2 3 A (2)(a)

The Person Responsible (PR) for the project applied on 6 July 2010 to change the location of the licensed research premises from the University of York (centre 0062) to the Hull IVF Unit (centre 0021) - specifically the Andrology Laboratory (Room 00-035) and the Cryostore (Room 041) within centre 0021. This was due to the desire to move closer to an IVF unit to better test the project's developments, to more effectively source embryos for research and because the PR and Licence Holder (LH) were provided academic posts on the Hull campus of the Hull-York Medical School. This re-location application was approved by the Research Licence Committee on 10 September 2010. The project in its new location is under the research governance structure of Hull-York Medical School.

The PR has been in post since the project's inception in 1995 and has completed the PR Entry Programme. He is a member of the HFEA's Horizon Scanning Group.

Title of research project:

Biochemistry of Early Human Embryos'

Summary for licensing decision

In considering overall compliance, the inspection team considers that it has sufficient information drawn from documentation submitted by the centre prior to inspection and from observations and interviews conducted during the inspection, to recommend the continuation of the centre's licence.

The Executive Licensing Panel is asked to note that there are no areas of practice requiring improvement. The inspector also notes that the research staff and staff on the treatment and storage licence at centre 0021, have (successfully) made considerable and commendable efforts to ensure the compliance of the project.

Recommendation to the Executive Licensing Panel:

The inspection team considers that there is sufficient information available to recommend the continuation of this research licence.

Summary of project

Lay summary of the research project:

Up to 1 in 6 couples find difficulty in conceiving. For many, one solution to their infertility is In Vitro Fertilisation and Embryo Transfer (IVF-ET) the so-called "test tube baby" treatment, which was pioneered in the UK in the late 1970s. This treatment has helped many thousands of couples to have children, but success rates remain disappointingly low with a live birth rate per treatment cycle in the UK of only around 23%. Moreover, since 2, exceptionally 3 embryos may be transferred in any one treatment cycle, there is a high risk of multiple births. While the birth of a baby is a cause for joy, multiple births can sadly bring problems; the babies are often underweight and peri-natal mortality is elevated; the parents may also find it difficult to cope with the sudden arrival of a large family.

There is now good agreement amongst doctors and embryologists that a solution to these problems would be to transfer single embryos with a high chance of forming a pregnancy. However, we know very little about how human embryos are formed and what makes some embryos healthier than others. The aim of our work is therefore to carry out a detailed examination of the development of the early human embryo. The focus is on nutrition and metabolism: how the embryo obtains and uses the nutrients it requires; for example, sugars and amino acids. We intend to study whether the pattern of nutrient consumption by an early human embryo relates to its health and developmental ability prior to transfer. In particular, we will study the way in which early human embryos consume and produce amino acids, which are the constituents of proteins, contribute pre-cursors for deoxyribose nucleic acid (DNA) and sources of cellular energy. This will be related to key developmental endpoints, including the ability to form a blastocyst, the stage at which an embryo would ordinarily begin to implant into the uterus, the number of cells (a good indicator of quality of the blastocyst) and the amount of cellular and molecular damage. These data will be important in defining the effectiveness of amino acid profiling in predicting early embryo health. In this way we will learn how to improve culture conditions and devise diagnostic methods that will allow the transfer of single healthy embryos with a high chance of giving rise to a pregnancy whilst minimising the risk of multiple births. Eventually, this will help ensure the health of babies born following natural conceptions as well as IVF. While we use cattle and pig embryos (made from abattoir-derived eggs) in our work, it is essential to carry out research on spare human embryos to ensure that the data reflect as closely as possible the situation in human IVF.

Objectives of the research stated at licence renewal on 18 November 2009:

To investigate:
a. Embryo viability and metabolism
b. Temperature effects on a)
c. The effects of low molecular weight heparin on a)
d. The effects of DNA damage on a)

Donation and use of embryos:

The centre submitted the annual ‘Research Information and Data Sheet’ for 2010 to the HFEA in accordance with the requirements of General Direction 0002. This submission indicated that no embryos were used in project R0067 in 2010 and provided a lay summary of the research undertaken which stated:

‘The project aims to define how the metabolic and biochemical activity of early embryos *in vitro* is related to their capacity to give rise to a successful pregnancy. We have built an extensive knowledge base indicating that the appearance or depletion of key nutrients in the culture medium relates to embryo health and viability, but the cell and molecular biological mechanisms underlying these data and their long-term implications are not yet understood. We are also investigating how the metabolism of an embryo may be influenced by external factors, such as the health of the mother and the type of embryo culture conditions. Our studies mostly focus on non-invasive methods in which we analyse the medium in which the embryo has been cultured. We then link these results retrospectively to key biochemical and morphological indicators of embryo health and viability. We have fascinating data from animal models, which we use in a separate laboratory to refine our hypotheses prior to using precious human embryos surplus to treatment, which indicate that embryo viability can be severely compromised by exposing eggs to high fat conditions.

‘Work will soon commence to discover whether a similar relationship exists for human embryos. The research associated with this license has been subject to an unavoidable pause whilst we await committee approval for the relocation of our laboratory. Such approval is apparently imminent, and we hope to resume our research soon.’

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.

Documented evidence was provided on inspection that the Local Research Ethics Committee (LREC) serving the research project has provided a favourable assessment of the ethical implications of the research project.

The project's licence renewal application was reviewed by a peer reviewer and the HFEA Research Licence Committee in November 2009, who both considered that the centre met appropriate ethical standards and had clear justification for, and no viable alternative to the use of human embryos in research. The licensed activities approved were the use of embryos in research and the storage of embryos. The licence was approved to allow research for the following purposes, as defined in Schedule 2, 3A (2) to the HFE Act 1990 (as amended):

- Promoting advances in the treatment of infertility
  HF&E Act (1990) as amended, Sch 2, 3A (2)(d)
- Increasing knowledge about the development of embryos
  HF&E Act (1990) as amended, Sch 2, 3A (2)(h)
- Increasing knowledge about serious diseases or other serious medical conditions
  HF&E Act (1990) as amended, Sch 2, 3A (2)(a)

The PR and LH stated on inspection that the project's aims, objectives and methodologies have not changed since renewal. Thus any future use of embryos will be in activities and for purposes considered by the LREC and by the Research Licence Committee to meet appropriate ethical standards and have clear justification.

What they could do better.

Nothing noted 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.

Discussions with the PR and LH, review of the centre's documented research procedures and embryo usage log, and inspection of the premises and equipment, indicated to the inspection team that the special status of the human embryo is respected. This was evidenced by several observations:

1. Centre 0021 has documented standard operating procedures (SOPs) for the processes by which patients are informed of the research and their consent is

taken. These procedures and the research information provided to patients have been audited for compliance with CoP requirements and corrective actions have been taken. Counselling is offered to those considering research donation and the research procedures, an information checklist in patient records and written information provided to patients, document this offer. Staff competence in providing research information to patients is assessed annually. Research procedures define the activities in which the donated embryos can be used, preventing their use in unlicensed activities (Standard Research Licence Condition (SRLC) R23). These features ensure that embryos are used in a respectful manner for only the purposes for which patients have provided valid informed consent, as required by Schedule 3 to the HF&E Act (1990) as amended.

2. Consent forms for research donation are verified as being in place by two embryologists in the clinical embryology laboratory. The consent forms will then be passed, in a sealed envelope marked with the research code, patient number and the signatures of the embryologists who have verified consent, to the research laboratory along with the donated embryos. This will allow retrospective audits of patient consents for research to be performed by an embryologist who is on the treatment and storage, but not the research, licence at centre 0021.
3. Documentary evidence was provided by the centre which indicates that their research practices and documented procedures have been audited against their research licence conditions. Corrective actions were taken and no non-compliances remain.
4. A risk assessment of the proposed research practices and documented procedures has also been performed which identified areas of regulatory risk and proposed corrective actions. These actions have all been implemented.
5. The PR stated that research recruitment practices ensure that no money or other benefit is given to patients donating embryos to the project, as required by SRLC R24. This is also clearly stated in the written information provided to patients.
6. The Lead Embryologist at centre 0021, but no other embryologists, works on the research project one day per week. Working practices have been developed and documented in research procedures which ensure that treatment and research roles are separated in the clinical embryology laboratory (SRLC R27).
7. All embryos donated to the project are marked with a research code when donated to research, as required by SRLC R26.
8. The centre has a procedure which documents that embryos should not be cultured for more than nine days post-fertilisation. The culture of each embryo is recorded on an embryo log sheet which is regularly reviewed (as prompted by the laboratory daily activities checklist) to prevent culture beyond nine days post-fertilisation. Together these measures prevent non-compliance with SRLC R28.
9. A log of stored embryos donated to the research project is maintained and is checked monthly to ensure no embryo is stored past its consented storage period contrary to Schedule 3 to the HF&E Act (1990) as amended.
10. A procedure has been established for embryo disposal at the end of experimental use or their statutory storage period, as recommended by CoP Guidance 22.3C Disposal is witnessed and recorded on the embryo log sheet.
11. The transfer of embryos to the research project and the disposal of fertilised

embryos from the research project are both witnessed. Witnessing steps are all recorded appropriately and will be audited at least annually.

12. Access to premises is controlled, preventing unlawful access to research consented material by unlicensed staff.
13. All equipment used by the project appeared to be well maintained and serviced appropriately. Servicing records were available for inspection.
14. The PR has ensured that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA, as per General Directions 0002

What they could do better.

Nothing noted at this inspection

Changes / improvements since the last inspection on 18 August 2009:

Area for improvement	Action required	Action taken
No regulatory issues requiring improvement were identified at the last inspection on 18 August 2009	None required	None required

f practice that require the attention of the Person Responsible

n sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been c
, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Stan
onditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well
in which these improvements should be carried out.

ical area of non compliance

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

actice and	Action required and timescale for action	PR Response	Executive Review

or area of non compliance

ajor 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, storag 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 toge may represent a major area of non compliance.

actice and	Action required and timescale for action	PR Response	Executive Review

er areas of practice that requires improvement

as of practice that requires improvement is any area of practice, which cannot be classified as either a critical or maj
compliance, but which indicates a departure from good practice.

actice and reference	Action required	PR Response	Executive Review

information from the Person Responsible

sent by the PR by email on 9 September 2011:

n most impressed with the set-up in Hull and delighted that the Licence could be transferred over from York. I thou
was professionally carried out in a constructive manner. I look forward to seeing Roger Sturmey* as PR and to
ta in due course.

ectors comment: A change of PR from Professor Henry Leese to Dr Roger Sturmey was discussed on inspectio
for this will be submitted by the current PR in the near future.

HFEA Executive Licence Panel Meeting

23 September 2011

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 5

Centre 0021 (R0067) – (Hull IVF Unit) – Interim Inspection Report

Members of the Panel:	Committee Secretary:
Peter Thompson, Director of Strategy & Information (Chair) Nick Jones, Director of Compliance Danielle Hamm, Policy Manager	Joanne McAlpine

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

The Panel also 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 this research licence relates to research project (R0067) entitled "Biochemistry of Early Human Embryos". The project was first licensed in 1995 and the current licence is active from 1 February 2010 to 31 January 2013.

2. The Panel noted that the project was renewed by the Research Licence Committee at its meeting on 18 November 2009, which considered the appropriate statutory tests set out in the HFE Act 1990 (as amended).

3. The Panel noted that the Person Responsible (PR) states in the report that the aims and objectives of the project have not changed since the project first became licensed, and the project has Ethics Committee approval.

4. The Panel noted the lay summary of the project and the potential benefits of this work.

5. The Panel noted the PR, Professor Henry Leese, is a member of the HFEA Horizon Scanning Group.

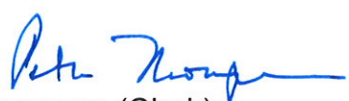
6. The PR for the project applied on 6 July 2010 to change the location of the licensed research premises from the University of York (centre 0062) to Hull IVF Unit (centre 0021). This was largely due to the wish to move closer to an IVF unit to better test the project's developments and to more effectively source embryos for research.

7. The Panel noted from the report that on inspection there were no areas of non-compliance identified by the Inspectorate.

8. The Panel noted the Inspectorate's recommendation to the continuation of the centre's licence without additional conditions.

Decision

9. The Panel endorsed the Inspectorate's recommendation to continue the centre's licence, with no additional conditions.

Signed:  Date: 4/10/11.
Peter Thompson (Chair)