Research Interim Inspection Report

Date of Inspection: 15 September 2011
Purpose of inspection: Interim Inspection of Research Licence
Length of inspection: 6.5 hours
Inspectors: Wil Lenton (HFEA, Lead)
Vicki Lamb (HFEA)
Renuka Sornarajah (Human Tissue Authority, Observer)

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 30 July 2009 and 18 November 2011.

Date of Executive Licensing Panel: 2 December 2011.

Centre details

Project Title	'In vitro Development and Implantation of Normal Human Pre-embryos and Comparison with Uni- and Poly- pronucleate Pre-embryos'.
Centre Name	University of Manchester (0175) St Mary's Hospital (0067) Manchester Fertility Services Ltd (0033)
Centre Number	0175/0067/0033
Research licence Number	R0026/12/a (0175) R0026/14/b (0067) R0026/13/b (0033)
Centre Address	Centre 0175: Ground Floor, Core Technology Facility (CTF), Faculty of Life Sciences, 46 Grafton Street, Manchester, M13 9NT Centre 0067: The Department of Reproductive Medicine, Regional IVF and DI Unit, Oxford Road, Manchester, M13 9WL. Centre 0033: Bridgewater Hospital, 120 Princess Road, Manchester, M15 5AT
Person Responsible	Professor Daniel Brison (0175; 0067 & 0033)
Licence Holder	Professor Sue Kimber (0175 & 0067); Dr Brian Lieberman (0033)
Treatment centres donating to this research project	0007 & 0067
Date Licence Issued	01/02/2010
Licence expiry date	31/01/2013
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) and the Code of Practice 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:
This project is based mainly at St Mary's Hospital (0067) and the University of Manchester (0175). Active research at Manchester Fertility Services Ltd (0033) has not been undertaken since 2009, when the scientist involved left to take up a different post.

The project was initially licensed in June 1996. The present licence commenced on 1 February 2010 and is due to expire on 31 January 2013.

The licence was varied by an Executive Licensing Panel (ELP) on 8 April 2011, to include a new room (C4231) in the Michael Smith building. The laboratory facilities on the second floor of the CTF building were transferred to this room following the licensing decision. The Person Responsible (PR) stated that all transferred equipment would be re-validated and re-commissioned prior to use.

The PR has successfully completed the PR Entry Programme (PREP number: R/1020/7) and is a member of the HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) and Horizon Scanning Group.

Title of research project R0026:
In vitro Development and Implantation of Normal Human Pre-embryos and Comparison with Uni- and Poly- pronucleate Pre-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 visit to draw a conclusion on the continuation of the centre's licence.

The ELP is asked to note that at the time of the inspection there was one major area of non-compliance that required improvement.

Since the inspection visit the PR has given a commitment to fully implement the following recommendations:

- Report to the HFEA any adverse incidents which impact on the quality and/or safety of donated embryos for use in research.

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.

In spite of the fact that clinical in vitro fertilisation (IVF) has been used as a treatment for infertility for more than 20 years, human embryos created by IVF continue to develop poorly in the laboratory, and the success rate of IVF is low. Only one in every 5 or 10 embryos goes on to form a baby after transfer to the womb.

The aim of this research is to investigate the way normal human embryos develop in the laboratory, and compare them to embryos which develop abnormally. This will help us to improve laboratory conditions to allow normal embryo development, which will increase success rates of IVF.

We have gathered extensive information on the types of genes which are switched on in early embryos, by analysing messenger RNA and proteins produced by these genes. We have focussed in the past on molecules involved in cell adhesion, cell-cell communication, and the regulation of cell death (apoptosis). More recently we have looked at genes that regulate cell fate, particularly the decision to remain pluripotent (i.e. remain capable of forming all tissues in the body) or differentiate. We are expanding these studies to look at many more genes simultaneously, using gene chip technology, as it is likely that genes work together in particular pathways to regulate embryo development. We continue to compare normal embryos to abnormal ones, to try to understand the molecular basis for the abnormalities. As part of this we are creating embryos for research purposes, for example from oocytes which were immature or did not fertilise in an IVF cycle and would normally have been discarded. We have recently been looking at the impact on embryo development of freezing oocytes and embryos and ovarian tissue, for the purposes of preserving the fertility of female cancer patients.

Progress made in 2010:

We have used DNA gene chips or “microarrays” to compare which genes are switched on (“expressed”) in human embryos at different stages of development, and more recently, in the stem cells of human embryos on day 5 of development after fertilisation, called the inner cell mass (ICM) cells. We have compared these cells to those which form the outside layer of the embryo on day 5, the trophectoderm (TE) cells, and also to human embryonic stem (hES) cell lines which come from the ICM.

We have identified a number of potentially important gene pathways which are expressed in human embryos and ES cells. Crucial pathways identified in all embryos and hES cell lines include cellular signalling pathways, as well as those involved in synthesising amino acids. Cell regulators (i.e. the p53 protein) were expressed in all blastocysts, ICMs, TEs and hES lines. ICMs and TEs expressed genes involved in cell death and in cell signalling. Protein expression of a number of these genes was also confirmed in human blastocysts. This work has identified a number of important regulatory pathways in early development and in pluripotent cells and will create a platform for further studies that will help to improve IVF

technology and develop hES-based therapies for treatment of disease. Future work involves examining the way embryos develop and their cells divide using time lapse imaging microscopy, and also looking at the effect of a form of rapid embryo freezing (vitrification) on gene expression profiles of embryos.

Publications (2010 only)

Gene expression analysis of a new source of human oocytes and embryos for research and human embryonic stem cell derivation. Sneddon SF, Desousa PA, Arnesen RE, Lieberman BA, Kimber SJ, Brison DR. Fertil Steril. 2010 Oct 5. [Epub ahead of print]

Objectives of the research:

The objectives of the research project remain the same as at the licence renewal in January 2010. The team continue to investigate the way normal human embryos develop in the laboratory, and compare them to embryos which develop abnormally.

Donation and use of embryos:

Projected use of material for project R0026 for 2009/2010 (research renewal application July 2009).

Material	Expected usage
Fresh Eggs	500 (immature)
Frozen Eggs	200
Failed to Fertilise Eggs	600
Fresh Embryos	600
Frozen Embryos	300

R0026 Embryo & Egg Usage in the period from 1 January to 31 December 2010.

1. Embryo Usage:

	Donating Centres					
	0007		0067		**Total**	
	Fsh	Frz	Fsh	Frz	**Fsh**	**Frz**
Donated:	0	48	454	89	**454**	**137**
Received or thawed	0	48	454	134	**454**	**182***
Used	0	45	291	88	**291**	**133****
Disposed of:	0	3	163	4	**163**	**7**

Fsh = Fresh embryos; Frz = Frozen embryos

* In table 1 above, the number of frozen embryos 'received or thawed' in this time period is greater than the number of embryos donated, as other previously donated frozen embryos will have also been used.

** In table 1 above, although 182 frozen embryos were initially thawed, only 133 survived the process and were utilised, with seven of these having to be disposed of due to poor development.

2. Egg Usage:

	Donating Centres								
	0007			0067			**Total*** **		
	Fsh	FF	Frz	Fsh	FF	Frz	**Fsh**	**FF**	**Frz**
Donated:	0	0	0	33	33	0	**33**	**33**	**0**
Submitted or thawed	0	0	0	33	33	0	**33**	**33**	**0**
Used	0	0	0	7	7	0	**7**	**7**	**0**
Disposed of:	0	0	0	26	26	0	**26**	**26**	**0**

Fsh = Fresh eggs; FF = Failed to fertilise eggs; Frz = Frozen eggs

*** In table 2 above, all the fresh eggs used were fresh failed to fertilise eggs from centre 0067. Although 33 fresh failed to fertilise eggs were donated, only seven were actually viable for subsequent use.

3. Table showing the number of Eggs and Embryos actually used in research against numbers originally expected to be used (1 January to 31 December 2010)

	Fresh Eggs	Failed to Fertilise Eggs	Fresh Embryos	Frozen Embryos
2010 Expected	500	600	600	300
2010 Actual	33	33	454	182

Note on embryo and egg usage in project R0026 during the period 1 January to 31 December 2010.

The inspection team considers that the research team has been efficient in its use of eggs and embryos during this time period. From tables 1, 2 & 3 above it can be seen that the team has worked towards its research objectives with the use of fewer eggs and embryos than had originally been estimated.

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.

The research licence was previously renewed in February 2010. It had received ethical approval from an appropriately-constituted local research ethics committee (LREC) which was acceptable to the licence committee at the last renewal; this approval remains in place.

The project's licence renewal application was reviewed by a peer reviewer and the HFEA Research Licence Committee (RLC) in November 2009. 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 storage of sperm; the storage of embryos; the use of donated embryos; the creation of embryos and the storage of eggs within ovarian tissue. 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
- increasing knowledge about the causes of miscarriage
- increasing knowledge about the development of embryos

During the inspection the PR stated that the project's aims, objectives and methodologies have not changed since the previous renewal application in 2009. Thus any future use of eggs / embryos will be in activities and for purposes considered by the LREC and the RLC 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.

From the review of ten sets of medical records on the day of inspection, it was determined that appropriate information is given to patients concerning the donation of material for use in research, by a trained member of staff (standard research licence condition (SRLC) R19) and that appropriate consents are in place for the use of embryos in the research project (SRLC R18).

An audit trail was successfully established for all embryos identified as being donated to research within the records reviewed. This involved anonymisation of embryos prior to use in

research, through to use in different parts of the project and disposal at the end of each completed process.

The PR stated that a research nurse coordinator, who is not directly involved in the patient's own treatment, is available to discuss the research project prior to donation of any licensed material (SRLC R22).

Through the review of research documentation it was established that the centre has a process in place to ensure that all licensed material used in research is uniquely coded (SRLC R26). The centre also has a documented procedure in place which ensures that embryos are not cultured for more than 14 days post fertilisation (SRLC R28) and only utilises embryos within their specified statutory storage period (SRLC R39).

The PR has ensured that appropriate records of egg/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 30 July 2009:

Area for improvement	Action required	Action taken as evidenced during this inspection
N/A		

Areas of concern: From the analysis of the centre's self assessment questionnaire and other information submitted to the HFEA, the following areas needed to be reviewed during this inspection.

Area of concern	Inspection findings	Assessment of whether the findings meet the requirement
1. In the time since you last completed a self assessment, has your centre reported to the HFEA any serious adverse events and/or serious adverse reactions that have occurred on any premises to which the centre's licence relates and any relevant third-party premises? (SRLC 85/86/87/88 & 89).	The centre utilises the University corporate governance framework when documenting any adverse incident, which are recorded in a log book. The log book was reviewed during the inspection and following discussions with the PR it was agreed that where an incident may impact upon the quality and safety of donated embryos these incidents would be reported to the Authority via the incident reporting system, within the required timeframes.	The centre should retrospectively report the incident discussed during the inspection upon receipt of this report and subsequently ensure that any future adverse incident, which may impact on the quality and safety of donated research embryos, is reported to the Authority via the incident reporting system, within the required timeframes. The PR agreed on inspection to implement these changes. **Further action required.**

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
No critical areas of non-compliance were found			

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
The centre has not reported an adverse incident which may have had an impact on the quality and/or safety of donated research embryos. (SRLC 40).	The centre should retrospectively report the incident discussed during the inspection upon receipt of this report and subsequently ensure that any future adverse incidents, which may impact on the quality and safety of donated research embryos, are reported to the Authority via the incident reporting system, within the required timeframes.	The PR has agreed to retrospectively report the incident highlighted during the inspection and will henceforth report any similar incident as per HFEA requirements.	The PR has agreed to report this incident on receipt of this report and any similar incident going forward as per HFEA requirements. These actions should ensure the centre's future compliance regarding this issue. The Executive will review this issue as part of any future inspection.

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
No other areas of non-compliance were found			

Additional information from the Person Responsible
The clinical department at St Mary's (licenced centre 0067) has a well established system of incident reporting which the research team will now also use.

HFEA Executive Licence Panel Meeting

2 December 2011

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

Minutes – Item 3

Centres 0033, 0067 and 0175 (R0026) – (Manchester Fertility Services Limited) & (St Mary's Hospital) & (University of Manchester) – Interim Inspection Report (Research)

Members of the Panel:	Committee Secretary:
Mark Bennett, Director of Finance & Facilities (Chair) Nick Jones, Director of Compliance Juliet Tizzard, Head of Policy & Communications	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 project (R0026) is based at St Mary's Hospital (0067) and the University of Manchester (0175).

2. The Panel noted that active research at Manchester Fertility Services Ltd (0033) has not been undertaken since 2009, when the scientist involved left to take up a different post.

3. The Panel noted that the project was initially licensed in June 1996 and the present licence commenced 1 February 2010 and is due to expire on 31 January 2013.

4. The Panel noted that it varied the centre's licence at its meeting on 8 April 2011 to include a new room (C4231) for the laboratory.

5. The Panel noted that the Person Responsible (PR) also sits on the HFEA Scientific & Clinical Advances Advisory Committee.

6. The Panel noted that, on inspection, there were a number of areas of practice that required improvement, including one major area of non-compliance relating to the reporting of adverse incidents with impact on quality and/or safety of donated embryos for use in research.

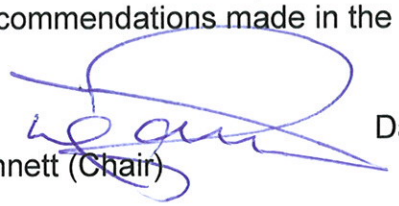
7. The Panel noted that, since the inspection, the PR has given a commitment to fully implement all of the recommendations within the report.

8. The Panel noted the Inspectorate's recommendation for the continuation of the centres' research licences with no additional conditions.

9. The Panel noted that the incident that has been reported t will be dealt with separately by a Licence Committee, as this is not within the remit of the Panel.

Decision

10. The Panel endorsed the Inspectorate's recommendation to continue the centres' licences, with no additional conditions, and endorsed the recommendations made in the report.

Signed:  Date: 22 Dec 2011

Mark Bennett (Chair)