HFEA Executive Licensing Panel Meeting

10 January 2014

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

Minutes – Item 4

Centres 0033 (Manchester Fertility), 0067 (St Mary's Hospital) and 0175 (University of Manchester) - Interim Inspection Report for Research Project R0171

Members of the Panel:	**Committee Secretary:**
Juliet Tizzard – Interim Director of Strategy (Chair)	Dee Knoyle
Ian Peacock – Analyst Programmer	**Observing:**
Matthew Watts – Regulatory Policy Manager	Sam Hartley – Head of Governance and Licensing

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 research project R0171 is carried out at three different centres, each centre holding a research licence for this project. Centre 0175 is a research only centre and centres 0067 and 0033 are treatment and storage with research centres.

2. The current research project, entitled “Derivation of human embryonic stem cell lines from embryos created from clinically unused oocytes or abnormally fertilised embryos” (R0171), was first licensed in August 2006. This research project includes the derivation of embryonic stem cells intended for human application.

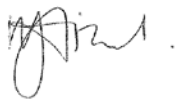
3. The Panel noted that the current licence is due to expire on 31 December 2015, having been renewed for three years by a Research Licence Committee (RLC) on 19 November 2012.

4. The Panel noted that at the time of the inspection on 8 October 2013, the Inspectorate observed one major and one other area of non-compliance. Since the inspection the PR has provided evidence that the recommendation for the major non-compliance is fully implemented and has given commitment to fully implement the outstanding recommendation within the set timescales.

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

Decision

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



Signed: Date: 24 January 2014
Juliet Tizzard (Chair)

Research Interim Inspection Report

Date of Inspection: 8 October 2013
Purpose of inspection: Interim Inspection of Research Licence
Length of inspection: 8 hours
Inspectors: Dr Vicki Lamb

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 15 September 2011 and 27 December 2013.

Date of Executive Licensing Panel: 10 January 2014

Centre details

Project title	Derivation of human embryonic stem cell lines from embryos created from clinically unused oocytes or abnormally fertilised embryos
Centre names and numbers	University of Manchester (0175) St Mary's Hospital (0067) Manchester Fertility (0033)
Research licence number	R/0171/3/a
Centre addresses	Centre 0175: Floor 2 Core Technology Facility, Faculty of Life Sciences, University of Manchester, 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: 3 Oakwood Square, Cheadle Royal Business Park, Cheadle, Cheshire, SK8 3SB
Person Responsible	Professor Daniel Brison (0175, 0067 and 0033)
Licence Holder	Professor Susan Kimber (0175); Dr Cheryl Fitzgerald (0067); Dr Brian Lieberman (0033)
Treatment centres donating to this research project	0008 0033 0067
Date Licence Issued	1 January 2013

Licence expiry date	31 December 2015
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:

Research project R0171 is carried out at three different centres, each centre holding a research licence for this project. Centre 0175 is a research only centre and centres 0067 and 0033 are treatment and storage with research centres. The current research project, entitled "Derivation of human embryonic stem cell lines from embryos created from clinically unused oocytes or abnormally fertilised embryos" (R0171), was first licensed in August 2006. This research project includes the derivation of embryonic stem cells intended for human application.

The current licence is due to expire on 31 December 2015, having been renewed for three years by a Research Licence Committee (RLC) on 19 November 2012. The RLC considered a desk-based assessment of the research licence application. The last time the centres were visited was on 15 September 2011. There are no additional conditions on the licences.

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 Executive Licensing Panel is asked to note that at the time of the inspection there was one major area of non-compliance and one 'other' area of non-compliance or poor practice.

Since the inspection visit the Person Responsible (PR) has provided evidence that the following recommendation has been fully implemented:

Major areas of non compliance:

- The PR should investigate the discrepancy between the number of embryos donated to the project at the treatment centre and the number of embryos received by the research centre and provide a summary report of the findings to the HFEA.

The PR has given a commitment to fully implement the following recommendation:

'Other' area of non-compliance or poor practice:

- The PR should review and amend the procedure for reporting adverse incidents and submit the revised procedure to the HFEA.

Recommendation to the Executive Licensing Panel:

The inspection team considers that overall there is sufficient information available to recommend the continuation of this centre's licence without additional conditions. In making this recommendation it is noted that the PR has responded to all recommendations made in this inspection report.

Summary of project

Lay summary of the research project:

The researchers plan to continue their current project to derive clinical grade embryonic stem cells from eggs and embryos donated by IVF patients at participating centres. If eggs are used they can be cultured or chemically activated to form embryos, with or without cryopreservation. They remove cells from embryos at different stages of development from day 3 to day 8 after fertilisation. This prevents any further development of the embryo well before the limit of 14 days post-fertilisation. They take the cells from the embryos and encourage them to grow in special culture conditions usually on a layer of supportive feeder cells. If the cells do develop, they can form embryo stem cells, and eventually, an embryonic stem cell (hESC) line (defined as 3 million cells or more, some of which have been placed in frozen storage). These hESC lines are tested for their ability to form all cell types in the body, to make sure that they are genetically normal and remain so after being cultured in the laboratory, and to make sure that they are not contaminated in any way which would make them unsuitable to be used in the treatment of disease. They also study the gene expression profile of the cell lines, and also some of the embryos or cells taken from the embryos, in order to increase their basic understanding of cell fate in embryos and hESC cells. This work will ultimately benefit IVF treatments by increasing the understanding of human embryo development.

Objectives of the research:

The researchers aim to continue their current research aims including:

(1) Derive new embryonic stem cell lines in line with the objectives of their current MRC funding, in order to generate a range of clinical grade embryonic stem cells with different HLA types.
(2) Study the gene expression profiles of isolated trophectoderm and inner cell mass cells, as a continuation of their existing studies.
(3) Extend objective (2) to include isolated cells from pre-blastocyst (early cleavage) stage embryos, in order to assess their pluripotent status by gene expression profiling, and by deriving embryonic stem cell lines from them.

Donation and use of embryos:

In the period from 1 January 2012 to 31 December 2012, the centre reported the use of 143 fresh embryos and 26 frozen embryos. No embryos were created for use in the project.

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 renewal of research licence R0171 was granted by the RLC on 19 November 2012, the licensed activities being the creation of embryos in vitro, keeping embryos, storage of embryos and use of embryos. None of these activities is prohibited by the HF&E Act 1990 (as amended). The renewal of the licence was approved to allow research for the following designated purposes:

- Increasing knowledge about serious disease or other serious medical conditions
  HFE Act 1990 (as amended) Schedule 2 3A(2)(a)
- Developing treatments for serious disease or other serious medical conditions
  HFE Act 1990 (as amended) Schedule 2 3A(2)(b)
- Promoting advances in the treatment of infertility
  HFE Act 1990 (as amended) Schedule 2 3A(2)(d)
- Increasing knowledge about the causes of miscarriage
  HFE Act 1990 (as amended) Schedule 2 3A(2)(e)
- Developing more effective techniques of contraception
  HFE Act 1990 (as amended) Schedule 2 3A(2)(f)
- Increasing knowledge about the development of embryos
  HFE Act 1990 (as amended) Schedule 2 3A(2)(h)

At the last renewal, the application's peer reviewer agreed that the use of human embryos was necessary and justified for the proposed research. Evidence of approval by an ethics committee was also provided.

What they could do better.

Nothing noted on 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.

An audit of records of the usage of five sets of embryos in the project demonstrated that:

- Comprehensive records of the usage of embryos in the research project are maintained from embryo donation to the project through to disposal at the end of the research process (but see comment in 'what they could do better) (RLC R13).
- 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 (RLC R28). The audit of records confirmed compliance with this requirement.
- All embryos donated to the project have been used for the objectives authorised by the licence to meet the defined statutory purposes (RLC R5 and R23).
- A storage log is maintained which records the storage consent expiry dates for any embryos in storage for research purposes. 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).

The research identifiers for the same five sets of embryos were used to track back to five sets of patient records at centre 0067 where the treatment had taken place. Audit of these five sets of patient records indicated that effective consent for the use of the embryos in the research project had been documented by the gamete providers (RLC R18).

Centre staff explained that they are in the process of transferring samples of derived stem cell lines to the UK Stem Cell Bank (RLC R30). Paperwork has already been sent and they are awaiting information from the UK Stem Cell Bank on when the samples can be transferred.

Evidence of traceability of equipment and consumables used during the derivation of stem cell lines was provided at the Human Tissue Authority inspection which occurred on the same day as the HFEA inspection. No issues were noted in relation to traceability (RLC R51, R68 and R69).

The PR has ensured that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA (General Direction 0002 and RLC R13, R14 and R15).

What they could do better.

The procedure for reporting adverse incidents states the incorrect timescale for reporting to the HFEA (General Direction 0011 and RLC R40).

The full range of serological tests required by HTA standards are not performed on patients donating material to this research project (RLC R66).

In one case, the audit of records showed a discrepancy, of one embryo, between the number of embryos donated to the project at the treatment centre and the number of embryos received by the research centre (RLC R76 and R77).

Changes / improvements since the renewal of the licence on 19 November 2012:

Area for improvement	Action required	Action taken as evidenced during this inspection
As the aim of this project is use embryos to derive embryonic stem cell lines for human application, the EUTCD requires additional serological testing to be carried out on the tissue providers (in this case the gamete providers). Compliance with these requirements are regulated by the Human Tissue Authority (HTA) The full range of serological tests required by HTA standards are not performed on patients donating material to this research project. RLC R66.	The PR should ensure that the full range of serological tests required by the Human Tissue Authority (HTA) standards are performed on patients donating material to this research project. By 30 November 2012.	The PR stated that this was not possible as there is no ethical approval to perform blood tests which are not part of routine IVF patient screening. Following consultation, the HTA is proposing to ask the other European Competent Authorities to support a submission to the European Commission to request amendments be made to the EUTCD in relation the testing requirements for embryonic stem cell lines. The HFEA has supported this submission. The HFEA recommends that compliance with this area of practice should be in line with the outcome of the HTA's submission to the European commission. No further action required at present.
It is not a condition of all third party agreements that the third party will meet the requirements of the relevant licence conditions and the guidance set out in the HFEA Code of Practice. RLC R83.	The PR should ensure that it is a condition of all third party agreements that the third party will meet the requirements of the relevant licence conditions and the guidance set out in the HFEA Code of Practice. To be performed during the routine review of third party agreements, and to be	This has been addressed by the PR. No further action required.

	reviewed at the time of the next inspection.	

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			

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
The full range of serological tests required by HTA standards are not performed on patients donating material to	No action is required until the outcome of the HTA's submission to the European commission is known.	Agreed	This is a satisfactory response. Further action will be taken by the Executive, if required, when the outcome of the HTA's

this research project (RLC R66).			submission to the European commission is known.
In one case, the audit of records showed a discrepancy, of one embryo, between the number of embryos donated to the project at the treatment centre and the number of embryos received by the research centre (RLC R76 and R77).	The PR should investigate the discrepancy and provide a summary report of the findings to the HFEA. If necessary the discrepancy should be reported to the HFEA as an incident. By 8 January 2014.	One of the embryos was arrested and assumed to be non-viable by the clinical embryology team, so they marked it down as discarded rather than going to research. When the research team saw it they decided it was useful for research and so accepted it, according to our normal procedures. We should have amended the patient record, and have now done this.	The PR provided a report of the investigation which was performed in October 2013. The apparent discrepancy was caused by a paperwork error, and no embryos were unaccounted for.

‘Other’ areas of non-compliance or poor practice

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
The procedure for reporting adverse incidents states the incorrect timescale for reporting to the HFEA (General Direction 0011 and RLC R40).	The PR should review and amend the procedure for reporting adverse incidents and submit the revised procedure to the HFEA. By 8 January 2014.	Agreed	This is a satisfactory response.

Additional information from the Person Responsible