



Research Licence Interim Inspection Report

Project Title	Studies of embryo development and metabolism
Centre Name	Assisted Conception Unit, Ninewells Hospital and Medical School
Centre Number	Centre 0004
Research licence Number	R0154-1-a
Centre Address	Assisted Conception Unit, Ward 35, Ninewells Hospital Dundee Scotland, DD1 9SY United Kingdom
Treatment centres donating to this research project	Assisted Conception Unit, Ninewells Hospital and Medical School, Centre 0004
Inspection date	5 February 2008
Licence Committee Date	18 June 2008
Inspector(s)	Debra Bloor
Person Responsible	Ms Anne McConnell
Nominal Licensee	Dr Madhurima Rajkhowa
Licence expiry date	30 November 2010

About the Inspection:

The purpose of the inspection is to ensure that centres are providing a quality service for patients in compliance with the HF&E Act 1990, sixth edition Code of Practice, licence conditions and directions.

The report is used to summarise the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where further improvement is required to improve patient services and meet regulatory standards. It is primarily written for the Licence Committee who make the decision about the centre's licence renewal application. The report is also available to patients and the public following the Licence Committee meeting.

This report covers the period between 9 March 2007 and 5 February 2008.

Brief Description of the Project

The primary aim of the research is to carry out non invasive metabolic studies of developing embryos and to investigate the expression of metabolic and biochemical markers using immunocytochemistry and molecular biology techniques: ultimately the work aims to contribute to the determination of the optimum culture conditions for embryo development. Good quality embryos reaching the blastocyst stage of development are not used in the local research but are donated to Roslin Cells Ltd. for use in HFEA licensed stem cell research project R0136.

Lay summary:

The success of in-vitro fertilisation has been slowly improving from research done throughout the world. We would like to culture spare embryos to determine what are the best conditions for their development in the laboratory before transfer to the womb and so improve in-vitro fertilisation for the future. We hope to identify metabolic or biochemical markers of embryo development to enable better embryo selection for transfer. Cells from the embryo have the potential to develop into stem cells, which can mature into any cell type in the body such as heart cells or brain cells. These cells could be used in the future to replace damaged heart or brain cells in adults. In Edinburgh a research group is trying to grow stem cells from human embryos. If any embryos in Dundee are suitable they will be transferred to the Edinburgh laboratory for this purpose.

Research activities	Research on human embryos	✓	
	Storage of licensed material	✓	
	Creation of embryos for research		
	Derivation of human embryonic stem cells		
	Cell nuclear replacement		

Changes/ improvements since last inspection

Work on the local research project was suspended between November 2006 and May 2008 following the extended absence of the primary research embryologist. Embryos not suitable for treatment and donated to research continued to be subject to extended culture and good quality embryos reaching the blastocyst stage of development continued to be transferred to Roslin Cells Ltd. for use in the HFEA licensed stem cell research project R0136. The culture medium from embryos subject to extended culture continued to be collected and stored for possible future metabolic studies.

Additional licence conditions and recommendations and actions taken by centre since last inspection

The current licence was issued with no additional conditions.

Summary for Licence Committee

Progress in the research has been hampered in the last year by the long term absence of the research embryologist. However, embryos have continued to be subject to extended culture and those reaching the blastocyst stage of development have been donated to research project R0136: culture medium has also been stored for future analysis.

There have been no changes to the premises or equipment or to the procedures for recruitment of donors since the renewal inspection when they were all considered appropriate.

Consents in a sample of patient records were consistent with the donation of embryos to research and procedures for providing information to patients considering donation were observed in the course of the inspection and were considered good.

The only area of improvement identified in the course of the inspection related to the development of a robust system for the accurate recording of the use of embryos in the research project.

The majority of the recommendations made in the renewal report have been implemented. The assessment of the risks of transfer of viable embryos to shared facilities and the implementation of research governance procedures has not been completed because of the suspension of the local research but it was agreed that the risk assessment would be completed before the research resumes and that audit of embryo development would be undertaken as appropriate in the next year.

The inspector supports the continuation of the centre's licence.

Proposed licence variations

None

Report of Inspection findings

1. Organisation

Desired Outcome: The centre is well-organised and managed and complies with the requirements of the HFE Act.

Summary of findings from inspection

Evidence of: *(Delete areas not reporting on)*

- Leadership and management
- Organisation of the centre
- Resource management
- Staffing
- Funding

Full time equivalent staff

Principal investigator	0.15
Administrators/ Support staff (receptionists, record managers, quality and risk managers etc)	The research is provided with administrative support by the staff of centre 0004.

Highlighted areas of firm compliance

The Person Responsible (PR) implemented the recommendations of the previous report related to changes in patient information and consents, the availability of counselling to those donating embryos to research and procedures for withdrawal of consent. Changes were also made to the labelling of dishes to protect the confidentiality of patients donating to research.

The nurse coordinator reported having undertaken relevant continued professional development (CPD) in the time since the last inspection and visited Roslin Cells Ltd. to be updated on the stem cell project to which the centre donates embryos.

Local funding is in place until September 2008.

Issues for consideration

The 2007 renewal inspection report made the following recommendations:

- The PR should risk assess the movement of labelled embryo culture dishes to the shared university laboratory and consider the safety and security of donated embryos, particularly in the event of emergency situations.
- Audits into research embryos development could be conducted, as part of research governance.

As work on the local research project was suspended between November 2006 and May 2008 the implementation of the recommendations has not been completed. At the time of the inspection, research was still not in progress and it is recommended that research is not resumed until the risks related to the movement of embryos to the shared research facilities

are assessed. When the research is fully operational it is also recommended that audits of embryo development are carried out.

Executive recommendations for Licence Committee

As outlined above

Areas not covered in this inspection

Research governance (as the project has not been fully operational in the last year).

2. Premises and equipment

Desired Outcome: The premises and equipment are safe, secure and suitable for their purpose.

Summary of findings from inspection: *(Delete areas not being reported on)*

- Suitability of premises

Highlighted areas of firm compliance
There have been no changes to the premises in the time since the last inspection when they were considered suitable.
Issues for consideration
Prior to February 2008, embryos reaching the blastocyst stage of development after prolonged culture were donated to Roslin Cells Ltd. This procedure is suspended at present pending finalisation of the technical agreement. As local research resumes poor quality embryos of more limited viability will be transferred to shared research laboratories for fixation and/or processing prior to molecular studies. It remains a recommendation that the risks of this transfer are assessed before the project becomes fully operational (see previous page).
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Safety of equipment Servicing and maintenance of equipment

3. Donation of material

Desired outcome: Ensure donors are recruited in a proper way and their consent is respected.

Summary of findings from inspection: *(Delete areas not being reported on)*

- Recruitment of donors
- Ensuring prospective donors have access to further guidance
- Ensuring prospective donors have time to consider donation properly
- Prevention of coercion of prospective donors

Highlighted areas of firm compliance
<p>Donation of material was considered in depth at the time of the 2007 renewal inspection: no changes to the procedures have been made in the intervening time.</p> <p>In the course of a routine review of patient records it was noted that the provision of patient information was recorded.</p> <p>In the course of the inspection it was confirmed that information for patients donating to research references the availability of an independent counsellor and procedures for withdrawing consent. The research nurse described a scenario in which a patient had revised their consent prior to donation, indicating that the procedures work in practice.</p> <p>An information session provided by the recruiting nurse to a couple considering donation to research was observed in the course of the inspection. The inspector considered that the information provided was clear and outlined relevant issues for consideration. The patients were asked to go away and consider and discuss the issues before reaching a final decision. Both patients confirmed that they had found the session informative and that they had been provided with the information that they needed in order to reach a decision. The inspector was confident that the patients had not been coerced in any way and that the patients had enough time to consider the implications of donation.</p>
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

4. Patient information and consents

Desired outcome: Ensure that patients are informed in order to give informed consent

Summary of findings from inspection: *(Delete areas not being reported on)*

- Consent forms
- Consent forms for projects deriving embryonic stem cells

Outcome of audit of records
<p>The records of four sets of patients donating embryos to research were reviewed in the course of the inspection. Consents were present and compatible with the donation of embryos to both the local research and to stem cell project R0136.</p> <p>Three embryos donated by a single couple and reported as used in research in treatment forms submitted to the HFEA did not appear in the centre's log and had not therefore been included in the annual progress report return. This is potentially a breach of standard S.7.3.2 of the COP¹.</p> <p>It is recommended that the PR undertakes a review of the procedures used to record the donation of embryos to research to ensure that the procedures used are robust.</p>
Highlighted areas of firm compliance
<p>Patient information was considered appropriate (subject to minor revision) at the time of the renewal inspection. With the exception of the implementation of the recommended changes, information has not been changed in the intervening time and no further review of information was carried out in the course of the interim inspection.</p>
Issues for consideration
<p>The procedures for the provision of patient consent to the secretary of the steering committee of the national stem cell bank (NSCB) were discussed in the course of the inspection. There was a lack of clarity about how a copy of the patients' consent would be provided to the NSCB in the event that a stem cell line is deposited: specifically, staff from centre 0004 were concerned that the identity of donors should not be revealed to the staff of research project R0136. It was agreed that the procedures should be clarified and documented to ensure effective transfer of the information if and when it is required. If, after discussion with the NSCB and or the PR of research project R0136 it is apparent that the patients' identity may be revealed to staff of research project R0136 then information provided to patients donating to the project through centre 0004 should be revised to reflect this.</p>
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Patient information for projects deriving embryonic stem cells Patient information

¹ S.7.3.2 of the COP states that the procedures for traceability of gametes and embryos shall also ensure that registers are kept of received, processed, stored and distributed or discarded gametes or embryos, enabling identification of (c) distributed gametes or embryos and hospitals or institutions to which gametes or embryos have been distributed (whether intended for application in the human body, or research purposes).

5. Scientific practice

Desired outcome: Procedures are robust to ensure material is used appropriately

Summary of findings from inspection: *(Delete areas not being reported on)*

- Ability to achieve set aims and objectives

Use of material
<p>The embryos used in the research project in 2007 were as follows: Fresh – 62 embryos to research, 48 discarded, 14 transferred to Roslin Frozen – 33 embryos to research, 31 discarded, 2 transferred to Roslin</p> <p>It had been estimated that the project would use 100 fresh and 25 frozen embryos.</p> <p>Fewer embryos were used in the project than estimated. The reasons provided for the use of fewer embryos than predicted were as follows: a) Cessation of collaboration with Institute for Stem Cell Research; b) Only embryos at the blastocyst stage are sent to Roslin Cells Ltd. while this was not the case with Institute for Stem Cell Research.</p> <p>It is estimated that 60 fresh and 30 frozen embryos will be used in 2008.</p>
Project objectives
<ul style="list-style-type: none">• Continue to culture embryos for the derivation of human embryonic stem cells through the supply of donated embryos to researchers in Edinburgh;• Continue to investigate the role of glucose-6 phosphatase catalytic subunits in developing embryos;• Study the role of preimplantation embryonic morphology and metabolism in the prediction of subsequent viability;• Analyse the demographic and clinical data of patients donating embryos to research.
Lay summary of research undertaken
<p>Donated embryos have been cultured beyond the day of embryo transfer to the blastocyst stage. Until August 2006 embryos with the potential to derive stem cells were transferred to the Institute of Stem Cell Research while those demonstrating developmental arrest were used in the local research study. The research team in Edinburgh then moved to Cambridge and all embryos were recruited for local research only until July 2007. Since July 2007, embryos have been transferred to Roslin Cells, Edinburgh. Two potential stem cell lines have been identified and are being characterised at present.</p> <p>Local research has focused on increasing the knowledge of embryonic development and metabolism by identifying proteins involved in metabolism at each stage of embryonic division. The spent culture medium from fifty treatment cycles has been stored for future analysis, which may lead to further insight into embryonic metabolism. It is hoped to correlate these data with embryonic developmental data and implantation outcome. This may lead to the identification of viability markers; we are at present exploring the possibility of identifying these markers in the laboratory.</p>

Due to illness of the research embryologist, no work has been done on the local research project from November 2006.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Standard operating procedures Quality assurance systems Minimisation of material loss and wastage

Report compiled by:

Name...Debra Bloor.....

Designation.....Inspector.....

Date.....25 February 2008.....

Appendix A: Centre Staff interviewed

Two members of the research team

Appendix B: Licence history for previous 3 years

Licence	Status	Type	Valid from	Valid to
R0154/2/a	Active	Research	01/12/2007	30/11/2010
R0154/1/a	Expired	Research	07/12/2004	30/11/2007

Appendix C:
RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number... 0004.....

Name of PR..... Anne McConnell.....

Date of Inspection...5 February 2008.....

Date of Response...22nd May 2008.....

Please state any actions you have taken or are planning to take following the inspection with time scales

A risk assessment (FMEA) relating to the transfer of embryos from the ACU to the research lab was carried out (attached). This demonstrated that no action was required. The SOP relating to this process is also attached.

Audit of case notes relating to the use of embryos in research was carried out for 2007. Laboratory record sheets are being revised which will allow for easier identification of embryos donated to research. The research embryologist has reintroduced a development record which records the fate of each embryo.

Clarification has been received from Dr Chris O'Toole that, should patients require to be contacted by the secretary of the Stem Cell Bank, this would be done through Ninewells (Centre 0004), therefore it is not necessary for identifying information to be provided to Roslin Cells Ltd.

I have read the inspection report and agree to meet the requirements of the report.

Name.....Anne McConnell...(received by email).....

Date.....22nd May 2008.....

2. Correction of factual inaccuracies

Please let us know of any factual corrections that you believe need to be made (NB we will make any alterations to the report where there are factual inaccuracies. Any other comments about the inspection report will be appended to the report).

Page 8 – ‘Three embryos donated and reported as used.....’ – I cannot recall this being discussed on the day of the inspection. There was a discrepancy between the data obtained from the HFEA registry and that reported by the research nurse, but it was noted that the data from the registry did not include frozen embryos donated to research.

Page 10 , use of material – a further reason for fewer embryos than estimated being provided was due to a significant reduction in the numbers of patients consenting to research.

