Research Licence 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	Centre 0004
Inspection date	6th March 2007
Licence Committee Date	9th May 2007
Inspector(s)	Miss Sarah Hopper Miss Grace Cunningham
Fee Paid - date	Invoice not yet sent
Person Responsible	Ms Anne McConnell
Nominal Licensee	Dr Madhurima Rajkhowa

About the Inspection:
The purpose of the inspection is to ensure that researchers comply with the HF&E Act 1990, 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 research licence application. The report is also available to patients and the public following the Licence Committee meeting.

Brief Description of the Centre and licensed project

The Assisted Conception Unit at Ninewells Hospital has held a HFEA research licence since December 2004 and this licence is due to expire in November 2007.

Ms Anne McConnell, the business manager for the unit, has been PR since this date.

The project's title is: **Studies of embryo development and metabolism** and the lay summary of the proposed research project, submitted by the centre is as follows:

"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."

The project is licensed for the following purposes:

- Promoting advances in the treatment of infertility (Human fertilisation and embryology act 1990 Sch 2 3 (2)(a)
- Increasing knowledge about the development of embryos (Human Fertilisation and Embryology Research Purposes Regulations 2001 s2 b)

Research activities of the Centre	Research on human embryos	Yes	
	Storage of licensed material	Yes	
	Creation of embryos for research	No	
	Derivation of human embryonic stem cells	No	
	Cell nuclear replacement	No	

Changes/ improvements since last inspection

There have been no changes in premises, procedures or staff since the last inspection.

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

The licence was issued with no additional conditions.

Summary for Licence Committee

Progress has been achieved in relation to the stated aims of the research projects.

Some issues were identified during the inspection and the following recommendations made:

- A number of amendments to patient information and patient consent forms are required
- The PR should produce a protocol detailing the response to patient withdrawal of consent.
- Counselling should be offered to those donating embryos to the stem cell project and patient information should reflect this. [1]
- 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.

The Peer Reviewer was satisfied with the renewal application and recommended it should be accepted in its current form.

The inspectorate recommends the renewal of the research licence for a further three years.

[1] As required in Code of Practice part 5.9 iv

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
- Research governance
- Funding

Full time equivalent staff

Principal investigator	0.5
Laboratory scientists	0.5
Collaborators	2
Administrators/ Support staff (receptionists, record managers, quality and risk managers etc)	4 full-time equivalent employed in Unit, not specifically attached to research programme)

Background information
The PR for this project is the business manager for the treatment and storage services provided at the Assisted Conception Unit, Ninewells Hospital. Research work is primarily carried out by one of the clinical embryologists at the centre. She shares her time between research and clinical work but the PR stated that a clear separation procedure is in place to ensure that she is not involved in clinical decisions for potential donors. This is achieved by allocating laboratory procedures so that the research embryologist is not involved in the grading of embryos when embryos are being selected for transfer or freezing. Research staff have had access to continuing professional education in the past year: the PR stated that the research nurse has attended every Human Embryonic Stem Cell Coordinators (hESCCO) conference to date and the embryologist was also able to attend the last meeting. Meetings held between staff involved in research and staff involved in the recruitment of donors are held when possible but the PR stated that organising team meetings can be difficult due to the work pressures experienced at the unit. Minutes from two meetings held in the past year were provided to the inspectorate. In addition to these meetings, the PR stated that the research nurse produces a monthly report about the recruitment of donors and this is shared with the research team via email.

Issues for consideration
The Medical Research Council (MRC) grant supporting this project terminated in November 2006. Since that date, the PR has managed to obtain a bridging grant from the MRC and this will last until 30th June 2007. Although it is proposed that further funding will be obtained to support the research nurse position this money will be connected to the stem cell aspect of the project (licensed stem cell work does not occur at this centre but embryos are distributed to centres that are licensed for this work). Plans have not yet been made of how to pursue funding for the local research project. Research work has been conducted by one of the clinical embryologists working at the Assisted Conception Unit and she stated that the time she can spend on the research work is dictated by clinical caseload. The embryologist reported that she has experienced difficulties in finding time to dedicate to the research and that she has been unable to carry out any research since November (though this was also a repercussion of a funding gap). This was addressed with the PR, who stated that they have recently employed a trainee embryologist and that as she becomes more skilled, the pressure on the embryologist involved in research should decrease so that more time can be spent on the project.
Executive recommendations for Licence Committee
Note that funding has not been secured for the duration of the research project.
Areas not covered in this inspection
Resource management Research governance

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
- Storage facilities
- Safety of equipment
- Servicing and maintenance of equipment

Background information
Embryos donated to research are cultured within a specific incubator in the treatment and storage laboratory before being snap frozen, frozen without cryoprotectant, and stored in a dewar. All storage dewars are locked and the laboratory is secured when unoccupied. Once snap frozen, embryos are stored in shared freezers within the university laboratories. These freezers are not locked. However, the embryos are stored within vestibules which are not labelled with patient identifying information. Furthermore, the PR and research embryologist stated that the embryos are non-viable by this stage.
Issues for consideration
When embryos are to be fixed in Paraformaldehyde for immunocytochemistry work, they are taken down to the university laboratory within the same building. The embryologist stated that they are transported to this laboratory in their culture dishes and that the dishes are not left unattended. The inspectorate have concerns about the security of this practice as identifying patient information is written on the culture dishes and the university laboratory is shared with many members of staff who are not on the HFEA licence. The PR was asked to risk assess this practice and to consider the safety of donated embryos, particularly in the event of emergency situations when the embryologist may have to leave the dishes unattended.
Executive recommendations for Licence Committee
Note security issues surrounding movement of viable embryos to the university laboratory.
Areas not covered in this inspection
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
- Ensuring patient consent is not breached
- Donor and patient records

Background information
Donors are recruited for this project by approaching patients undergoing fresh cycles or through communications with patients who have had treatment and have embryos remaining in storage. A research nurse, in a position funded by the MRC, discusses research with patients in both situations. She also attends patient information evenings so that she can introduce herself. For patients undergoing fresh cycles, information regarding the research project is sent out along with the general cycle information around six weeks before patients attend the centre for their first appointment. The research nurse looks through the returned consent forms and in particular assesses the returned HFEA forms (previously 006 and 007) to look for patients who have indicated willingness to consent to research. If consent to research is indicated, the research nurse then approaches the patients at their next appointment. If, following this discussion, the patients are still willing to donate to research consent forms are filled out in the presence of the research nurse. If couples wish to have some time before making a decision, the research nurse organises to meet them the next time that they attend the centre. The research nurse stated that she only discusses the research project and obtains consent from the patients if both partners are present. Patients who have embryos in storage are written to two years after the date of initial storage and thereafter on an annual basis. The letters are sent to determine whether or not they would like the embryos to remain in storage or whether they would like them to be used for other purposes for example donation to research or another couple, or to be discarded. A final letter is sent to patients six months prior to the five year expiry date. Should patients wish to donate their embryos, they are invited to come into the unit and discuss this with the research nurse. If attending the unit is not convenient, the research nurse stated that she contacts patients via telephone for a discussion.
Issues for consideration
Counselling for patients wishing to donate to the stem cell project is not mentioned in the patient information or by the research nurse[2]. It was suggested that the availability of counselling could be included in research information and also in the embryo storage letters.

[2] As required in Code of Practice part 5.9 iv

A written protocol is not in place for the actions to be taken if a patient withdraws their consent to research. The PR should ensure that the procedure for responding to patient withdrawal of consent is documented and disseminated to all members of staff.
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)*

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

Background information
Two sets of research information are given out to patients: information regarding the local research project and information about stem cell projects carried out at other licensed centres.
Outcome of record audit
Five research records were audited and cross referenced with the original patient files. All HFEA and specific research consents were seen to be in place and were appropriately completed.
Issues for consideration
The patient information for the local research project requires some amendments: • Contact details for an independent person to discuss aspects relating to research should be added to patient information • Local research patient information does not include contact details should they wish to withdraw consent. This information should be added. Consent forms completed by patients wishing to donate embryos to the stem cell project based at the Institute for Stem Cell Research Edinburgh (centre 0166) do not include confirmation that the patients are aware that any stem cell lines created may continue indefinitely and may be used in different research projects. However, the PR states that the relationship with centre 0166 has now ended, as the PR has moved to a different centre, and it is planned that donated embryos will be sent to the Roslin Institute (0202). Information generated by this centre will be provided to patients at Ninewells hospital and the PR stated that she will send copies of this to the HFEA for approval.
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

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)*

- Standard operating procedures
- Quality assurance systems
- Minimisation of material loss and wastage
- Ability to achieve set aims and objectives

Summary
The research team stated that they ensure that embryos are not cultured for longer than 14 days as all embryos used within the local research project are fixed by day seven of development. The PR stated that patients are not recruited when it is known that the research embryologist will be on annual leave and frozen embryos are kept in storage until the research embryologist is ready. Embryos donated for use in stem cell projects are couriered from the centre once they reach the blastocyst stages. Frozen donated embryos are not moved into a separate research dewar but remain in their original location until they are removed and thawed for use. As such, donated embryos are not specifically audited but are included in the storage audit carried out under the treatment and storage licence. According to the PR this audit was conducted in May 2006 and no major discrepancies were noted.
Embryo usage
During 2006 195 fresh embryos have been donated to the project and of these 179 were used locally and 12 sent to centre 0166. 16 frozen embryos have been received and 6 of these were used locally and 8 at centre 0166. The numbers of donated embryos received is higher than previously anticipated. The PR stated that this is because recruitment of fresh embryos was higher than expected. The research team expects to use 100 fresh embryos and 25 frozen embryos in the next 12 months but this does depend on whether they are awarded a bridging grant. The donated embryos were cultured beyond the day of transfer, up 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. The 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. The research team hope to correlate this data with embryonic developmental data and implantation outcome. This may lead to the identification of viability markers.

The PR stated that progress has been slow due to the development of the techniques and the time available to the research embryologist.

Renewed objectives:

- 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 G-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

"The principal aim of this study continues to be culture of spare embryos for derivation of embryonic stem cell lines. Human embryo stem cells can be made to develop into different specific cell types which may have the potential for medical use in the future, for safety testing of new medicines and treatment and the study of disease.

Couples undergoing treatment at the Unit have donated spare embryos that are unsuitable for their treatment or for freezing to this project. The donated embryos are cultured in the laboratory up to the blastocyst stage. Any embryos developing to this stage were transferred to the Institute of Stem Cell Resarch, Edinburgh until August 2006, and from February 2007 to Roslin Cells Edinburgh. The percentage of embryos developing to blastocyst are small as these are spare embryos which are potentially of poorer grade.

The secondary aim of this study is to carry out local research on embryo development and metabolism looking specifically at glucose metabolism in early stage embryos. Currently, there is very little information available regarding appearance of glucose transport proteins in embryos at this stage. Embryos which have not proceeded to the blastocyst stage have been frozen to perform these studies. Embryos at specific stages of development, for example two cells or four cells have been pooled to recover sufficient RNA for analysis of glucose transport related proteins. In addition, some embryos have been stained with specific stains to look for the same protein markers (immunohistochemistry). So far, three pathways have been identified in early stage embryos. Further work needs to be done to confirm these findings. In addition, culture media from 50 treatment cycles has been snap frozen for analysis of glucose metabolism markers and other key elements. We are carrying out assessments of various methods to analyse the very small volumes of culture media for accurate assessment of these markers. Information from this analysis will be correlated to stage of embryos and to cycle outcome. We hope that the information may provide better understanding of embryonic energy requirements with potential for improvement in culture media."

Peer reviewer comments

The Peer reviewer stated that: "it appears that progress has been reasonable. A larger than anticipated number of embryos has been recruited to the project and enzyme subunits of interest have been identified as targets for further investigation. Some objectives of the study have been postponed and at the present rate it seems unlikely that the applicants will meet all their objectives within the current time period of the license. In light of this and their own

comments they may wish to review the allocation of research time to this project. The justification for the applicants' original proposal remains valid and whilst the results obtained so far are limited this remains an interesting project, undertaken by a well qualified team and one which in time should yield valuable results".

The Peer reviewer concluded that the application should be accepted in its current form.

Spot check of stored donated material
The embryologist stated that fewer frozen embryos are donated to research compared to fresh embryos. Once consent to donation is received from these patients, the embryos are removed from storage and used within research. The embryologist stated that there is rarely a delay before embryos are used and that at the time of inspection just two sets of embryos were waiting to be used in research. Both sets of embryos were tracked from records to tank and no discrepancies were found.
Issues for consideration
During the research audit, it was noted that some embryos considered to be unsuitable for freezing on day 2 went on to become blastocysts. The PR was asked whether or not this is monitored and whether they had any concerns about their protocol for embryo requirements for freezing. The research embryologist stated that the blastocysts created were generally of poorer quality and questionable genetic normality. The inspectorate looked through a number of research records and although it was noted that some embryos did progress to the blastocyst stage, the inspectorate did not consider that this was at a concerning level. The inspectorate were also reassured by the clear separation of research and clinical embryology practices (see section one) that has been put in place. It was recommended that audits into research embryos development could be carried out, as part of research governance. This would also ensure that the laboratory freezing protocol could be monitored and reviewed if ever necessary.
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

Report compiled by:

Name……Sarah Hopper ……..

Designation…Inspector… ……

Date……06/03/07……

Appendix A: Centre Staff interviewed

PR and two members of the research team.

No conflicts of interest were declared

Appendix B: Licence history for previous 3 years

R0154/1/a became active in December 2004 and will expire on the 30th November 2007.

28th October 2004:
Licence Committee met to discuss the proposed research project R0154.
The Committee noted that the peer reviewers were satisfied that this project represented a useful contribution to research. Members agreed that the project falls under the specified purposes under paragraph 3(2)a of schedule 2 to the Human Fertilisation and Embryology Act 1990: "promoting advances in the treatment of infertility"; and paragraph 2(2)a of the Human Fertilisation and Embryology (Research Purposes) Regulations 2001: "increasing knowledge about the development of embryos". The Committee noted that the Person Responsible for this research project was also listed as the Person Responsible for the Fertility Centre at Ninewells Hospital. Members recalled that it has been their custom to require that research projects have a Person Responsible who is a different person to the Person Responsible of the treatment centre, in order to eliminate any perceived conflict of interest. The Committee therefore agreed that it was minded to grant a licence but only if another Person Responsible is nominated for the project or if another Person Responsible is nominated for the centre. The Committee further agreed that they were content to leave the decision as to the suitability of any proposed Person Responsible for the project up to the Executive.

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number……0004……

Name of PR……Anne McConnell……

Date of Inspection……6th March 2007……..

Date of Response……23rd April 2007……

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

1. Organisation

Extension of funding beyond 30th June 2007 has not yet been confirmed**.**

2. **Premises and Equipment**

The practice regarding labelling of embryo culture dishes has been changed. Once embryos have been donated to research – a unique identifying number is given to each patient. Dishes will now be labelled with the study code only once the embryos have been accepted for research. An internal audit of the SOP for transfer of embryos is planned at the next available opportunity, when there are embryos suitable for transfer.

3. Donation of material

Patient information leaflets (enclosed) have been amended to mention the availability of counselling.

A standard operating procedure has been written for withdrawal of consent (enclosed).

4. Patient information and consents

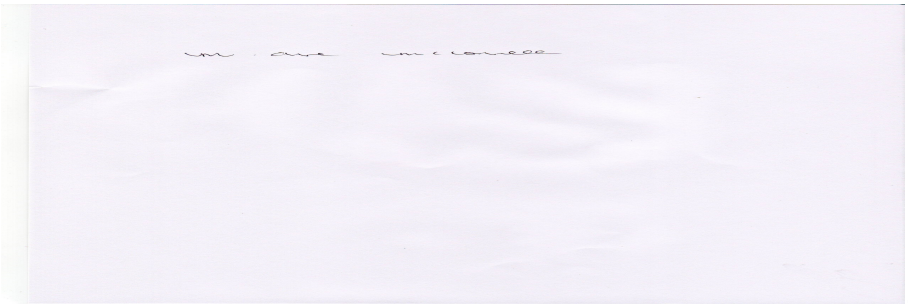
Patient information for the local consent has been amended to include details of an independent person and contact details should patients wish to withdraw consent (enclosed).

Patient information leaflets and consent forms relating to the research carried out at Roslin Cells Ltd are enclosed.

5. Scientific Practice

It is planned to carry out an audit of embryo development; this will be carried out as an ongoing process by the research embryologist, with presentation of data at the end of her current project. There are no immediate concerns regarding freezing policy based on the data to date.

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

Signed……  ……
……

Name……Anne McConnell……

Date……23.4.07……
……

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).

Section 1 – full-time equivalent staff: Principal investigator: 0.5 Laboratory scientists: 0.5 Collaborators: 2 (Professor A Burchell and Professor R Hume) Administrators/support staff: 4 full-time equivalent employed in Unit, not specifically attached to research programme)

We also welcome comments about the inspection on the inspection feedback form, a copy of which should have been handed out at the inspection. If you require a copy of the feedback form, please let us know.

Please return this section of the report to:
Dr Chris O'Toole
Head of Research Regulation, HFEA
21 Bloomsbury Street
London
WC1B 3HF

Research Licence Committee Meeting

9 May 2007
New Century House Corporation Street Manchester

MINUTES Item 1

Project R0154: Studies of embryo development and metabolism
Based at Ninewells Hospital (0004)
Licence Renewal

Members of the Committee:

Emily Jackson, Lay Member – Chair
Clare Brown, Lay Member
Richard Harries, Lay Member
Maybeth Jameson, Consultant Embryologist, Glasgow Royal Infirmary
William Ledger, Professor of Obstetrics and Gynaecology, University of Sheffield

In Attendance:

Frances Clift, Legal Adviser
Chris O'Toole, Head of Research Regulation
Claudia Lally, Committee Secretary

Observing
Sue Price, Consultant in Clinical Genetics, Oxford Regional Genetics Service

Providing Scientific Advice:
Neva Haites, Professor of Medical Genetics, University of Aberdeen

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

The following papers were considered by the Committee:

- papers for Licence Committee (25 pages)
- no papers were tabled.

1. The papers for this item were presented by Sarah Hopper, HFEA Inspector. Ms Hopper informed the Committee that the renewal inspection visit to this centre took place in March this year. The inspection report notes that progress has been made in relation to the stated aims of the research project and that the peer reviewer was satisfied with the renewal application and recommended that it should be accepted in its current form. However, a number of recommendations were made by the inspection team: to amend patient information and consent forms, to develop a protocol for when patients withdraw their consent to donate,

to offer counselling to people donating embryos, to risk assess the movement of labelled embryo culture dishes to the shared university laboratory and to audit embryo development.

2. The Committee noted that the response by the Person Responsible to the inspection report indicates that all these recommendations have now been implemented by the research team.

3. The Committee agreed that the lay summary of work submitted to the Authority falls short of the standards expected. In particular, the report should be more informative about what the study has achieved to date and additionally, should be written in properly lay-friendly terms. The Committee asked the Executive to request a new version of the lay summary for inclusion on the website. They asked the Executive to send a good example of a lay summary for another research project, to illustrate what is required.

4. The Committee applied the statutory tests in considering the application. To start, the Committee identified the activities under consideration as the use of embryos for research and the storage of embryos for use in research. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

5. The Committee agreed that in the context of the project of research these activities appear to be necessary or desirable for the following specified purposes:

- Human Fertilisation and Embryology Act 1990 Schedule 2
  3(2)(a) Promoting advances in the treatment of infertility.

- Human Fertilisation and Embryology (Research Purposes) Regulations 2001:
  2(2)(a) Increasing knowledge about the development of embryos.

6. The Committee agreed that they continued to be satisfied that the proposed research could not be undertaken without the use of human embryos.

7. The Committee agreed that they were satisfied with the patient information and consent forms submitted by the centre, now that the patient information has been amended to mention the availability of counselling and to include details of who patients can contact in order to withdraw consent to the use of materials in research.

8. The Committee were satisfied that the requirements for the grant of a licence under Section 16 of the Human Fertilisation and Embryology Act 1990 are satisfied, and decided to grant a licence for the research for a period of three years. However, the Committee noted that the centre has not yet been requested

to pay the licence fee because the current licence is not due to expire until November 2007. The Committee therefore requested that the Executive ensures that the renewed licence is not issued to the centre until the fee has been received.

Signed……. … Date……..
Emily Jackson (Chair)