Research Licence Inspection Report

Project Title	The effect of biomass reduction on embryo development after biopsy of either one or two blastomeres
Centre Name	Assisted Conception Service, Glasgow Royal Infirmary
Centre Number	0037
Research licence Number	R0175
Centre Address	ACS Suite, Glasgow Royal Infirmary 10 Alexandra Parade Glasgow G31 2ER
Treatment centres donating to this research project	0037
Inspection date	29th May 2007
Licence Committee Date	25th July 2007
Inspector(s)	Miss Sarah Hopper Dr Vicki Lamb
Fee Paid - date	Invoice due to be sent on the 1st July 2007
Person Responsible	Dr Maybeth Jamieson
Nominal Licensee	Dr Helen Lyall

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 Service at Glasgow Royal Infirmary has held an HFEA research licence since September 2006 and this licence is due to expire on the 31st August 2007.

The licence is held for a project entitled: **The effect of biomass reduction on embryo development after biopsy of either one or two blastomeres.** The lay summary of the proposed research project, submitted by the centre is as follows:

"Some couples are at risk of transmitting a genetic disorder to their children. This is because one or both of them carry a gene for that specific disorder. One option for these couples is to become pregnant and then undergo a prenatal test such as amniocentesis or chorionic villus sampling at 10-16 weeks. If the fetus is found to be affected then the couple have to decide whether they wish to continue with the pregnancy or have a termination.
Other couples suffer repeated miscarriages due to the fetus having a chromosome abnormality. In vitro fertilisation followed by Perimplantation Genetic Diagnosis (PGD) allows the diagnosis of abnormalities in embryos at an early stage, before they are replaced in the womb. This involves removing one or two cells from an embryo and performing a test on each cell. Only embryos free from the specific genetic disease are transferred to the patient.
Some tests are more reliable if more than one cell is removed and tested but there is debate about the effect this has on the embryo's development. This study aims to assess the impact of removed cell size and cell number upon subsequent development of the embryo.
Embryos which are unsuitable for treatment and, which have been donated for research, will be examined to quantify the impact of the size of the cells removed as well as the number".

The project is licensed for the following purposes:

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)

Research activities of the Centre	Research on human embryos	**X**	
	Storage of licensed material		
	Creation of embryos for research		
	Derivation of human embryonic stem cells		
	Cell nuclear replacement		

Summary for Licence Committee

The inspectorate were satisfied with the organisation of the project and with the changes made by the PR since the last inspection.

Some improvements are required:

- It was suggested that the procedure for consenting patients (including when and how information is given) should be documented in a protocol.
- Ensure that fixed material leaving the licensed premises does not hold patient identifying information.
- Ensure that patient information is subjected to version control and that only approved copies of the information are distributed to potential donors.

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

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
- Staffing
- Funding

Full time equivalent staff

Principal investigator	1
Laboratory scientists	1
Administrators	0
Collaborators	0
Support staff (receptionists, record managers, quality and risk managers etc)	The clinical team at centre 0037 are responsible for obtaining consent from patients who wish to donate embryos to the project.

Background information
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 a clear separation procedure is in place to ensure that she is not involved in clinical decisions for potential donors. This is achieved by ensuring that she is not involved in the grading of embryos when embryos are selected for transfer or freezing. This policy is outlined in the project protocol and evidence of this procedure in practice was seen in patient records belonging to patients donating embryos to the research project. Research issues are discussed at the laboratory team meetings, which are held on a weekly basis. Evidence of such discussions was found/ seen in the minutes of a recent laboratory meeting. The PR stated that information about the research project is also shared with other departments at the unit during the weekly multi-disciplinary meetings. A presentation about the research project was given to all staff on the 25th February 2007. A copy of the presentation was provided to the inspection team. The PR stated that she plans for the principal investigator to give another presentation later this year. Audits into compliance with the consenting procedures have not been carried out in the past year. The PR stated that this was because few embryos had been donated in the past year. Shortly after the project was first licensed, the principal investigator left full time employment at the centre. A new embryologist was recruited who has considerable experience in embryo biopsy. The original principal investigator initially attended the centre once a week to assist with the biopsy programme and with training of the new member of staff. This change in staffing had a slight effect on the progress of the research which did not being until December 2006.

The project will continue to be funded by Centre 0037 and the renewal application has been approved by the local research ethics committee.
Issues for consideration
None.
Executive recommendations for Licence Committee
None
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
- Safety of equipment
- Servicing and maintenance of equipment

Background information
There have been no changes in the premises or equipment used in the project since the last inspection. Embryos donated to research are biopsied using the micromanipulation equipment in the treatment laboratory. Following culture within a designated incubator in the treatment laboratory the embryos are spread onto slides which are then taken up to the university laboratory for fixation and analysis. The Research embryologist confirmed that these slides are anonymised by marking them with the patient's date of birth and a research number. This procedure is documented in the research SOP. Equipment within the laboratory is serviced regularly and a maintenance record for key pieces of equipment is kept.
Issues for consideration
Although the SOP states that slides should be anonymised when leaving the licensed premises, patient names were seen to be written on two of the slides which had been subjected to analysis in the university laboratory. The PR was informed and now plans to audit the compliance with the anonymising procedure.
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Storage facilities – embryos are not stored for research use.

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
- Ensuring patient consent is not breached
- Donor and patient records

Background information
The nursing team are responsible for providing patients with the information about the research project and for providing the associated consent form. This information is given once patients have responded to down regulation and are attending the unit for their first scan. Consent is then taken from the patients on the day of egg collection. This system ensures that patients have two weeks to consider the information before making a decision about whether to consent to the research project. The nursing research coordinator and PR both stated that due consideration had been given to the provision of information, as they did not want patients to feel overwhelmed. The nursing research coordinator and research embryologist stated that the current system is working well and that they had recently noted an increase in the number of embryos donated to the project. The research embryologist thought that patients were more receptive to participating in research, perhaps due to the clarity of the revised HFEA consent forms. In the next year the PR plans to produce a leaflet providing general information about research. This will be incorporated into the patient information packs which are provided to patients at the start of treatment. In addition, the PR is planning to design a poster explaining the research project which will be displayed in the patient waiting areas. This poster will include the HFEA lay summary about the project. Although during the last inspection, the PR stated that she planned for the nursing team to receive training on providing information about the research project; this has not yet taken place. The PR was reminded to consider including information about the research project and the procedure for consenting patients in the induction programme for future new members of staff.
Issues for consideration
It was suggested that the procedure for consenting patients (including when and how information is given) should be documented in a protocol.
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Prevention of coercion of prospective donors

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
Patient information has been revised since the last inspection in response to requests by the previous Licence Committee. The sentence which refers to translocations has not been altered as recommended by the Licence Committee as the PR felt that this would result in complicating the patient information. A local research ethics committee have approved the information in its current format. The PR has amended the patient information sheet to include contact details for an independent person that patients could call if they wish to discuss the project with a person not directly involved with the work.
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.
Issues for consideration
The information for patients had recently been revised but an older version of the information sheet still appeared to be in circulation. The PR had already noted that different versions were in use and has taken steps to ensure that the information is version controlled: previous copies of the information have been deleted from the shared folder and replaced by the single, approved document. The project involves photographing embryos on day one of their development, an additional step which is not currently taken during all treatment cycles. This involves removing the embryos from the incubators on an additional occasion. This is not mentioned in the patient information and it was recommended that this process should be clarified for patients. The PR has since amended the paperwork to inform patients that photographs will be taken of their embryos at the time of the fertilisation check. The revised paperwork will be attached to this report for approval by a Licence Committee.
Executive recommendations for Licence Committee
Consider the revised patient information.
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
- Minimisation of material loss and wastage
- Ability to achieve set aims and objectives

Summary
Although the centre has been licensed to conduct research since September 2006, work did not begin until December 2006 due to a change in staff involved in project. A protocol for witnessing the movement of embryos to the research project has recently been created and was supplied to the inspection team. This includes the need to check consent for research in all consent forms. The protocol was considered to be satisfactory although a reference to the protocol for disposal of embryos was recommended. The PR informed the inspectorate that they plan to document witnessing practices and that the laboratory sheets will be amended to include a box for these signatures.
Embryo usage
During the period 01/09/2006 to 16/04/2007 33 fresh embryos were received by the research team and 17 of these were used in the project. In the initial application, the PR had expected to use 100 embryos each year. At the time of application, a total of 33 embryos had been donated to the project. Seventeen met the inclusion criteria on day three of development and were randomised into the study. These embryos were fixed on day six and eight have been stained to confirm the efficacy of the nuclear staining protocol. The PR stated that the first set of analysis will be carried out when 50 embryos have been randomised. Since the inspection, the PR has provided further information on how many embryos were used within the study (see Licence Committee papers). By the 30th May 2007 93 embryos had been photographed at the time of fertilisation check. 32 were considered unsuitable for transfer or freezing on day 2 and continued in culture. Of the 32 embryos which continued in culture, 25 met criteria for inclusion in the study and were incorporated into the project. The PR anticipates that 150 fresh embryos will be used in the project in the next 12 months. Although frozen embryos are not currently used in this project, the PR stated that she may consider this in the future.
Lay summary of research undertaken
This study is designed to investigate the effects on subsequent development of removing either one or two cells from an embryo. This is the technique used to perform preimplantation genetic diagnosis for couples at risk of passing on a genetic disorder to their children. The study commenced in December 2006 and a total of 33 embryos have been donated by couples undergoing IVF or ICSI treatment. These embryos were not suitable for the patients'

treatment or for cryopreservation. The embryos were cultured for 24 hours after the time of embryo transfer and 17 were at a suitable stage to be included in the study. These then had either one or two cells removed in the same way that biopsy is carried out for preimplantation genetic diagnosis (a control group had no cells removed). The embryos continued in culture for a further 3 days when they were observed and fixed for analysis. No embryos remained in culture for longer than six days from the time they were fertilised. It is still too early to analyse the results of the project but it has been shown that the fixation and cell staining methods are working adequately.
Peer reviewer comments
The Peer reviewer stated that the project needs a full 12 months before evaluation and recommended a review at that time. In conclusion, the reviewer stated that the application should be accepted in its current form.
Spot check of stored donated material
Not applicable as embryos are not stored for research
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Quality assurance systems

Report compiled by:

Name……Sarah Hopper …….

Designation…Inspector… …….

Date……29/05/07……

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

Licence	Status	Type	Active From	Expiry Date
L0037/11/d	Active	Treatment with Storage	01/10/2006	31/12/2008
R0175/1/a	Active	Research Project	01/09/2006	31/08/2007

R0175

The research licence was granted on the 1st September 2006. No additional conditions or recommendations were placed on this licence.

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number……037

Name of PR……..Maybeth Jamieson

Date of Inspection……29th May 2007

Date of Response……19th June 2007

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

A section on obtaining consent for research projects has been added to the SOP for obtaining consent.

The witnessing SOP has been amended to include reference to the SOP for disposal of embryos

The study SOP has been changed to include a check on all slides leaving the laboratory to ensure that they are not marked with any identifying information. An audit has been scheduled.

All documentation for the project is included in the revised document control process with a single version of each document available on the Unit intranet.

An electronic copy of the revised consent form is attached.

As you noticed, there is a typo in the lay summary of research undertaken (bottom of page 9). The last sentence in para 1 ('performing a test on each cell') should be deleted.

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

Signed

Name Maybeth Jamieson

Date 19/6/2007

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 9 of 13. Summary – 3rd paragraph: all stages are already witnessed; it is only the laboratory sheets which require redesign to include specific boxes for research witnessing.

The front sheet has the inspection date as the 28th – it was the 29th.

Additional information requested in the report:
Page 4 of 13 (Staff) There are no administrators or collaborators involved in the study
Page 9 of 13 (Embryo usage) A flow chart showing how embryos were used is attached

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

25 July 2007
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 4

Research Project R0175: The effect of biomass reduction on embryo development after biopsy of either one or two blastomeres.
Based at Glasgow Royal Infirmary (0037)
Licence Renewal

Members:

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

In Attendance:

Marion Witton – Head of Inspection
Frances Clift, Legal Adviser
Joanne McAlpine, Acting Committee Secretary
Barbara Lewis, Observer

Conflicts of Interest: Maybeth Jamieson declared a conflict of interest in relation to this item and withdrew from the meeting.

The following papers were considered by the Committee:

- papers for Licence Committee (45 pages)
- no papers were tabled.

1. The papers for this item were presented by Ms Sarah Hopper. Ms Hopper informed the committee that the original research licence was granted in September 2006 and the renewal inspection visit took place on 29 May 2007.

2. Ms Hopper confirmed that the recommendations made by the inspection team have been actioned by the PR and the peer reviewer has agreed that the research licence should continue in its current form.

3. The Committee applied the statutory tests in considering the application. To start, the Committee identified the activity under consideration as the use of

donated embryos in research. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

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

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology Act 1990 Schedule s(2)(a)

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

6. 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 include contact details for an independent person that patients could call if they wish to discuss the project with a person not directly involved with the work.

7. The Committee were satisfied that the requirements for granting a licence under section 16 of the Human Fertilisation and Embryology Act 1990 were fulfilled and decided to renew the licence for research for a period of three years.

Signed…… … Date……..
Richard Harries (Chair)