Research Licence Initial Inspection Report

Project Title	Genetic analysis of human preimplantation embryos
Centre Name	Edinburgh Fertility and Reproductive Endocrine Centre,
Centre Number	0201
Research Licence Number(s)	R0181
Centre Address	Edinburgh Royal Infirmary Old Dalkeith Road Edinburgh EH16 4SA
Donating treatment centre numbers	0201
Inspection date	27 June 2007
Licence Committee Date	25 July 2007
Inspector(s)	Dr Chris O'Toole Dr Debra Bloor
Fee Paid – date (if applicable)	
Person(s) Responsible	Dr Susan Pickering
Nominal Licensee	Dr K Joo Thong
Licence expiry date	Initial Licence Application

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 relates to an application for an initial research licence.

Brief Description of the Project

Lay summary of research project

Preimplantation Genetic Diagnosis (PGD) is a technique used to test early human embryos for the presence of a specific genetic disease before implantation into the womb and is useful for couples who have a family history of genetic disease. To carry out PGD, sophisticated genetic analysis of single cells is required and such tests have not always been reliable or consistent and have also proved extremely costly to develop. A new technique has recently been discovered which greatly enhances the amount of genetic information which can be generated from a single cell and use of this technique may simplify the PGD procedure significantly. The aims of this project are to apply this new technology to single cells and then to expand substantially the downstream genetic analysis using high-density genotyping. We will then test the reliability and accuracy of such methods on single embryonic cells and assess whether such technology can be used to develop a basic test for aneuploidy as well as the specific risk analysis for each embryo.

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

Summary for Licence Committee

This is an initial application for a research licence.

The title of the proposed project is: Genetic analysis of human preimplantation embryos

The centre has proposed that the project be licensed for the following purposes:
3(2)(e) developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.
and the Human Fertilisation and Embryology Regulations 2001;
s2(a) Increasing knowledge about the development of embryos.

One peer reviewer agrees that the proposed research would be necessary or desirable for the above two purposes. The second reviewer said that the proposed research was necessary or desirable for only one of the above purposes namely:
3(2)(e) developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

The research project has the approval of the local research ethics committee.

The centre has requested a two year licence

This centre has not previously held a research licence. The proposed Person Responsible has been involved in licensed research for several years at other licensed centres. Dr Pickering is in the process of completing the Person Responsible Entry Programme.

The Executive recommends that a research licence be granted for one year.

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	Susan Pickering
Scientists	4
Laboratory technicians	
Support staff (receptionists, record managers, quality and risk managers etc)	Staff from centre 0201

Summary
Dr Susan Pickering, the proposed Person Responsible (PR), is an experienced embryologist and has extensive knowledge of preimplantation genetic diagnosis. Dr Thong, the proposed Nominal Licensee, is a consultant subspecialist in reproductive medicine/consultant obstetrician and gynaecologist and has held the post of PR at centre 0201 since 1998. The management and co-ordination of resources is shown on the organisational chart from the quality manual. The quality management system is certificated to ISO 9001:2000. The centre holds weekly multi-disciplinary team meetings. All members of staff are expected to attend. The weekly meetings cover patient treatments, discussion of difficult cases, HFEA communications, incidents, complaints, training, quality and governance issues. Research issues will also be discussed at these meetings. The proposed PR will carry out the embryo biopsy aspect of the project. The isolated blastomeres will then be passed to clinical scientists within the hospital's Department of Medical Genetics for genetic testing. The clinical scientists are all HPC registered. The centre has the necessary funding for this project.

Issues for consideration
None.
Executive recommendations for Licence Committee
None.
Areas not covered in this inspection
None

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

Summary
The licensed research will take place within the licensed Edinburgh Fertility and Reproductive Endrocrinology Centre. These facilities are secure and embryos used in the research project will only be accessible to persons named on the HFEA licence.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

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 (**Not applicable – new research application)**

Summary
Donors will be recruited from the Assisted Conception Unit in the Edinburgh Fertility and Reproductive Endocrine Centre. The centre is proposing to use both fresh and frozen embryos in this study. The fresh embryos will be those that have abnormally fertilised or are classified as being poor quality at the end of patients' treatment cycles. Patients undergoing routine assisted reproductive treatment attend the centre for an initial consultation with a doctor. Patients will be given the general research information sheet during this initial consultation. Patients then have a further meeting with a nurse to discuss their treatment in detail. The nurse will also discuss the research projects carried out at the centre and ask whether the patient would consider donating embryos to research. If the couple say yes to the research project they will be given the information sheet and consent form. The consent forms will be completed when the patient returns to the centre for their pre-treatment scan. The completed consents will then be checked and placed in the patient's medical notes. The patients will then have treatment as normal. Following fertilisation and, if applicable, after embryo transfer, couples with abnormally fertilised or poor quality surplus embryos will be identified. Two embryologists will check the patient's notes to determine whether these couples have consented for these surplus embryos to be used in research. If yes, the embryologists will check that the HFEA and specific research consents are present. The handover of embryos to the research scientist will be witnessed and the embryologist will then complete the laboratory record sheet. Patients with embryos in storage are sent a letter, outlining the options available within one year of the date of the storage period expiry. If a couple state that they wish to donate their embryos to research they will be asked to attend the clinic to discuss the research project. If, after this discussion, they still wish to donate embryos to research then the couple will be given the detailed information sheet and consent forms. Couples will be given the opportunity to take these forms home to read and discuss. The couple will then complete the consent forms. These will be checked by two embryologists. The removal of the embryos from the storage dewars will be witnessed as will the handover of embryos to the research scientist will be witnessed and the embryologist will then complete the laboratory record sheet.

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)*

- Patient information
- Consent forms
- Patient information for projects deriving embryonic stem cells **(Not applicable)**
- Consent forms for projects deriving embryonic stem cells **(Not applicable)**

Outcome of audit of records
Not applicable as this inspection was in relation to an application for an initial research licence.
Summary
In general the patient information and consent forms contain all the relevant information. At the request of the local research ethics committee information for patients contains the following statement: *"if requested, results of this research can be provided for your information."* The inclusion of this statement and its meaning was discussed in depth during the course of the inspection. The proposed PR clarified that the only information that would be fedback to patients would be general information relating to the outcome of the research project. Patients would not be given specific information regarding the analysis of their embryos.
Issues for consideration
In order to avoid misinterpretation of the above statement by patients the centre is advised to consider including in the verbal discussions with patients an explanation that they may receive general information about the project but they will not receive specific information about the outcome of any genetic tests carried out on their embryos.
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

Use of material
The centre expects to use up to 75 fresh, poor quality or abnormally fertilised embryos and 25 frozen-thawed embryos per year.
Project objectives
The centre's objectives for research are: 1. To assess the reliability of SNP haplotypes at any genetic location and compare the results obtained with those from more conventional genetic assays. 2. To design locus specific SNP haplotyping assays for a key disease gene, cystic fibrosis transmembrane conductance regulator (CFTR)
Lay summary of proposed research
Preimplantation Genetic Diagnosis (PGD) is a technique used to test early human embryos for the presence of a specific genetic disease before implantation into the womb and is useful for couples who have a family history of genetic disease. To carry out PGD, sophisticated genetic analysis of single cells is required and such tests have not always been reliable or consistent and have also proved extremely costly to develop. A new technique has recently been discovered which greatly enhances the amount of genetic information which can be generated from a single cell and use of this technique may simplify the PGD procedure significantly. The aims of this project are to apply this new technology to single cells and then to expand substantially the downstream genetic analysis using high-density genotyping. We will then test the reliability and accuracy of such methods on single embryonic cells and assess whether such technology can be used to develop a basic test for aneuploidy as well as the specific risk analysis for each embryo.
Peer reviewers comments
The Peer reviewers have recommended that the project be accepted in its present form.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

Report compiled by:

Name……Dr Chris O'Toole…….

Designation……Head of Research Regulation…….

Date……12 July 2007…….

Appendix A: Centre Staff interviewed

Dr Susan Pickering
Dr Thong
3 clinical scientists
1 embryologist

Appendix B: Licence history for previous 3 years

Not applicable – initial application

Appendix C:
RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number……

Name of PR…….

Date of Inspection……..

Date of Response……

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

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

Name…….

Date……

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).

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 1

Research Project R0181: Genetic analysis of human preimplantation embryos
Based at Edinburgh Fertility and Reproductive Endocrine Centre (0201)
Initial Research Licence Application

Members:	In Attendance:
Richard Harries – Chair, Lay Member	Marion Witton – Head of Inspection
Clare Brown, Lay Member	Frances Clift, Legal Adviser
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary	Joanne McAlpine, Acting Committee Secretary
William Ledger – Professor of Obstetrics and Gynaecology, University of Sheffield	Barbara Lewis, Observer
Rebekah Dundas – Lay Member	

Conflicts of Interest: Maybeth Jamieson declared a conflict of interest with this item and therefore contributed to the discussion but did not take part in any decision making.

The following papers were considered by the Committee:

- papers for Licence Committee (94 pages)
- no papers were tabled.

1. The papers for this item were presented by Debra Bloor, HFEA Inspector. Dr Bloor informed the Committee that this is an initial application for a licence to carry out research into the application of a novel technique for use in preimplantation genetic diagnosis.

2. Dr Bloor informed the Committee that the PR for the research project, Dr Sue Pickering, has considerable research experience.

3. Dr Bloor confirmed that at the time of the inspection the PR Entry Programme had not been completed but it has since been received and assessed as satisfactory.

4. Dr Bloor explained that the application had been considered by two peer reviewers. One peer reviewer agreed that the research would be useful for developing methods for detecting abnormalities in embryos before implantation and increasing knowledge about the development of embryos. The second peer reviewer thought that the small number of embryos studied would not significantly add to the knowledge of embryos but supported the claim that the research would be useful for developing methods for detecting early abnormalities in embryos.

5. Dr Bloor informed the Committee that the research had been approved by the local research ethics committee. During the inspection visit the premises, equipment and laboratory were found to be suitable.

6. Dr Bloor stated that the patient information regarding the research project was comprehensive and accessible but there was a statement included in the patient information which lacked clarity. This statement was discussed at length in the course of the inspection and subsequent to the review of the draft inspection report the PR reported that the statement has now been amended.

7. In response to a question raised by the Committee regarding the number of embryos identified for use in this project, Dr Bloor explained that the figure of 100 embryos was based on what was practically available and not what was required for this study. Dr Bloor confirmed that the centre has acknowledged that the number of embryos needed cannot be predicted at this stage because it is using a novel technique.

8. The Committee questioned whether embryo biopsy was part of the project and who the researcher would be. Dr Bloor confirmed that the PR would undertake all the biopsy work.

The Committee discussed a few suggestions that they felt would be useful to the project, and asked Ms Hopper to communicate the advised suggestions directly with the PR of the project.

- the centre puts documented procedures in place to demonstrate that the selection of embryos for treatment/freezing will not been influenced by research
- the results of the research are monitored and the research study stops if the objectives of the research are achieved prior to the use of 100 embryos, and that HFEA should be informed when the research is concluded successfully

9. The Committee applied the statutory tests in considering the application. To start, the Committee identified the activity under consideration as the use of embryos in research. The Committee noted that this activity is not prohibited under the Human Fertilisation and Embryology Act 1990.

10. The Committee agreed that this activity appears to be necessary or desirable for the following specified purpose:

- developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation
  Human Fertilisation and Embryology Act 1990 Schedule 3(2)(e)

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology Act 1990 Schedule s2(a)

11. The Committee agreed that they were satisfied that the proposed research could not be undertaken without the use of human embryos.

12. The Committee agreed that they were satisfied with the patient information and consent forms submitted by the centre subject to some minor amendments to the consents form. The Committee advised that to avoid misinterpretation of the following statement: "If requested, results of this research can be provided for your information." The Centre should consider including in the verbal discussions with patients an explanation that they may receive general information about the project but they will not receive specific information about the outcome of any genetic tests carried out on their embryos.

13. 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 grant a licence for the research for a period of twelve months.

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