New Research Licence Inspection Report

Project title	The vitrification of blastocysts following biopsy at the early-cleavage stage or blastocyst stage of embryo development – A Pilot Study
Proposed research licence number	R0187
Centre name	IVF Hammersmith
Proposed centre number	0078
Centre address	IVF Hammersmith, Hammersmith Hospital, Du Cane Road, London, W12 0HS
Proposed donating treatment centre numbers	0078
Inspection date	4 August 2008
Licence Committee date	3 September 2008
Inspector(s)	Sarah Hopper Chris O'Toole
Fee paid - date	Yes
Proposed person Responsible	Mr Geoffrey Trew
Proposed nominal licensee	Mr Stuart Lavery

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About the Inspection:

The purpose of the inspection is to ensure that research is carried out in compliance with the HF&E Act 1990, seventh 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 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.

Lay summary of the project

This study aims to combine, for the first time, the techniques of blastocyst culture, biopsy and vitrification in an attempt to indentify the most efficient method of freezing embryos for those patients who may need pre–implantation genetic diagnosis (PGD) of their embryos in oder to avoid the transmission of genetic disease to their resultant children.

Embryo biopsy can be performed at different stages of embryo development. They have been traditionally performed at cleavage–stage, when the embryo is three days old, but they can also be performed at blastocyt–stage, when the embryo is five to six days old. There is increasing evidence to suggest that embryo biopsy at blastocyst–stage of development may be advantageous, as it causes potentially less damage to the embryos. After embryo biopsy and subsequent embryo transfer, remaining good quality can be frozen for a patients' future treatment.

Vitrification (ultra–rapid freezing) has been shown to offer increased freeze/thaw survival rates over the more conventional "slow" freezing protocols currently in use for blastocysts. This study may help to answer the question of whether vitrification is a better method of freezing biopsied embryos and also at which stage it is better to biopsy the embryos to achieve the highest freeze/ thaw survival rates.Information gained from such a study may inform clinicians and patients on the most effective and efficient way of storing embryos

Proposed research activities	Storage of licensed material	✓
	Creation of embryos* in vitro	
	Use of donated embryos for research	✓

Summary for Licence Committee

This is an initial application for a research licence.

The centre applying for the licence, IVF Hammersmith, has been established since 1988 and has held a number of research licences previously.

The aims of proposed research project are to determine the most efficient method of freezing embryos following embryo biopsy.

The centre is proposing that the research is necessary or desirable for the following purposes:

- promoting advances in the treatment of infertility
  Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)

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

At the time of writing this report the proposed Person Responsible (PR) has not submitted the PR entry programme.

The PR has requested that a licence be granted for one year.

The research proposal has been commented on by two reviewers. Both reviewers agree that the research would be necessary or desirable for the following purposes:

- promoting advances in the treatment of infertility
  Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)

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

One reviewer has recommended that the project be accepted but , at the time of writing this report, the second reviewer still had concerns about the proposed research.

It is recommended that that the application be considered subject to the following:

- A procedure for reporting serious adverse events to the HFEA should be developed to ensure compliance with General Licence Condition A.4.1 and Code of Practice (7th edition) Standards S.9.4.1 and S.9.4.2.

Report of Inspection findings

1. Organisation

Desired Outcome: The research 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
- Research governance
- Funding

Full time equivalent staff

Principal investigator	Dr Paul Knaggs
Scientists	9 members of the embryology team
Laboratory technicians	
Support staff (receptionists, record managers, quality and risk managers etc)	

Highlighted areas of firm compliance
The Person Responsible is an experienced clinician in reproductive medicine. The PR is not the PR of the Treatment and Storage Licence at Centre 0078. The principle investigator is a senior embryologist within IVF Hammersmith with many years of research experience. All embryologists within IVF Hammersmith will be involved in licensed research activities. All staff, who will be involved in the research project, are employed by the Imperial College Healthcare NHS Trust. The project will be funded through IVF Hammersmith. The principle investigator has held meetings with the laboratory and nursing staff to discuss the proposed research. The unit plans to hold regular research meetings and research will be discussed at the unit meetings. These meetings are minuted and available to all staff.
Issues for consideration
The proposed PR has not yet submitted the PR Entry Programme. A procedure for reporting serious adverse events to the HFEA should be developed to ensure compliance with General Licence Condition A.4.1 and Code of Practice (7th edition) Standards S.9.4.1 and S.9.4.2.

Executive recommendations for Licence Committee
It is recommended that compliance with the recommendations listed above be monitored in the course of future inspections.
Areas not covered in this inspection
All covered.

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

Highlighted areas of firm compliance
The research will be carried out within the laboratories at IVF Hammersmith. Access to the laboratories is restricted to persons named on the centre's licence. The laboratories were appropriately equipped and deemed suitable for the proposed research activities.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
Servicing and maintenance of equipment – these issues were covered at the last inspection of the centre's treatment and storage licence.

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
Both self-funding and NHS funded patients attending IVF Hammersmith will be given the opportunity to donate supernumerary embryos to this research programme. Supernumerary embryos are those which are not transferred (i.e. those remaining after an embryo transfer). Consent to donate embryos to the research project will be sought before patients begin their treatment, at the time of their pre-treatment appointment, and patients will receive full information about the project prior to this so they can give informed consent. On the day of embryo transfer, patients will be informed of the quality of their embryos and asked whether they wish to freeze embryos for future clinical use. Patients declining embryo cryopreservation for future clinical use may wish to donate these embryos to the research project. The PR has explained that patients may wish not to freeze embryos for future clinical use for a variety of reasons such as: • The embryos may not be considered of suitable quality (see below) by the embryology team to survive the freezing/ thawing process intact and have a reasonable chance of establishing an ongoing pregnancy. It should be noted that embryo cryopreservation and further frozen-thawed embryo transfer cycles are unlikely to be funded by the NHS and patients may take this into account when deciding whether to freeze embryos. • They may not be able to afford the cost of freezing embryos • They may have moral/ ethical or religious reasons for not wanting to freeze embryos. Embryo grading will be performed without the embryologist having access to the patient consent forms. These will be removed from the patient laboratory records at oocyte recovery (OR) and placed in a separate file in the OR laboratory. The patient's wishes with regard to embryo cryopreservation are to be noted on the patients' lab sheets which will remain with the oocytes/ embryos in the ET/ ICSI laboratories. This separation will ensure that the embryologist grading the embryos is not influenced in their grading decisions by knowing whether the patient has given consent to participate in research.

Additionally the embryologist grading embryos on the morning of embryo transfer will not talk to the patients regarding freezing/ research prior to embryo transfer. The embryologist speaking to patients prior to embryo transfer will recombine the consent forms with the patients' laboratory records and explain the grades of the embryos to the patient in an independent manner explaining which embryos may be suitable for grading based on the objective grading of another embryologist.

The policy at IVF Hammersmith has been to recommend to patients that they freeze good and very good quality embryos for their future clinical use. This policy gives a 75% chance of an embryo surviving the thawing process with ≥50% cell survival with a subsequent transfer of 2 such embryos giving a clinical pregnancy rate of 30% at the time of writing. It is important to note that it is entirely the patients decision whether or not to freeze embryos and some patients may wish to freeze poor or very poor quality embryos for future use even if such embryos have a much reduced (but undefined) chance of survival and subsequent pregnancy.

Patients who do not freeze embryos and do not wish to participate in the research study will not prejudice their current or future treatment in any way.

Supernumerary embryos that have been donated to research will be considered to have entered the study if they remain in the culture system after the patient has undergone embryo transfer and left the unit. A patient is free to withdraw their consent at anytime up to the time of their departure from the unit after embryo transfer.

Additionally, embryos which have been donated to the research project will be photographed to enable verification of their grading at a later date should the need arise

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

Highlighted areas of firm compliance
The patient information and consent forms contain all the necessary information and were considered to be satisfactory.
Issues for consideration
None
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
PR estimates that 150 fresh embryos will be used within the year. This will be supplied by IVF Hammersmith (0078). Embryos will be subjected to biopsy (no genetic analysis or other manipulation will be performed on removed cells) followed by vitrification. The vitrified embryos will then be thawed to assess survival rates.
Project objectives (lay summary provided by PR)
This study aims to combine, for the first time, the techniques of blastocyst culture, biopsy and vitrification in an attempt to identify the most efficient method of freezing embryos for those patients who may need preimplantation genetic diagnosis (PGD) of their embryos in order to avoid the transmission of genetic disease to their resultant children. Embryo biopsy can be performed at different stages of embryo development. They have been traditionally performed at cleavage–stage, when the embryo is three days old, but they can also be performed at blastocyt–stage, when the embryo is five to six days old. There is increasing evidence to suggest that embryo biopsy at blastocyst–stage of development may be advantageous, as it causes less potential damage to the embryos. After embryo biopsy and subsequent embryo transfer, remaining good quality can be frozen for a patients' future treatment. Vitrification (ultra–rapid freezing) has been shown to offer increased freeze/thaw survival rates over the more conventional "slow" freezing protocols currently in use for blastocysts. This study may help to answer the question of whether vitrification is a better method of freezing biopsied embryos and also at which stage it is better to biopsy the embryos to achieve the highest freeze/ thaw survival rates. Information gained from such a study may inform clinicians and patients on the most effective and efficient way of storing embryos The embryos used in the research project will be placed in a dedicated incubator for culture to the blastocyst stage. Labels placed on the lids of the incubator, identifying the contents will include a “discard by” date (usually up to day 8 of embryo development) to ensure embryos are kept no longer than 14 days.
Peer reviewers comments
The application has been reviewed by two peer reviewers. The first reviewer agreed that the research is necessary or desirable for the following

purposes:

- promoting advances in the treatment of infertility
  Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)

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

The reviewer stated that the research was important because "*if successful, this approach would be extremely useful in preimplantation genetic diagnosis and may improve the cumulative pregnancy rates in such cycles significantly."*

The reviewer also stated that the use of human embryos was justified because the technique of freezing using vitrification "*has not been applied before in biopsied human embryos*."

The first reviewer recommended that the application be accepted in its current form.

The second reviewer also agreed that the research is necessary or desirable for the following purposes:

- promoting advances in the treatment of infertility
  Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)

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

The reviewer stated that the research was important because even though *"There are sound theoretical reasons and some initial evidence for biopsy for PGD to be carried out at the blastocyst stage. It is essential that the advantage of blastocyst biopsy be confirmed. Furthermore the ability to store supernumerary blastocysts after diagnosis will be vital to increase efficiency and to support the transfer of only one embryo at a time."*

The reviewer also stated that the use of human embryos was justified because "*Animal studies would add nothing relevant. Biopsy at cleavage stages, biopsy at blastocyst stage, blastocyst culture and blastocyst cryopreservation are all in use clinically. The questions to be answered relate to clinical applicability and therefore must be carried out on human embryos."*

The second reviewer did raise a number of issues in relation to the proposed methodology. These were raised with the principle investigator and the responses sent back to the reviewer. At the time of writing this report the reviewer still had some issues with the proposed research. An update will be presented to the Committee.

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

Report compiled by:

Name…Chris O'Toole and Sarah Hopper …….

Designation……Inspector…….

Date……14 August 2008……

Appendix A: Centre staff interviewed

Principle investigator

Appendix C

RESPONSE OF PERSON RESPONSIBLE TO THE SITE VISIT

Centre
Number…0078……..…

Name of PR Mr Geoffrey Trew

Date of Inspection…4 August 2008……..…....

Date of Response……30 August 2008……..….....

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

A further protocol “Dealing with Adverse incidents” has been compiled which further strengthens an existing protocol for dealing with non-conformities arising in the ISO 9001 quality system

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

Signed…Paul Knaggs……..…

Name…Dr Paul Knaggs
Date…28/08/08

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 Debra Bloor
Head of Inspection, HFEA
21 Bloomsbury Street
London
WC1B 3HF

Research Licence Committee Meeting

16 September 2008
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 1

Research Project RO187: The vitrification of blastocysts following biopsy at the early-cleavage stage or blastocyst stage of embryo development – a pilot study
based at Hammersmith IVF (0078)
Initial application

Members of the Committee:	In Attendance:
Emily Jackson, Lay Member – Chair	Chris O'Toole, Head of Research Regulation
Richard Harries, Lay Member	Claudia Lally, Committee Secretary
Clare Brown, Lay Member	
Neva Haites, Professor of Medical Genetics, University of Aberdeen	Providing Legal Advice to the Committee: Sarah Ellson, FFW Solicitors

Declarations 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 (108 pages)
- no papers were tabled.

1. The papers for this item were presented by Sarah Hopper, HFEA Inspector and Dr O'Toole, Head of Research Regulation. Ms Hopper described the aim of the project, which is to identify the most efficient method of 'freezing' embryos for those patients whose embryos require preimplantation genetic diagnosis. The study will try to learn whether vitrification is a better method of 'freezing' biopsied embryos than conventional freezing methods and also to learn at which stage it is better to biopsy the embryos to achieve the highest 'freeze/thaw' survival rates.

2. Ms Hopper summarised the findings of the initial inspection visit, which took place on 4 August 2008. She informed the Committee that IVF Hammersmith was established in 1988 and has previously held a number of research licences. Ms Hopper described the significant area for consideration arising from the

inspection, which was that the proposed Person Responsible had not yet completed a Person Responsible Entry Programme (PREP) assessment.

3. Dr O'Toole discussed the peer reviews of the project. She informed the Committee that the first peer reviewer had recommended that the project be licensed in its current form but had some questions about the licensable activities being requested. The second peer reviewer had responded twice in writing regarding the application and had telephoned Dr O'Toole on Friday 12 September and informed her about a number of reservations about the project. In particular, the peer reviewer had questioned the originality of the project and stated that only one aspect of the research was of possible value: that of researching whether biopsied blastocysts will survive vitrification. The peer review had suggested that the more appropriate way of addressing this question was by means of a multi-centre controlled trial. The peer reviewer had also questioned the tone of the patient information and its description of the process of vitrification.

The Committee's Decision

4. The Committee considered the comments of the second peer reviewer about the originality of the project. The Committee concluded that its originality lay in its aim to consider whether, following PGD, blastocysts remain stable following vitrification, a question to which the answer is unknown and for which some evidence is still required. The Committee noted that the value of this aspect of the proposed project was accepted by the second peer reviewer.

5. The Committee further agreed that the proposed methodology seemed appropriate, in that the survival rate of blastocysts will be compared to embryos in an early stage of development, as a control. The Committee also agreed that those aspects of the research which repeat former licensed research would also be valuable, since they will explore whether the findings of that former research will hold under a variety of different controlled conditions. The Committee also noted that the theme of the research is particularly relevant at the present time, where increasing numbers of IVF patients are being offered blastocyst transfer.

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

7. The Committee agreed that the activities appear to be necessary or desirable for the following specified purposes:

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

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

In making this decision, the Committee took account of the fact that it is desirable that research is undertaken to investigate whether biopsied embryos will survive the vitrification process.

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

9. The Committee considered the patient information and consent forms to be used for the project and agreed that a number of improvements were required to the patient information. In particular, the Committee called for improvements to the tone of the information, improved grammatical accuracy and correct terminology for the description of the vitrification process. The Committee asked that the Executive work with the centre to ensure that these improvements are made.

10. The Committee considered the suitability of the proposed Person Responsible and on the basis of his curriculum vitae noted that Mr Trew appeared to fulfil the requirements set out in the Human Fertilisation and Embryology Act 1990. However, the Committee noted that Mr Trew had failed to complete the Person Responsible Entry Programme (PREP) assessment, and therefore agreed that the following condition would be applied to the licence:

    - The Person Responsible must satisfactorily complete and submit the Person Responsible Entry Programme (PREP) assessment before the commencement of any licensed research work.

11. The Committee agreed that the statutory tests for the granting of a licence were satisfied and decided to grant a licence for the project, subject to the above condition. Since this was a novel project of research this licence was for 12 months.

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