



Research Licence Interim Inspection Report

Project Title	Indicators of oocyte and embryo development
Centre Name	Centre for Reproductive Medicine
Centre Number	0013
Research licence Number	R0155/2/a
Centre Address	University Hospitals Coventry and Warwickshire NHS Trust Clifford Bridge Road Coventry CV2 2DX
Treatment centres donating to this research project	0013
Inspection date	15 th November 2007
Licence Committee Date	9 th January 2008
Inspector(s)	Miss Sarah Hopper Dr Vicki Lamb
Fee Paid - date	N/A interim inspection
Person Responsible	Dr Geraldine Hartshorne
Nominal Licensee	Dr Sue Montgomery
Licence expiry date	31 October 2008

About the Inspection:

The purpose of the inspection is to ensure that research is conducted 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.

This report covers the period between November 2006 and November 2007.

Brief Description of the Project

The Centre for Reproductive Medicine was granted a research licence, R0155, to investigate "Indicators for oocyte and embryo development" on the 18 October 2004. The licence was last renewed in November 2005 and is due to expire on the 31 October 2008.

The licensed purposes of the project, as laid down in Schedule 2 of the Human Fertilisation and Embryology Act 1990, are to promote advances in the treatment of infertility; increasing the knowledge of miscarriages; developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation and increasing knowledge about the development of embryos.

The lay summary of the project reads as follows:

"The purpose of this investigation is to identify and characterize particular markers of egg and embryo development with a view to improving our ability to identify embryos which are developing normally or abnormally. Certain features of embryos will be studied at different stages of development, firstly to provide baseline information on key developmental aspects of eggs and embryos and secondly to allow us to test the effects of particular techniques or conditions in vitro upon the markers selected. We will look at various markers, including some which are purely observational and others which will assess the chromosomal structure and the genetic control of the eggs and embryos using invasive experimental techniques. The eggs and embryos to be tested will have been produced in different ways, for example, for some; the final stages of maturity will have been gained under laboratory conditions, whereas in others this stage will have occurred in the body. Some embryos will have had micromanipulation to remove damaged areas, whereas others will not. The effects of such handling upon the selected markers will be studied. Only eggs and embryos that are no longer required by the patients or are of no use in their treatment and would otherwise be discarded will be used in this project."

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

Changes/ improvements since last inspection

<p>There have been no changes to the premises since the last inspection. Some changes have been made to the equipment used in the project; a new incubator and time-lapse microscope are now in place.</p> <p>Some staff changes have occurred since the last inspection: one researcher has left the team due to the conclusion of her contract and another researcher is currently on maternity leave and is due to return in April 2008. Following this inspection an additional researcher has joined the team.</p>

Recommendation from last inspection	Action taken
Meetings between researchers and clinical staff should be formalised. It is important that all members of the team who may have contact with patients considering donating embryos to research are able to explain the current areas of research.	No action taken. The PR reported that minutes are not taken at these meetings but that if there are any important points these are emailed to relevant persons.
The PR was asked to evaluate the security of records and material (including reagents) within the research laboratory and take measures to ensure the confidentiality of records at all times	The window within the research laboratory door has been covered to render it opaque and a no-access sign in place. Patient records and donated embryos were seen to be stored securely on the day of the inspection.
The PR should assess the risk to her staff of not having a low oxygen alarm in the embryology laboratory.	Although the PR reported that an informal risk assessment has been conducted, according to the laboratory staff this has not been documented formally.
A protocol for patient withdrawal of consent to research should be written.	A protocol for response to patient withdrawal of consent has been written and was supplied at inspection.
Patient information should be amended to provide guidance on how to withdraw consent and to include contact details for a named individual.	On the day of inspection the patient information provided to the inspection team did not include these amendments. However, the PR has since explained that the changes had been made but the wrong

	version of patient information provided to the inspection team. The correct version of patient information has been sent to the Executive. This has been updated to advise patients how to withdraw consent to donation to research and details for the person that they should contact.
A protocol for disposal of embryos which outlines the maximum time that embryos can be cultured for should be documented.	The protocol has been amended to include how long embryos can be kept in culture for.

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

C	N/A
A	Complied Y/N

Summary for Licence Committee

<p>The Executive recommends that the continuation of the centre’s licence without additional conditions.</p> <p>The Committee are however, asked to note the following:</p> <ul style="list-style-type: none"> • The inspectorate’s concerns about security of embryos undergoing time-lapse recording within the CSRI laboratory (see section 2). This has been highlighted due to the potential of a breach of Code of Practice Standard 6.3.8. The Licence Committee are asked to make their own findings and recommendations on this. • An oxygen monitor is not in place within the embryology laboratory where a number of liquid nitrogen storage dewars are stored. (see section 2) • That one set of embryos have been used in research without the consent of one of the gamete providers (see section 3) • The PR’s proposed approach to obtain consent for donation of fresh embryos from patients (see section 3)
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Proposed licence variations

None

Report of Inspection findings

1. Organisation

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

Summary of findings from inspection

Evidence of:

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

Full time equivalent staff

Principal investigator	Dr Geraldine Hartshorne
Scientists	Embryology staff at centre 0013
Laboratory technicians	1
Support staff (receptionists, record managers, quality and risk managers etc)	Two members of administration staff at centre 0013 have a role in sending letters to patients who have embryos in storage at the centre.

Summary

The PR has completed the PR entry programme and her responses were considered to be satisfactory by the Executive.

The PR has responded to HFEA requests for information promptly and submitted the progress report for this project on time. The inspectorate considers that this is evidence of a well organised management system.

Auditing systems are in place; the PR stated that she had audited patient consent forms just prior to the inspection. As a result of this audit a non-conformity was noted and has been reported to the HFEA as an incident (see section 3).

There have been some staffing changes in the past year. One researcher is now on maternity leave but is expected back in April 2008 and another member of the team has left the centre due to the conclusion of her contract.

The project is currently funded from resources at CRM, which has a small research budget. This covers a modicum of consumables. Staff research time is available depending upon the clinical workload. Resources to invite consent from patients donating frozen embryos, and to maintain the research embryo bank, are provided within the CRM infrastructure. Additionally, short term research staff support has been provided since 31 April 2007 via a related project funded by the University of Warwick's Research Development Fund. This project was funded to work on human fetal ovarian tissue, however, due to unexpected delays with the ethical approval (now resolved), permission was granted by the University for the researcher to work on the present project with a view to working up imaging methodology which is helpful for both projects. The PR reported that no changes of funding can be envisaged at present,

however, applications for research support are actively continuing.
Issues for consideration
The PR has not put into place all the recommendations following the last inspection; meetings between researchers have not been formalised as previously suggested but the PR stated that any important points are communicated to staff via email.
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:

- Suitability of premises
- Storage facilities
- Servicing and maintenance of equipment

Summary

Work on the project is carried out within two laboratories within the hospital curtilage. Currently embryos are thawed within the research laboratory centre at the centre for reproductive medicine and they are then transported to be fixed with the Clinical Sciences Research Institute (CSRI) within the main hospital. This area was inspected at the renewal inspection in 2005 and considered to be suitable. Both laboratories were visited during the course of this inspection.

There have been no changes to the premises since the last inspection. A new incubator and time-lapse microscope have been purchased.

Patient identifying information was seen to be stored within the PR's office at the Centre for Reproductive Medicine. The office is located on the first floor of the unit and access to this area is restricted, via a swipe card system, to licensed staff or accompanied unlicensed persons. The PR reported that when her office is unoccupied it is locked. The PR has stated that additional information about the donated embryos, a card index and a file of consent forms, are stored within the laboratories at the Centre for Reproductive Medicine.

Currently embryos donated to research are stored in a research dewar which is stored in the centre's embryology laboratory. This was seen to be locked and fitted with a low nitrogen alarm. A second research storage dewar is stored within the CSRI laboratory and although not currently in use was seen to be locked.

Issues for consideration

An oxygen monitor is still not in place within the embryology laboratory where the research embryo tank is stored. This monitor has been on order since 2005. The PR reported that the unit have not received funding for this piece of equipment from the Trust. An informal risk assessment has been conducted and the PR stated that the risks to staff are minimal as the room is large and has frequent air changes. However, a risk remains and until a monitor and alarm system is fitted a formal risk assessment should be conducted.

The PR has recently acquired a time-lapse microscope. It is planned that this will be sited with the university laboratories at the Clinical Research Institute (CSRI) in a dark room. This room was seen to be secured by keypad lock but access is available to around 6 university researchers who are not on the licence. To use the time-lapse microscope dishes of live embryos will be positioned on the microscope continuously for up to 7 days. Due to the timings of this work the embryos will not be constantly accompanied by licensed personnel. Due to the fact that the room will be shared with other university researchers it is possible that

persons not under the supervision of the PR could have access to donated embryos. The PR was asked to consider how she can safeguard the security of the embryos and ensure compliance with Code of Practice Standard 6.3.8 which requires that “Gametes and embryos shall be stored in a designated security area with controlled access. Access to the security area shall be authorised by the Person Responsible and a monitoring system shall be in place to ensure high standards of security. Only named individuals, for whom access is essential in the course of their work, shall be authorised”.

Executive recommendations for Licence Committee

Note that a low oxygen monitor is not in place within the embryology laboratory where the research tank, and 6 other storage tanks, are stored.

Consider the security of embryos when being recorded by time-lapse microscope.

Areas not covered in this inspection

Safety 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:

- 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

Summary
<p>There have been no changes in the methods of recruiting donors or checking donor consents since the last inspection.</p> <p>Donors are recruited from the Centre for Reproductive Medicine. In the past two years the donor recruitment programme has not included patients undergoing fresh treatment cycles, due to staffing constraints, but donors have been recruited by approaching patients who have embryos in storage. Patients are written to three months before the consent for storage is due to expire and given the following options; discard the embryos, donate the embryos to another couple or donate the embryos to research.</p> <p>Once the deposition form is received and if consent to research is indicated, the patients are provided with specific information about the project and the embryos are then transferred from the clinical storage dewars to the research dewar. A research specific consent form is completed by patients and a copy of this kept within the patient records.</p> <p>If any restrictions on consent are made, i.e. to be used within this study but not secondary research, the patients are given the opportunity to make this known and this information is passed on to researchers. Evidence that researchers are made aware of restrictions placed on the use of donated material was clear within the research files.</p> <p>As requested at the last inspection a protocol has been written which outlines the procedures to be followed if a patient withdraws consent to research.</p>
Issues for consideration
<p>In the past two years patients have not been approached for the donation of fresh embryos. The PR has stated that this is due to the time pressures involved with consenting patients for the donation of fresh material. At the last inspection the PR stated that she would like to change their approach to donor recruitment. Rather than providing information before treatment commences the PR had planned to ask patients whether they would like to donate embryos at the time of egg collection. The Licence Committee which considered the last interim inspection report discussed the relative advantages of consenting patients for donating to research at different points in their treatment and agreed that it was important to ensure that patients were not asked to make the significant decision about donating to research at a stressful point in their treatment when they were likely to be preoccupied. The Committee therefore agreed that it would be inappropriate to approach patients for the first</p>

time about donating to research either at the point of egg collection or at the point of embryo transfer. The Committee did not object to the patients being asked to sign a consent form at egg collection or embryo transfer but only on the condition that full information and a chance to answer any questions had been provided to patients at a much earlier point in their treatment.

The PR has reported that as she felt it was not reasonable for nurses and doctors who saw patients in clinic, at an early stage in their treatment, to provide them with additional information on top of the already complex information that they were receiving. She stated that this would involve an additional discussion, when only very few of those patients would ultimately be able to donate material. Thus patients and staff would go to considerable time and effort, but because of the limited availability of research staff to deal with it, or likelihood of other treatment outcomes not generating research material, such as abandoned cycles, full fertilisation, blastocyst culture, full freezing, etc, this effort would not be productive, and may even be detrimental. The PR stated that the unit is not staffed to a level where such extensive additional non-productive workload could be accommodated. The PR stated that as this would involve considerable extra work at CRM for relatively little gain, the approach suggested by the Licence Committee has not been adopted. The PR still wishes to approach patients at egg collection, to request abnormally fertilised/poor quality (uncryopreservable) embryos and any oocytes that were immature at collection or remained unfertilised at the end of 24 hours, and would appreciate review of this decision.

During the inspection the PR reported that in her recent audit of patient consents she had noted that on one occasion embryos which were donated to research had been created using donor sperm. The consent form from that sperm donor had not been checked prior to using the embryos in research and after contacting the sperm bank the PR discovered that the gamete donor had not given consent to research (apparently it is the policy at this particular sperm donor bank not to request research consent from sperm donors). The PR stated that in response to this incident she has amended the protocol to reduce the risk of a reoccurrence of the incident. A copy of this amended protocol was supplied to the Executive on the day of inspection. This event has been reported to the Executive as an incident.

Executive recommendations for Licence Committee

Note that on one occasion embryos have been used in research without the consent of one of the gamete providers (sperm donor). Schedule 3 6- (3) of the HFE Act 1990 requires that “An embryo the creation of which was bought about *in vitro* must not be used for any purpose unless there is effective consent by each person whose gametes were used to bring about the creation of the embryo to the use for that purpose of the embryo and the embryo is used in accordance with those consents”.

Note that the PR would like the Licence Committee to reconsider their decision about the timings around providing patients information and obtaining consent for the donation of fresh embryos.

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:

- Patient information
- Consent forms

Outcome of audit of records
<p>Five patient records were audited for evidence of consent to research and to track how the embryos were used in the research project. From these records it was noted that all embryos were incorporated into the research project during the statutory storage period. Research records contained information on when the embryos were incorporated into the research project and what the end point was in each instance.</p> <p>In four sets of patient records all relevant consent forms were seen to be in place. One patients' record included a general consent to research but did not contain evidence of the patients' consent to this specific project. Code of Practice Standard 8.3.2 requires that "The Centre shall also ensure that before Donors give their consent to the use of their gametes and / or embryos in a research project, they are given oral information, supported by relevant written material, which confirms: (a) the specific research project, including any tests that may be performed on embryos or cells derived from the embryos as part of the licensed research project. Without a specific research consent form in place within the patient records it is not possible to determine whether the patient was provided with information about the specific research project.</p>
Summary
<p>Patient information and consent forms were reviewed and considered to be appropriate at the last renewal inspection. The PR has confirmed that changes have not been made to the information since this date.</p>
Issues for consideration
<p>Patient information provided to the inspectorate on the day of inspection did not include specific guidance on how patients could withdraw their consent to research to do this or who specifically to contact is not clear. An amendment to the patient information to reflect this as suggested at the last interim inspection.</p> <p>However, following the inspection the PR contacted the HFEA to explain that the recommended changes had been made but that the wrong version of patient information had been provided to the inspection team. The PR attached the correct information and this was seen to include guidance on how patients can withdraw consent and whom they should contact. The PR should ensure that the correct version of patient information is being supplied to patients.</p>
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:

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

Use of material
<p>In the twelve month period from 28/04/2006 to 31/07/2007 226 frozen embryos were thawed and 178 survived the thaw process and were used within the project. All of the embryos were donated by patients who had received treatment at centre 0013.</p> <p>The PR stated that the numbers of embryos used vary from the original proposal due to the number of staff available to perform the work. This year, the PR had two staff members actively engaged in research and the PR stated that this explained the higher than expected usage of embryos.</p> <p>The PR has estimated that they expect to use 100 frozen embryos during the next 12 month period.</p>
Renewed project objectives
<p>The PR has stated that the research objectives remain the same. The research team plans that future work will advance those areas in which they have already made progress in, namely, telomere measurement and oxidative stress measurements, as potential indicators of embryo viability, as well as additional work on FISH with a view to developing PGD capacity. The PR has stated that these are clearly directly relevant to the stated objectives for this project. Furthermore the PR explained that grant applications will continue with a view to making progress in these areas, and gaining data in additional areas, such as in vitro maturation, that has currently been afforded limited opportunity for research.</p>
Lay summary of research undertaken
<p>Since the last report, the research undertaken has been in three areas.</p> <ol style="list-style-type: none">1. Telomere measurement in embryos.2. Exploring the feasibility of detecting embryo viability or stress via imaging of mitochondria.3. Establishing methods for introduction of pre-implantation genetic diagnosis. <p>The Lay summary provided by the PR states:</p> <p>“This year, we have started to look at oxidative stress in embryos. Oxidative stress can occur when embryos undergo changes in their biochemistry, caused, for example, by being in laboratory conditions, rather than inside the body. We are using coloured dyes that show us how much oxidative stress embryos are experiencing. The data that we have collected so far will help us to find out whether this stress is related to the embryo’s chances of developing normally. They may also help us to gain support for a more detailed study of this area. We have also started to develop methods that could be used for pre implantation genetic</p>

diagnosis, in future, under a new collaboration with genetics specialists at the Regional Genetics Laboratory. Please note, only eggs and embryos that are no longer required by the patients or are of no use in their treatment and would otherwise be discarded are being used in this project.”
Peer reviewers comments
Not applicable – interim inspection.
Laboratory audit outcome
The research dewar is audited by the embryology team at centre 0013. The scientific inspector was informed that no discrepancies were noted during the most recent audit of the tank. A spot check audit of stored research material was not performed at this interim inspection. The spot check conducted at the last interim inspection (November 2006) passed without discrepancies and a repeat spot check of stored material is to be conducted at the renewal inspection in mid 2008.
Summary
The protocol for disposal of embryos outlines the maximum time (14 days) that an embryo can be cultured for. Research records have been maintained which indicate each time material is handled and manipulated. These logs also record the fate of the embryos used in research. To ensure that researchers are aware of the embryos which are about to expire, the consent forms are stored in order of statutory storage expiry date. The PR demonstrated this system to the inspectorate.
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.....15th November 2007.....

Appendix A: Centre Staff interviewed

Geraldine Hartshorne (PR)

Appendix B: Licence history for previous 3 years

R0155/2/a:

Active from: 01/11/05

Expires: 31/10/08

No conditions or recommendations on licence

Licence	Status	Type	Active From	Expiry Date
R0155/2/a	Active	Research Project	01/11/2005	31/10/2008
R0155/01/b	Never Issued/Amended before offered to centre	Research Project	01/11/2005	31/10/2008

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number.....13.....

Name of PR.....Geraldine Hartshorne.....

Date of Inspection.....14 November 2007

Date of Response.....18 December 2007.....

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

P3 recommendation re performing a risk assessment on risk of no low oxygen alarm in embryology lab.

The embryology lab is part of the CRM suite and it therefore falls under the CRM risk management programme. A risk assessment of oxygen depletion due to working with liquid nitrogen was carried out for the entire lab in June 07 and it features on the Unit's risk register. The embryology processes involved in research were not separate from that risk assessment. A separate risk assessment has not been performed.

We were notified yesterday that the CRM's requested oxygen deficiency monitor has now been formally signed off by the Trust and finance, and we are awaiting notification of an installation date.

P4. Re use of embryos for research without consent of the sperm donor (IN0718), further to your email of 28 November 2007, I wrote to the Louis Hughes unit in London on 29 November 2007, explaining the situation and requesting them to contact the donor with the information. I have not received a reply.

P6. Minutes of meetings of research staff have not been implemented. This is because most meetings are 1 to 1 and not formal, and minuting would add work but not add value. There are too few research staff to make formal meetings viable. As stated, any important matters are communicated via email so that there is a dated and timed record of what was said.

P7. Discussions are ongoing at CSRI to review the siting of the new microscope, laboratory access arrangements and/or licensing of additional staff. A meeting is planned for 10 January 2008.

P9. under Issues for Consideration, 6th line. We wish to approach patients at the time of oocyte collection, not the time of embryo transfer. We would be requesting not only abnormally fertilised or poor quality (uncryopreservable) embryos but also any oocytes that were immature at collection or remained unfertilised at the end of 24 hours.

I would like to stress two things.

First, this used to be the timing of our approach for many years, and caused no problems. We never received a complaint relating to the approach, and there was no indication that patients suffered distress, changed their minds or were otherwise disadvantaged. Patients were usually pleased that there was something positive that could come out of their material that was unable to be used otherwise.

Second, our unit has a liberal approach to embryo cryopreservation, such that all 'spare'

embryos that may potentially survive cryopreservation are routinely stored (unless patients do not consent), regardless of the number available. Patients are not charged for embryo freezing or initial storage. They are charged for continued storage only after 1 year, or at transfer. Thus there would be no difference in the material available to the patient for their treatment, whether or not they consent to research.

P11. It is our normal practice to write in the notes narrative section when patient information and consent forms are sent to patients direct from the unit (as opposed to those whose request for disposal is sent via finance dept- who do not have access to notes). Thus the general consent and the specific consent forms are normally sent at the same time. I am not sure whether you checked this in the set of notes where this was apparently lacking. This would provide evidence that we did provide the full information to the patients.

I have read the inspection report and agree to meet the requirements of the report – with the exception of minuting meetings with research staff.

Name.....Geraldine Hartshorne.....

Date.....20 December 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).

P3. States: 'in the past year one research technician has joined this team'. This is not correct. The researchers are myself, Sue Montgomery (nominal licensee), Hiu-Pak Wong (recently added, since the inspection), Sarah Turner (nee Ellis, on maternity leave), and occasionally scientific staff at CRM. Others who have access to licensed material in the course of their roles as technical personnel at the CSRI, and are therefore named on the licence, are: Catherine Butcher, Suresh Kumar and David Baber.

P7. 3rd para under Summary: The 'list of embryos available for research' is in fact a card index which is stored in the embryology lab, and a file of consent forms, which is stored in the research lab.

P7. Embryos could be positioned on the time lapse microscope continuously for up to 7 days.

P9. under Issues for Consideration, 6th line. We wish to approach patients at the time of oocyte collection, not the time of embryo transfer. We would be requesting not only abnormally fertilised or poor quality (uncryopreservable) embryos but also any oocytes that were immature at collection or remained unfertilised at the end of 24 hours.

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
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