Research Interim Inspection Report

Date of Inspection: 17 June 2010
Length of inspection: 5 hours
Inspectors: Andrew Leonard; Paula Nolan

Inspection details: The report covers the pre-inspection analysis, the visit and information received between 1 October 2008 and 15 June 2010.

Date of Executive Licensing Panel (ELP): 10 September 2010

Purpose of the Inspection report

The purpose of the inspection is to assess whether research using human embryos is carried out in compliance with the HF&E Act 1990, Code of Practice, licence conditions and directions and that progress is made towards achieving the stated aims of the project.

The report is used to summarise the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the Authority's Executive Licensing Panel which makes the decision about the centre's licence renewal application.

Centre details

Licence Number	R0186/1/b
Project Title	Genetic screening of the preimplantation embryo
Centre Name	The Assisted Conception Unit, Birmingham Women's Hospital.
Centre Number	0119
Centre Address	Centre for Human Reproductive Science, The Assisted Conception Unit, Birmingham Women's Hospital, Edgbaston, Birmingham, B15 2TG
Person Responsible	Dr Jackson Kirkman Brown
Licence Holder	Dr Sue Avery
Donating centres	0119
Date Licence Issued	01/10/2008
Licence expiry date	30/09/2011
Additional conditions	NONE

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Report to Executive Licensing Panel

Brief description of the centre and its licensing history:

Centre 0119 has held research licences since 2004. The research premises comprise the clinical embryology laboratory in the Assisted Conception Unit, Birmingham Women's Hospital (*i.e.* HFEA centre 0119). The project uses a dedicated research incubator in the laboratory as well as air flow cabinets and an embryo biopsy microscope with micromanipulation stage which are also used for treatment activities. The Person Responsible (PR) is a Senior Lecturer with the University of Birmingham, with many years of research experience, and also the Director of Research and Development at the Centre for Human Reproductive Sciences in Centre 0119. The PR has completed the PR entry programme.

The lay summary of project R0186 states:
When embryos are produced by IVF, during the first few days after fertilisation when they are still just a few cells, one or two of these cells can be taken without affecting the health of a future child. The reason to do this is to use genetic screening to check for severe debilitating illnesses or things which would cause a miscarriage and the associated upset. In an ideal world these can be avoided as IVF creates a number of embryos and so we could only pick those without problems to put back.

One problem with these diagnoses is that in the early embryo not all cells are the same and the one cell that you sample may not be representative - you could make a misdiagnosis. Through use of embryos that would otherwise be disposed of we aim to establish clear and safe techniques to make an accurate diagnosis in these early embryo stages.'

The project was first licenced from 1 October 2008. It was approved for the use of embryos in research and the storage of embryos for the following purposes, as defined in Schedule 2 3A (2) to the HFE Act 1990 (as amended):

- (d) promoting advances in the treatment of infertility,
- (e) increasing knowledge about the causes of miscarriage,
- (g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- (h) increasing knowledge about the development of embryos.

Recommendation to the Executive Licensing Panel:

Two major non-compliances were noted on inspection and reported to the PR. The PR has taken appropriate actions in both cases to address them. The inspection team therefore need make no recommendations to the Executive Licensing Panel regarding these matters.

The inspection team considers that overall there is sufficient information available to recommend the continuation of the centre's licence without additional conditions.

Details of inspection findings

Lay summary of the research project:
'When embryos are produced by IVF, during the first few days after fertilisation when they are still just a few cells, one or two of these cells can be taken without affecting the health of a future child. The reason to do this is to use genetic screening to check for severe debilitating illnesses or things which would cause a miscarriage and the associated upset. In an ideal world these can be avoided as IVF creates a number of embryos and so we could only pick those without problems to put back.

'Currently one problem with these diagnoses is that in the early embryo not all cells are the same and the one cell that you take and sample may not be representative - you could make a misdiagnosis. Through use of embryos that would otherwise be disposed of we aim to establish clear and safe techniques to make an accurate diagnosis in these early embryo stages.'

Objectives of the research (as stated in the licence application in July 2008):
'Through a better understanding of early genetic screening of the embryo we can hope to better understand causes of miscarriage and the early stages of embryo development and also gain knowledge for treatment and diagnosis of the same. As part of our study we will repeatedly sample blastomeres from an embryo and screen for the number of chromosomes and, or other genetic mutations. This should enable us to better clarify the 'mosaicism' observed in the early embryo which currently confounds accurate pre-implantation diagnosis of conditions such as aneuploidy.'

Summary of the research undertaken since the granting of the licence on 1 October 2008:
No project progress report was required for this inspection. The project was expected to utilise 30 fresh and 30 frozen embryos annually. Thirty one embryos were used in project R0186 between 1 October 2008 and 31 December 2009, whereas no embryos were used between 1 January 2010 and 17 June 2010. No embryos were stored for future use. Twenty three embryos have been biopied, 13 repeatedly, and the blastomeres frozen for subsequent molecular biological analysis by the West Midlands Regional Genetics Service (WMRGS). Initial test hybridisation experiments have been performed and the detailed analysis of blastomere chromosomal complement is likely to start soon.

Peer review comments:
It is standard practice to request peer review of research licences at renewal inspections only. No peer reviews were therefore available or were required for this interim inspection. Peer reviewers supported the issuing of the licence on 1 October 2008

Donation and use of embryos:
Between 1 October 2008 and this inspection, project R0186 received 31 embryos from centre 0119. These have been subjected to repeat embryo biopsy according to the project's experimental protocols; no embryos are held in storage.

Regulatory principles

Focus

- **Protection of the embryo (Principles 12, 3, 5, 6, 8 are relevant)**
- **Good governance and record keeping (Principle 13 is relevant)**
- **Areas of concern** – The analysis of the centre's self assessment questionnaire (SAQ) and the information the centre has submitted to the HFEA have identified that the following areas needed to be looked during the inspection visit to this centre.
    - No SAQ was submitted as the centre was not asked to provide one for this interim inspection
    - The requirements arising from the last inspection in July 2008. These were checked to ensure they were completed and are discussed in the relevant principles and in the change/improvements section at page 16:

The HFEA regulatory principles with inspection findings

▶ Ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos **(Principle 12).**
What the centre does well: Research project R0186 was provided a HFEA research licence on 1 October 2008. That new licence application was considered by two peer reviewers and the HFEA Research Committee who both considered that the centre met appropriate ethical standards and had clear justification for, and no viable alternative to, the use of human embryos in research. The project has not changed since, so these assessments remain valid. The research project was approved in 2008 by the appropriate Local Research Ethics Committee (LREC). The PR stated on inspection that ethical approval is still in place and will remain so until the PR, as project lead, informs the LREC that the project has terminated.
What they could do better: No issues identified

Have respect for the special status of the embryo when conducting licensed activities **(Principle 3)**.
What the centre does well In discussions with the PR, it was apparent to the inspection team that the special status of the human embryo is respected. This was evidenced by several observations: 1) Access to premises is controlled 2) There is dedicated equipment for the project, which is all well maintained and serviced appropriately. 3) The PR has ensured that appropriate records of embryo usage are maintained. 4) Protocols have been established for allowing embryos to perish before they reach the end of their statutory storage or at the end of experimental use, as recommended by CoP Guidance 22.3. These procedures are witnessed and recorded on the embryo's log sheet which is then securely stored. 5) The centre have documented SOPs for the licensed processes at the centre which take account of patient consent and ensure embryos are effectively used in a respectful manner.
What they could do better The projects SOPs do not incorporate a specific check or statement that viable embryos are not cultured for more than 14 days post fertilisation, contrary to Licence Condition R28. The SOP which documents the process for culturing and repeat biopsy of the research donated embryos should state that embryos will not be cultured for more that 14 days post-fertilisation and should describe processes by which the embryos culture age is monitored to ensure embryos are discarded before the 14th day of culture post-fertilisation.

Give prospective and current patients and donors sufficient, accessible and up-to-date information to enable them to make informed decisions (**Principle 5).**
What the centre does well Patient information and consent forms were reviewed against the 8th edition of the CoP and were considered to be compliant.
What they could do better. No issues identified

Ensure that patients and donors have provided all relevant consents before carrying out any licensed activity (**Principle 6).**

What the centre does well

Donors are recruited at centre 0119 by a research recruiter/consenter who is independent of the research project. Written and verbal information regarding the research project is given when the patients attend an information session to introduce them to the clinic. They are advised verbally and in writing that research donation will not have any influence on their clinical treatment. Patients can indicate whether they are interested in research donation using a tick box in their clinical consent forms and are told that this is not a commitment. The patients next attend a clinical consenting consultation, after which, if they have indicated an interest in research consent, they can discuss research consent with the research recruiter/consenter and are provided with further information. Patients next attend for ultrasound scanning, after which they can discuss research consent with the research recruiter/consenter and can sign consent forms if they so choose. When research consents have been signed, they are stored in the patient record and a checklist on the front of the record is amended to indicate the research consent has been provided. The research recruiter/consenter has attended local Trust training for consenting patients and has had his competence to inform patients regarding the research and take research consents assessed. Further consent training on an accredited course is planned.

Centre 0119 has selection criteria for patients to donate embryos to research. If patients have signed research consents and these are present in the patient record, all who choose not to freeze embryos are approached about their use in research, as are all patients with embryos of too low a quality for freezing for clinical use. With the agreement of the patients, these fresh embryos are transferred to the research incubator by the clinical embryologist involved in treatment. Patients with cryopreserved embryos are approached if they request research information in response to their annual letter asking what they wish to do with their stored embryos. They are provided patient research information and a consent form and offered the opportunity to discuss donating with the recruiter/consenter, on the telephone or in person. The embryos of patients who send back completed consent forms are taken into the research programmes, however they remain stored in their original dewar location until required. They are then taken with witnessing from the dewar, thawed and cultured in the research incubator before being used in the research project.

When embryos are placed in the research incubator, the clinical embryologist on the research licence then transfers the embryos to an anonymised dish marked with just a research code and returns them to the same incubator. The embryos and their fate are documented anonymously in the research embryo usage log. The clinical embryologist performs the embryo culture, repeat biopsy and blastomere storage which occurs as part of the research activity. The researchers see no patient identifying information after anonymisation, nor does such information leave centre 0119.

What they could do better. No issues identified

▶ Ensure that all premises, equipment, processes and procedures used in the conduct of licensed activities are safe, secure and suitable for purpose **(Principle 8).**
What the centre does well Electronic card key locks are fitted in centre 0119 to the corridor doors controlling access to non-patient areas as well as to the doors to the embryology laboratory and the cryostore. These locks are accessible to licensed centre staff only. Experimental notes and records, which do not contain any identifying information, are kept within the embryology laboratory or the Centre for Human Reproductive Sciences within centre 0119. These arrangements ensure that embryos and records are maintained under lock and key and the security of the centre was considered appropriate. The laboratory is appropriately equipped for the proposed research, with a research dedicated incubator, and air flow cabinets and an embryo biopsy microscope fitted with a micromanipulation stage. Laboratory equipment has been validated. The PR considers that the researchers have all equipment required for the project. The laboratory is cleaned and maintained by the licensed staff. All apparatus is on service contracts. Health and Safety and Fire Safety inspections and risk assessments on the premises have been performed and appropriate risk control measures are in place. All procedures used by the research project have been risk assessed.
What they could do better: No issues were noted

▶ Conduct all licensed activities with regard for the regulatory framework governing treatment and research involving gametes or embryos within the UK, including: maintaining up-to-date awareness and understanding of legal obligations responding promptly to requests for information and documents from the HFEA, co-operating fully with inspections and investigations by the HFEA or other agencies responsible for law enforcement or regulation of healthcare **(Principle 13).**
What the centre does well: The PR has implemented all the requirements detailed in the report of the inspection on 18 July 2008. The centre has an incident reporting and investigating protocol compliant with HFEA requirements. The PR has in the past been prompt in responding to requests for information from the HFEA Executive, and was so during and after this inspection. The centre has documented protocols for the processes from receipt of embryos through to their use and disposal.
What they could do better: The research donation protocols should document that once embryos have been donated to research, they can not be returned for treatment, to prevent the possibility that research donated embryos could be used in treatment, contrary to HFE Act (1990) as amended, Section 15 (4). The PR should ensure that the procedures are amended accordingly.

Changes / improvements since the last inspection on 18th July 2008

Issues at last inspection	Observations at this inspection
Issue 1 A procedure for reporting serious adverse events to 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.	An incident reporting SOP was produced after the last inspection and provided to the Executive. The present version was observed on inspection and was considered compliant with HFEA requirements. No further actions are necessary.
Issue 2 It is essential that the research PR ensures that the scoring of embryos to select for freezing for later clinical treatment is not performed by the clinical embryologist on the research licence application, who may have a role in subsequent research use of embryos not selected for freezing.	This issue was said by the research PR to have been discussed with the clinical embryology team and the embryologist concerned after that inspection. It was documented in the team meeting minutes that the embryos of all research consented patients should be graded for freezing by embryologists other than the clinical embryologist on the research licence. No further actions are needed
Issue 3 The PR should develop a suitable documented procedure for recording and reviewing patient consent, which ensures that patient consent is not breached. If the procedure used for transfer of donated material to project R0173 is used, the PR should take into account recommendations made by the inspection team after inspection of that project, specifically: 1) To clearly define in centre procedures when embryos are entering the research programme and to ensure consents are checked and the donated materials anonymised at the point of transfer to research 2) It is important that the research PR and his research assistants only provide information to patients	On this inspection, a research consent procedure was present which documents the consenting practices outlined in principle 6. A procedure was also observed for the transfer of embryos to research, which defines the point at which embryos enter the research pathway and ensures consents are checked and describes the need to transfer embryos to anonymised dishes. All consenting is carried out by the recruiter/consenter who is independent of the research project, while the research PR is available to provide additional information if needed. These observations indicate the centre has satisfied the requirements of the inspection report regarding these issues and no further actions are needed

Issue 3 (Continued) about the HFEA licensed research projects, but do not obtain consent from the patients for donation to them. Consent taking should be performed by staff at Centre 0119 including the research nurse.	
Issue 4 Patient information does not provide contact details for somebody independent of the research with whom patients can discuss donation. It also does not inform patients that they can see a counsellor to discuss the implications if they choose to donate, as required by Code of Practice, 7th Edition, G.6.7.2 (a). This information should be added to the information sheet or provided verbally to the patients.	At this inspection, patient information and consent forms were reviewed against the 8th edition of the CoP. These documents have been updated with two labels which clearly provide: a) That an appointment can be made with an independent counsellor if the patients need to discuss the implications of the embryo donation to research. b) The contact details for the PR and the research recruiter/consenter who should be contacted 'for any queries'. The research recruiter/consenter is well informed about the project but is not funded by it or dependent on it in any way. No further actions are needed
Issue 5 Patient information discusses the provision for patients to vary or withdraw their consent up to the point that embryos are passed over to the research laboratory, as required by Code of Practice, 7th Edition, S.8.3.1 and G.5.13.1 (g). It says that this can be achieved by asking any member of staff. It is recommended that the information provides contact details for a named individual through whom this can be achieved, as well as relating that it can be discussed with any member of staff.	The research recruiter/consenter stated that he discusses the variation and withdrawal of consent with all patients. Patients are advised that they should contact the PR or the research recruiter/consenter if they wish to vary or withdraw their research consent and shown the contact details in the patient information. These discussion points were seen to be included in the consenting checklist. No further actions are needed

Areas of practice that require the attention of the Person Responsible

The section sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been classified into critical, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Standard Licence Conditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well as the timescales in which these improvements should be carried out.

Critical area of non compliance

A critical area of non compliance is an area of practice which poses a significant direct risk of causing harm to a patient, donor or to an embryo. A critical area of non compliance requires immediate action to be taken by the Person Responsible

Area of practice 1	Action required	PR Response	Executive Review
NONE			

TRIM reference: 2009/ Version: 0
Doc. Name: Inspection Report Template - Research Interim
Release date: 1 October 2009
Review date: 30th Sept 2010

Major area of non compliance

A major area of non compliance is a non critical area of non compliance:

- which poses an indirect risk to the safety of a patient, donor or to an embryo through the procurement, use, storage or distribution of gametes and embryos, which do not comply with the centre's licence;
- which indicates a major shortcoming from the statutory requirements;
- which indicates a failure of the Person Responsible to carry out his/her legal duties
- a combination of several "other" area of non compliance, none of which on their own may be major but which together may represent a major area of non compliance.

Area of practice 1	Action required	PR Response	Executive Review
The SOP for embryo culture does not incorporate a check that viable embryos are not cultured for more than 14 days post fertilisation, noncompliant with Licence Condition R28. .	The SOP for embryo culture should state that researchers should regularly review culture records to ensure that viable embryos are not cultured for more than 14 days post fertilisation. This change should be made by 1 November 2010	A change has been made to reflect an extra level of security to ensure that culture beyond 14 days of intact embryos does not occur.	The Lead Inspector considers that the PR has taken appropriate corrective action and the projects activities are now compliant with the requirements of Licence Condition R28

Area of practice 2	Action required	PR Response	Executive Review
The centre's procedures do not document that once embryos have been donated to research, they can not then be used in treatment. This is required to prevent the possibility that research donated embryos could be used in treatment, contrary to HFE Act (1990) as amended, Section 15 (4). .	The centre's procedures should document that once embryos have been donated to research, they can not be used in treatment. This change should be made by 1 November 2010	This was considered clear in the existing documentation, but more explicit statements have been included.	The Lead Inspector considers that the PR has taken appropriate corrective action and the projects activities are now compliant with the requirements of HFE Act (1990) as amended, Section 15 (4)

Other areas of practice that requires improvement

Areas of practice that requires improvement is any area of practice, which cannot be classified as either a critical or major area of non compliance, but which indicates a departure from good practice.

Area of practice 1	Action required	PR Response	Executive Review
NONE			

Additional information from the Person Responsible

HFEA Executive Licence Panel Meeting

10 September 2010

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 3

Centre 0119 (Birmingham Women's Hospital) - Interim Inspection Report (Research R0186)

Members of the Panel:	Committee Secretary:
Mark Bennett, Director of Finance & Facilities (Chair) Nick Jones, Director of Compliance Hannah Darby, Policy Manager	Terence Dourado

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

The following papers were considered by the Panel:

- Interim inspection report, 17 June 2010
- Licence Committee Minutes 16 September 2008; Initial licence application inspection report

The Panel also had before it:

- HFEA Protocol for the Conduct of Meetings of Executive Licensing Panel
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Directions 0000 – 0012
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Consideration of Application

1. The Panel noted that the Centre's has held research licences since 2004 and that its research project (R0186) was first licensed on 1 October 2008

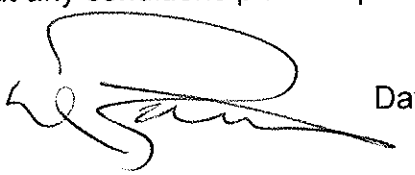
2. The Panel noted that the Person Responsible (PR) is a Senior Lecturer at the University of Birmingham, with many years of research experience. Furthermore, it noted that the PR has completed the PR entry programme (PREP).

3. The Panel considered the Research Interim Inspection Report and was satisfied that the Centre is compliant. It was satisfied that the PR had taken appropriate actions to address two areas of non-compliance.

4. The Panel considered what measures had been put in place to prevent culture of embryos beyond 14 days, but was satisfied this had been checked by the Inspector.

Decision

5. The Panel agreed to the continuation of the Centre's research licence without any conditions placed upon it.

Signed:  Date: 21/9/10

Mark Bennett (Chair)