Research Interim Inspection Report

Date of Inspection: 23 November 2010
Length of inspection: 2 hours
Inspectors Vicki Lamb (Lead, HFEA)
Bhavna Mehta (Support inspector, HFEA)
Terence Dourado (Observer, HFEA)

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between March 2009 and the date of the Executive Licensing Panel.

Date of Executive Licensing Panel: 18 February 2011

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.

Centre details

Project Title	Improving methods for pre-implantation genetic diagnosis of inherited genetic disease and predicting embryo quality
Centre Name	Guys Hospital
Centre Number	0102
Research licence Number	R0075
Centre Address	Stem Cell and Embryology Research Laboratories Assisted Conception Unit 11th Floor Tower Wing Guy's Hospital London, SE1 9RT
Person Responsible	Professor Peter Braude

Licence Holder	Mr Yacoub Khalaf
Treatment centres donating to this research project	Salisbury Fertility Centre (0197) Chelsea and Westminster Hospital (0158) Herts and Essex Fertility Centre (0030) Lister Fertility Clinic (0006) Sussex Downs Fertility Centre (0015) South East Fertility Clinic (0208) BMI Chelsfield Park ACU (0086) The Woking Nuffield Hospital (0144)
Inspection date	23 November 2010
Executive Licensing Panel Date	18 February 2011
Date Licence Issued	1 September 2009
Licence expiry date	31 August 2012
Additional conditions applied to this licence	None

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Report to Executive Licensing Panel

Brief description of the centre and its licensing history:

Guy's Hospital has held this HFEA research licence since July 1994.

The centre was last inspected on 26 February 2009 and a Research Licence Committee agreed to the renewal of the research licence in May 2009.

A new research facility has been built on the 11th floor of the Tower Wing, Guy's Hospital. The new premises were inspected on 5 June 2008 and the licence varied to reflect the new address of the premises on 18 June 2008. The new research facility comprises of two dedicated research laboratories situated within the new assisted conception unit. New equipment has also been purchased for use in the new laboratories.

Title of research project:

Improving methods for pre-implantation genetic diagnosis of inherited genetic disease and predicting embryo quality

Summary for licensing decision:

In considering overall compliance, the executive considers that it has sufficient information drawn from documentation submitted by the centre prior to inspection and from observations and interviews conducted during the inspection visit to conclude that:

- the PR is suitable and has discharged his duty under section 17 of the HF&E Act 1990 (as amended)
- the premises are suitable
- the practices are suitable
- the centre has submitted appropriately completed documentation in accordance with General Direction 0008

Activities to be licensed

The activities to be licensed are:

- Use of embryos for research
- Storage of embryos
- Creation of embryos in vitro

The above activities have been licensed previously.
None of these activities are prohibited by the HF&E Act 1990 (as amended)

The use of embryos for research is necessary or desirable for the following purposes:

- Promoting advances in the treatment of infertility
  HFE Act 1990 (as amended) Schedule 2 3A(2)(d)
- Increasing knowledge about the causes of congenital disease
  HFE Act 1990 (as amended) Schedule 2 3A(2)(c)
- Increasing knowledge about the causes of miscarriages
  HFE Act 1990 (as amended) Schedule 2 3A(2)(e)
- Developing methods for detecting the presence of gene or chromosomal abnormalities
  HFE Act 1990 (as amended) Schedule 2 3A(2)(g)
- Increasing knowledge about the development of embryos
  HFE Act 1990 (as amended) Schedule 2 3A(2)(h)
- Increasing knowledge about serious disease
  HFE Act 1990 (as amended) Schedule 2 3A(2)(a)
- Enabling any such knowledge to be applied in developing treatments for serious disease
  HFE Act 1990 (as amended) Schedule 2 3A(2)(b)

These purposes have been licensed previously.

The use of human embryos is necessary because this research is concerned with the work up for PGD testing as well as investigating whether the genetic make up of human embryos is the same in both the trophectoderm and inner cell mass.

Patient information and consent forms

The patient information and consent forms were not reviewed as this was an interim inspection.

Recommendation to the Executive Licensing Panel:

The inspector considers that overall there is sufficient information available to recommend the continuation of this research licence without additional conditions.

Details of inspection findings

Lay summary of the research project:
The approved lay summary of the research project is as follows:

Preimplantation genetic diagnosis (PGD) is a reproductive option for couples at substantial risk of conceiving a pregnancy affected with a known genetic disease who wish to avoid the emotional burden associated with an affected child, termination of pregnancy or recurrent miscarriages. PGD has been offered as a service at Guy's and St Thomas' for over ten years, and it is now the busiest and most successful unit in the country.
PGD has been used for single gene diseases such as cystic fibrosis, for diseases which only affect males by selecting female embryos, and for couples with chromosome rearrangements. For single gene diseases, one cell is removed from a 3-day old embryo and tested for the mutation. A separate PGD test has to be developed for every different mutation, requiring substantial resources not always available in state-run medicine. In addition, these tests are technically difficult and very sensitive to contamination with non-embryo DNA.
Over the duration of our previous licence, we developed a new technique at Guy's, Preimplantation Genetic Haplotyping (PGH) which improves the reliability of single cell genetic testing and enables it to be extended to a wide range of diseases. It has also allowed us to move away from sexing embryos as a means of avoiding some genetic disease as we can use PGH to detect and distinguish unaffected males in addition to unaffected or carrier females.
We intend to work over the next three years, further developing this approach for a wider range of genetic disorders, and to see whether we can extend the approach to include tests for some serious or lethal chromosomal trisomies such as Edward, Patau and Down syndrome. Further research will look at effect of mosaicism on diagnosis, and the impact of mitochondrial function during early development.

Objectives of the research:

1. To improve the accuracy of PGD and to estimate reliability of those diagnoses by examining embryos deemed not suitable for transfer.
(a) We have examined a number of commercial kits for extracting and amplifying DNA for PGD testing using blastomeres from embryos that are not suitable for transfer, in order to determine if they are better than our in house methods. So far none have been.
(b) The purchase of a small robotic precision liquid handling work station as part of our grant from the Guys and St Thomas Charity, enabled us to use utilise robotic technology to simplify and speed up processes for handling an increase in caseload without compromising quality.
(c) Assessment of the reliability of diagnosis using embryos deemed unsuitable for transfer due to genetic disease, has been undertaken as part of a mulitcentre study under the auspices of the ESHRE PGD consortium to compare to consistency of the results.

2. To apply genetic techniques to an increasing range of genetic diseases.
Over the duration of our licence, we have continued to refine Preimplantation Genetic Haplotyping (PGH) which improves the reliability of single cell genetic testing and enables it to be extended to a wide range of diseases. PGH has also allowed us to move away from sexing embryos as a means of avoiding some genetic disease as we can use it to distinguish unaffected males in addition to unaffected or carrier females. We have now applied this approach to 37 more serious genetic disorders. We have also designed tests for the three most common serious whole chromosome trisomies (resulting in Down's, Edwards and Patau syndromes) and developed patient information leaflets, which have now been introduced into the clinic. These tests were validated by extensive testing on amplified DNA from research embryos and from transferred embryos where the pregnancy outcome was known.

3. To improve methods of assessing embryo quality in order to improve embryo selection procedures at transfer.
The increased rate of multiple pregnancy associated with traditional IVF practices and the consequential maternal and fetal risks posed has resulted in a push towards adopting single blastocyst transfer (SBT). Blastocysts for transfer or cryopreservation following embryo biopsy for PGD or during routine IVF are selected on the basis of morphological criteria. However, other than outcome following transfer, there has been little attempt to assess developmental potential other than by estimates of efficiency for stem cell derivation. By examining embryos deemed unsuitable for freezing and hence would be discarded using fluorescent staining techniques we have been able to refine selection criteria enabling us to freeze more embryos for patient use.

Peer review comments:

As this was an interim inspection, no peer review was obtained.

Donation and use of embryos:

In the period from 1 January 2009 to 31 October 2010, the centre reported the use of 92 fresh embryos and 248 frozen embryos.

Regulatory principles

Focus

- **Protection of the embryo**
- **Good governance and record keeping**
- **Areas of concern** – No areas of concern were identified prior to the inspection

▶ 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. This principle was not inspected on this interim inspection
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. **Research and training (Guidance note 22)** The centre has a documented procedure for ensuring that embryos do not develop beyond 14 days (Licence Condition R28). An audit of a sample of laboratory records performed in the course of the inspection confirmed compliance with this requirement. Although the research centre is associated with a treatment centre, only two of the research staff have clinical roles. In discussion with the research staff they are aware of the need to separate their research and clinical roles. Centre staff confirmed that embryos are witnessed by two staff members when transferred to research and evidence of this was seen on inspection. Additionally, the inspectorate saw laboratory books during the inspection that demonstrated each embryo is uniquely labelled (Licence Condition R26). Embryos obtained for research cannot be used for another purpose (Licence Condition R23), or transferred back for treatment once they have been allocated to research. There is a facility monitoring system to record the conditions within the incubators. The laboratory cleaning rota was seen by the inspection team. Keypad locks and swipe card access were seen to be in place on doors to critical areas. Staff confirmed that records are kept securely.
What they could do better. No issues identified

▶ 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. **Research and training (Guidance note 22)** Frozen embryos that are no longer required by patients for treatment purposes may be donated to this research project. Patients are contacted as part of the donating centres' bring-forward systems prior to the expiry of the embryos' consented storage period. The "decision form" sent to these patients gives the option to either extend storage for treatment (where possible), allow to perish, donate to other couples for treatment or to donate to research. If patients choose to donate to the project, the research co-ordinator sends them the specific patient information and consent form related to this project. She speaks to the patients about the research, answers any questions and ensures the consent forms are completed. She will not have been involved in the patients' treatment (Licence Condition R22). Fresh embryos are only obtained from centre 0102. The research coordinator will answer any questions that patients have in relation to the research. The PR confirmed that the time between the patients receiving information about the research and being asked to give consent is generally between two and eight weeks.
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. **Research and training (Guidance note 22)** The research co-ordinator travels to the donating centres when the embryos are being transferred to research to compare the patient signatures in the records held at the donating centre and those on the consent to research. The PR confirmed at inspection that he is satisfied that the consenting procedures at the donating centres are robust. A sample of five records of consent were reviewed at inspection. All consents were present. There is a SOP to cover the need to check donor consents when the embryos have been created from donor gametes. The consented storage periods for embryos in store for research were checked and all embryos were seen to be stored within their consented storage periods (Licence Condition R36).
What they could do better. No issues identified

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.

Research and training (Guidance note 22)

The training file of one member of the team was seen. Training and competence assessments had been signed off.

Centre staff are aware of the requirement to report adverse incidents to the HFEA, although none have occurred since the last inspection.

An organisation chart is in place for the research centre and was provided to the inspection team.

Premises and facilities (Guidance note 25)

The inspection team considered the premises to be suitable for the activities carried out (Licence Condition R10). The premises were seen to have appropriate security measures, appropriate equipment, including monitoring and personal protective equipment, and appeared adequately resourced.

The research licence was displayed at the licensed premises (Licence Condition R4).

What they could do better.

No issues identified

Changes / improvements since the last inspection on 26 February 2009:

Area for improvement	Action required	Action taken
There was no procedure in place to ensure embryos are not cultured beyond 14 days.	Procedure to be put in place to ensure embryos are not cultured beyond 14 days.	A procedure was developed and provided to the inspectorate prior to the LC meeting on 20 May 2009.

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	Reference	Action required	Timescale for action	PR Response	Executive Review
None noted at this inspection					Email received from PR on 10 January 2011 stating: We are content with the reports.

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	Reference	Action required	Timescale for action	PR Response	Executive Review
None noted at this inspection					

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	Reference	Action required	Timescale for action	PR Response	Executive Review
None noted at this inspection					

Additional information from the Person Responsible

HFEA Executive Licence Panel Meeting

18 February 2011

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 1

Centre 0102 (Guy's Hospital) – Interim Inspection Report (Research R0075)

Members of the Panel:	Committee Secretary:
Peter Thompson, Director of Strategy & Information (Chair) Mark Bennett, Director of Finance & Facilities Nick Jones, Director of Compliance	Joanne McAlpine

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

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 Direction 0008 (where relevant), and any other relevant Directions issued by the Authority
- 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 was first licensed for this research project (R0075) in July 1994.

2. The Panel noted that the centre was last inspected on 26 February 2009 and a Research Licence Committee agreed to the renewal of the research licence in May 2009.

3. The Panel noted that the aim of this research project is for the improving methods for pre-implantation genetic diagnosis (PGD) of inherited genetic disease and predicting embryo quality.

4. The Panel noted the previous Research Licence Committee minutes of 20 May 2009.The Committee agreed at that time that none of the proposed activities were prohibited by the Act and that the Committee concluded that the research purposes for this project were both necessary and desirable.

5. The Panel noted that PGD has been offered at the centre for over ten years, and is one of the busiest and successful units in the country.

6. The Panel noted that during the period of 1 January 2009 and 31 October 2010, the centre reported 92 fresh embryos and 248 frozen embryos.

7. The Panel noted that there were no areas of non-compliance identified on the inspection, and noted the Inspectorate's recommendation for the continuation of the centre's licence in respect of this particular research project with no additional conditions.

8. The Panel noted that the Inspectorate is satisfied that the Person Responsible (PR) is suitable, the premises and practices are suitable and the centre has submitted the appropriate documentation in accordance with General Direction 0008.

Decision

9. The Panel agreed that there was a good history of compliance at the centre and that this research project appeared to be well run.

10. The Panel endorsed the Inspectorate's recommendation to the continuation of the centre's licence in respect of research project R0075, with no additional conditions.

Signed: Peter Thompson Date: 2/3/11.
Peter Thompson (Chair)