Human Fertilisation and Embryology Authority

Minutes of the Licence Committee

Meeting held at Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF on
7 May 2015

Minutes – item 1

Centre 0102 (Guys Hospital) – research renewal application, R0075

Members of the Committee:	Andy Greenfield (Chair, lay) Kate Brian (lay) Margaret Gilmore (lay) Anita Bharucha (lay)
Legal Adviser:	Dawn Brathwaite, Mills & Reeve
Members of the Executive:	Sam Hartley, Head of Governance and Licensing Trent Fisher, Secretary

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:

- licence renewal assessment
- licence renewal application form
- peer review
- previous Licence Committee minutes for the last three years
    - 26 June 2014 – research renewal update for project R0133
    - 7 March 2014 – interim inspection report for R0075
    - 17 July 2012 – renewal inspection report for R0075

The committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)

- HFEA decision trees
- 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

Background

1. Research project R0075 “Improving methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality” was first licenced in July 1994. The current licence is due to expire on 31 August 2015.

Discussion

2. The committee noted that, at the time of the desk-based inspection, which took place on 2 March 2015, there were no areas of practise requiring improvement.

3. The committee had regard to its decision tree. The committee was satisfied that the application was submitted in the form required and contained the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fees had been paid. The committee noted that the application was made by the Person Responsible (PR) for the research project.

4. The committee was satisfied that the PR possesses the required qualifications and experience and that the character of the PR is such as is required for supervision of the licensed activities. It was further satisfied that the PR will discharge his duties under section 17 of the Act. The committee noted that the inspectorate was satisfied that the PR had satisfactorily completed the PR entry programme.

5. The committee was satisfied that the premises to be licensed are suitable for the conduct of licensed activities as stated by the inspectorate.

6. The committee was satisfied that the renewed research licence would not apply to more than one research project and that the activities applied for, permitted under the Act, are ‘creation of embryos’, ‘keeping embryos’, ‘using embryos’ and ‘storing embryos’.

7. The committee noted that the use of human embryos is necessary because a main aim is to study processes during the development of the human embryo. This can only be fully achieved using human embryos.

8. The committee was further satisfied that the activities to be licensed are necessary or desirable for the following purposes, specified in schedule 2 paragraph 3A(1) and 3A(2) of the Act, for the following reasons:

    - *Increasing knowledge about serious disease or other serious medical conditions:*
      This is addressed by proposed studies on epigenetics and on genomic imbalances in the early human embryo, which aim to increase understanding of pre-implantation processes in relation to later development of disease.
    - *Increasing knowledge about the causes of congenital disease or congenital medical conditions:*
      This is addressed by proposed studies on the genetics of early embryos, including the impact of genomic imbalances and mitochondrial DNA mutations and how these can modify the phenotypic spectrum of congenital disease.
    - *Promoting advances in the treatment of infertility:*
      This is to be addressed by studies on assessment of embryo quality, for example, by possible positive effects on human embryo quality from exposure to triiodothyronine (a thyroid hormone). A further aim is to develop better strategies for embryo culture and testing during IVF.
    - *Increasing knowledge about the causes of miscarriage:*
      This is addressed by the use of live imaging of embryo development (embryoscopy) with the objective of correlating early embryo development with implantation and pregnancy loss.
    - *Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation:*
      This is addressed by developing new PGD methodology for detecting genetic abnormalities, particularly for de novo mutation carriers and couples where family members are unavailable or uninformative.
    - *Increasing knowledge about the development of embryos:*
      This is addressed by molecular analyses of early human embryos. The analyses include the construction of molecular-level databases, i.e. collecting microRNA and related transcriptomic profiles of ICM and TE development in normal embryos.

9. The committee was satisfied that the proposed project does not involve the mixing of sperm with the egg of an animal.

10. The committee was satisfied that the inspectorate had previously seen the patient information and consent forms and that these met the statutory requirements.

11. The committee was satisfied that the research project had received the necessary level of research ethics approval required for the project.

12. The committee noted that the recommendation from the inspectorate to renew the centre's research licence for a period of three years without any additional conditions.

Decision

13. The committee agreed to renew the research licence for project R0075 for a period of three years with no additional conditions.

14. The licenced activities are:
    - creation of embryos
    - keeping embryos
    - using embryos
    - storing embryos

Signed: Date: 20 May 2015

Andy Greenfield (Chair)

Research Renewal Report: Desk based assessment

Purpose of this inspection report:
The HFEA licenses and monitors establishments undertaking human embryo research. This is a report of an evaluation of whether this centre complies with essential requirements when carrying out such research. Licences for individual research projects can be granted for up to three years and this report provides information on the centre's application for a renewal of its existing licence. The Authority's Licence Committee uses the application and this report to decide whether to grant a new licence and, if so, whether any additional conditions should be applied to that licence.

Date of assessment: 2 March 2015

Purpose of assessment: Renewal of a licence to carry out research

Inspector: Dr Vicki Lamb

Assessment details:
The report covers the performance of the centre since the last inspection, findings from the desk based evaluation, and communications received from the centre. For this assessment, an inspector completed a robust desk-based evaluation of appropriate documentation. There was no site visit.

Date of Licence Committee: 7 May 2015

Centre Details:

Project title	Improving methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality
Centre name	Guys Hospital
Centre number	0102
Research project 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 (PR)	Dr Dusko Ilic
Licence Holder	Mr Yacoub Khalaf
Treatment centres donating to this research project	Sussex Downs Fertility Centre (0015) Herts and Essex Fertility Centre (0030) BMI Chelsfield Park ACU (0086) Bourn Hall Clinic (0100) The Woking Nuffield Hospital (0144) Chelsea and Westminster Hospital (0158) Salisbury Fertility Centre (0197) South East Fertility Clinic (0208)

Date licence issued	1 September 2012
Licence expiry date	31 August 2015
Additional conditions applied to this licence	None

Contents

Section 1: Summary report

Brief description of the centre and its licensing history:

Centre 0102 is a treatment and research centre. The current research project, entitled “Improving methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality” (R0075), was first licensed in July 1994.

The current licence is due to expire on 31 August 2015, having been renewed for three years by a Research Licence Committee (RLC) on 17 July 2012, and last inspected on 17 December 2013. There are no additional conditions on the licence.

Summary for licensing decision:

Taking into account the essential requirements set out in the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended), the HF&E Act 2008 and the HFEA Code of Practice (CoP), the inspection team considers that it has sufficient information to conclude that:

Administrative requirements:

- the centre has submitted an appropriately completed application form;
- the centre has submitted the supporting information required by General Directions 0008;
- the application has designated an individual to act as the Person Responsible (PR);
- the proposed licence applies to one project of research;
- the centre has submitted fees to the HFEA in accordance with requirements.

Research activities applied for:

An application has been made for the following activities for the purpose of research:

- creation of embryos in vitro
- keeping embryos
- storage of embryos
- use of embryos

The project does not involve the derivation of human embryonic stem cell lines for human application. Research Licence Conditions R41-89 are therefore not applicable to this research project.

Purposes for which research activities may be licensed:

The research project is currently licensed for the following purposes:

- increasing knowledge about serious disease or other serious medical conditions;
- increasing knowledge about the causes of congenital disease or congenital medical conditions;
- promoting advances in the treatment of infertility;
- increasing knowledge about the causes of miscarriage;
- developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation;
- increasing knowledge about the development of embryos.

The PR and peer reviewer consider that the research project will meet the purposes defined in Schedule 2 3A (1) and (2) of the HF&E Act 1990 (as amended) as follows:

- increasing knowledge about serious disease or other serious medical conditions

  The PR has stated that the proposed research addresses the purpose by:
  'Investigation of the epigenetics of early embryos to understand the relationship between IVF processes and imprinting abnormalities leading to diseases such as Angelman syndrome, Beckwith-Wiedemann syndrome and Russell-Silver Syndrome.'

  The peer reviewer agrees and has stated:
  'This is addressed by proposed studies on epigenetics and on genomic imbalances in the early human embryo, aiming to increase the understanding of pre-implantation processes in relation to later development of disease.'

- increasing knowledge about the causes of congenital disease or congenital medical conditions

  The PR has stated that the proposed research addresses the purpose by:
  'Understanding how genomic imbalances and mitochondrial DNA mutations modify phenotypic effects of congenital disease.'

  The peer reviewer agrees and has stated:
  'This is addressed by proposed studies on genetics of early embryos, i.e. on genomic imbalances and mitochondrial DNA mutations and how these can modify phenotypic effects of congenital disease.'

- promoting advances in the treatment of infertility

  The PR has stated that the proposed research addresses the purpose by:
  'We are assessing effects of triiodothyronine on quality of embryos. We are also validating quality of embryos obtained using splitting embryos methodology.'

  The peer reviewer agrees and has stated:
  'This is to be addressed by studies on assessment of embryo quality, e.g. by possible positive effects on human embryo quality from exposure to triiodothyronine (a thyroid hormone). A further aim is to develop better strategies for embryo culture and testing during IVF.'

- increasing knowledge about the causes of miscarriage

  The PR has stated that the proposed research addresses the purpose by:
  'Use of embryoscopy to correlate early embryo development with implantation and pregnancy loss.'

  The peer reviewer agrees and has stated:
  'This is addressed by the use of embryoscopy with the objective to correlate early embryo development with implantation and pregnancy loss.'

- developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation

  The PR has stated that the proposed research addresses the purpose by:

‘Developing new PGD methodology for detecting genetic abnormalities, particularly for de novo mutation carriers and couples where family members are unavailable or uninformative.’

The peer reviewer agrees and has stated:
‘The applicants propose to “continue developing new PGD methodology” ..,“particularly for de novo mutation carriers and couples where family members are unavailable or uninformative”.’

- Increasing knowledge about the development of embryos

The PR has stated that the proposed research addresses the purpose by:
‘We are assessing effects of triiodothyronine on quality of embryos. We are also validating quality of embryos obtained using splitting embryos methodology.’

The peer reviewer agrees and has stated:
‘This is addressed by molecular analysis of early human embryos. The analysis includes the building of molecular level databases, i.e. collecting microRNAs and transcriptomics profile of ICM and TE from normal embryos.’

Prohibited research activities:
The activities to be licensed are not prohibited by the HF&E Act 1990 (as amended) including those activities specifically prohibited by Sections 3, 3ZA, 4 or 4A, or by Schedule 2, paragraph 3 of the Act.

Use of embryos:
The use of human embryos is considered necessary. This is based on the application and comments by the peer reviewer:
‘A main aim is to study processes during the development of the human embryo. This can only be fully achieved using human embryos.’

The PR wishes to create embryos in vitro by splitting. He wishes to use this technique to decrease the demand for embryos, particularly in the validation of new media or laboratory techniques. One of the genetically identical split embryos can be used as a control, with the other being cultured under test conditions. This splitting approach provides a means of avoiding the misinterpretation of results that are not due to the test environment but are attributable to the different genetic features of embryos. Using the splitting technique would mean that a smaller number of embryos are required to obtain statistically meaningful data.

The PR holds another research project licence at this centre, and a Licence Committee of 26 June 2014 agreed to retain creation of embryos on the renewed licence for that project as the PR wished to create embryos by splitting for similar reasons to those for this project.

The peer reviewer also supports the activity of ‘creation of embryos in vitro’, stating: *‘The applicants also wish to introduce splitting embryos methodology to decrease the demand of embryos, particularly in validation of new media or laboratory techniques. If successful, this could hypothetically reduce the numbers of embryos needed in later follow up projects. Alternatively, it is possible that successful development and testing of twinned embryos could enhance the efficacy of future studies.’*

PR considerations:
The PR is suitable and has discharged his duty under Section 17 of the HF&E Act 1990 (as amended).

Premises:
The premises are considered suitable. This is based on information submitted with this application, and the previous inspection visit in December 2013.

Recommendation:
The Licence Committee is asked to note that at the time of the assessment there were no areas of practice that required improvement:

The inspector recommends the renewal of the centre's licence for a period of three years without additional conditions.

The inspection team recommends that the licence issued should include the following activities that the centre has applied for:

- creation of embryos in vitro
- keeping embryos
- use of embryos
- storage of embryos

For the following purposes:

- increasing knowledge about serious disease or other serious medical conditions
- increasing knowledge about the causes of congenital disease or congenital medical condition
- promoting advances in the treatment of infertility
- increasing knowledge about the causes of miscarriage
- developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- increasing knowledge about the development of embryos

Section 2: Summary of the research project

This section summarises information submitted in the research licence application.

Lay summary of the research project:

Understanding fully the molecular events during implantation is necessary in order to manipulate them in a creative way, developing translational strategies to improve implantation rates and lead to higher pregnancy rates in assisted conception procedures. The researchers will continue to build molecular level databases on normal development of preimplantation embryos. Over the past 50 years steady progress in improving mammalian embryo culture media has been achieved, however current culture media still remains sub-optimal. To decrease the number of embryos used in validation of new media or techniques, the researchers intend to introduce an embryo-splitting technique. If successful, they will be able to obtain genetically identical twin embryos. One of them can be used as a control, whereas other can be cultured under new conditions. In such a way, they will avoid genetic background bias that can lead to misinterpretation of the data and that increases the number of embryos needed to validate the process. If the researchers can prove that the technique yields embryos of a quality indistinguishable from non-manipulated embryos, other researchers may also wish to adopt the same practice, particularly in the validation of new media or laboratory techniques.

Objective of the research:

The researchers wish to continue to improve their PGD and IVF programmes by introducing and developing better strategies and protocols for embryo culture and testing. They also wish to understand more about the biology and genetics of early human embryos.

Summary of the research undertaken to date:

With their Italian partners the researchers have developed a technique of mechanical separation of inner cell mass (ICM) from trophectoderm (TE). Using expertise in single cell analysis they have started building mRNA, transcriptomics, and methylation profile ICM and TE databases from normal embryos. Understanding fully the molecular events during implantation is necessary in order to manipulate them in a creative way, developing translational strategies to improve implantation rates and lead to higher pregnancy rates in assisted conception procedures.

Work last year concentrated on developing and improving methodologies for culturing and testing early embryos. This work involved the use of 142 frozen embryos.

Donation and use of embryos:

In the period from 1 January 2014 to 31 December 2014, the centre reported the use of 142 frozen embryos. The PR estimates that 150 frozen embryos will be used in each year of the renewed licence.

Section 3: Details of the assessment findings

Principle:

3. Have respect for the special status of the embryo when conducting licensed activities.

What we inspected against:

Research Licence Conditions (RLC) R23, R24, R26, R27, R28, R29, CoP Guidance Note 22.

What the centre does well.

Observations during the last inspection in December 2013 provided assurance that the special status of the human embryo would be respected:

- processes, documented in Standard Operating Procedures (SOPs), were in place to ensure that no embryo obtained for the purposes of the research project would be kept or used for any purpose other than the purposes of the research project (RLC R23).
- recruitment practices ensured that no money or other benefit would be given to those donating embryos to research unless authorised by directions (RLC R24).
- each embryo used in the research project was uniquely labelled (RLC R26)
- documented procedures had been established to ensure that clinical and research roles are separated (RLC R27).
- procedures had been established to ensure that embryos would not develop after 14 days or the primitive streak has appeared (if earlier) (RLC R28).

What they could do better.

Nothing noted.

Principle:

5. Provide prospective and current patients and donors with sufficient, accessible and up-to-date information in order to allow them to make informed decisions.

6. Ensure that patients and donors have provided all relevant consents, before any licensed activity is undertaken.

What we assessed against:

Information, counselling and consent; CoP Guidance Note 22, RLCs R18, R19, R20, R22.

What the centre does well.

Provision of information and counselling to those consenting to donate to research

Patient information and consent forms were inspected at the last inspection in December 2013 and were assessed as being compliant. The PR has confirmed that the forms have not changed since that time. This provides assurance that;

- prior to giving consent, those donating to research are given a suitable opportunity to receive proper counselling about the implications of their donation (RLC R18);
- necessary information is provided to patients prior to giving their consent (RLC

R19);

- a designated individual, who is not directly involved in the patient's treatment, is available to discuss with the patient the project of research and the possibility of donating material to the project (RLC R22). Contact details for this designated individual are provided in the patient information.

Consent for storage

Stored embryos are obtained only from centres to which a HFEA licence applies (RLC R33). The PR confirmed that no embryos are kept in storage for longer than the consented storage period

What they could do better.

Nothing noted.

Principle:

8. Ensure that all premises, equipment, processes and procedures used in the conduct of licensed activities are safe, secure and suitable for the purpose.

What we assessed against:

Premises and facilities; RLC R10

What the centre does well.

Premises and facilities

The premises are suitable for carrying out the licensed activities (RLC R10). This conclusion is based on the centre's SAQ and the last research inspection visit in December 2013.

What they could do better.

Nothing noted.

Principle:

10. Maintain proper and accurate records and information about all licensed activities

What we inspected against:

Information and record keeping; RLC R14, General Directions 0002.

What the centre does well.

The PR has provided all necessary information requested during this assessment within the required timescales. Fully completed research information and data sheets have been submitted to the HFEA within the prescribed timescales in 2014 and 2015 (RLC R14 and General Directions 0002).

What they could do better.

Nothing noted.

Principle:

11. Report all adverse incidents (including serious adverse events and reactions) to the HFEA, investigate all complaints properly, and share lessons learned appropriately

What we inspected against:

Incidents; RLC R40.

What the centre does well.

Processes are in place to detect, report to the HFEA and investigate adverse incidents (RLC R40).

What they could do better.

Nothing noted.

Principle:

12. 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.

What we assessed against:

HF&E Act 1990 (as amended), Schedule 2 (3(5) and 3A).

What the centre does well

The research project has been approved by the National Research Ethics Service Committee London – Westminster (formerly St Thomas' Ethics Committee). Evidence was provided by the PR that this approval remains active and covers the research activity described in the licence application.

The research project does not include any activities that have been prohibited by the HF&E Act 1990 (as amended).

A peer review was obtained for this renewal application and it is supportive of the licence renewal. Justifications that the activities to be licensed are necessary or desirable to meet the statutory purposes, have been provided by the PR and the peer reviewer, as discussed in detail in the 'Summary for Licensing Decision'. The PR and peer reviewer have also provided reasons why the use of human embryos is necessary. Overall, the peer reviewer has agreed that it would be appropriate to carry out the proposed research.

What they could do better.

Nothing noted.

Principle:

13. 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;
- co-operating fully with inspections and investigations by the HFEA or other agencies responsible for law enforcement or regulation of healthcare.

What we inspected against:

Licensing; RLCs R1, R3. The Person Responsible; HF&E Act 1990 (as amended) Section 16 & 17, RLC R8.

What the centre does well.

Licensing

Information obtained at the last inspection, a review of the SAQ and discussions with the PR confirm that all licensed research activities will be performed only at the licensed premises under the supervision of the PR (RLC R1). The PR provided all information requested in support of this inspection within the required timescales (RLC R3).

The Person Responsible

The PR has a key role to play in implementing the requirements of the HF&E Act 1990 (as amended) and is the person under whose supervision the licensed activities are authorised. The PR has the primary legal responsibility under Section 17 of the HF&E Act 1990 (as amended) to secure:

- that suitable practices are used in undertaking the licensed activities;
- that other persons working under the licence are suitable and;
- that the conditions of the licence are complied with.

The PR is suitable and has discharged his duty under Section 17 of the HF&E Act 1990 (as amended) and RLC R8. This conclusion is based on the centre's SAQ and on-going monitoring by the inspectorate that indicates that there are no outstanding non-compliances associated with the research project.

The PR has suitable qualifications and experience for the activity authorised by the licence (HF&E Act 1990 (as amended), Section 16 (2)(ca)). The PR has successfully completed the HFEA PR Entry Programme (PREP number R/ 1184/8).

What they could do better.

Nothing noted.

Section 4: Monitoring of the centre's performance

Following an interim inspection in December 2013 no recommendations for improvement were made.

Section 5: 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 areas 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 and reference	Action required and timescale for action	PR Response	Executive Review
None			

Major areas 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 and reference	Action required and timescale for action	PR Response	Executive Review
None			

‘Other’ areas of practice that requires improvement

Other areas of practice that require 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 and reference	Action required and timescale	PR Response	Executive Review
None			

Additional information from the Person Responsible
Thank you for the renewal assessment. Nothing to add.