Research Interim Inspection Report

Date of Inspection: 16 January 2013
Purpose of inspection: Interim Inspection of Research Licence
Length of inspection: 5 hours
Inspectors: Vicki Lamb

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 23 November 2010 and 29 March 2013.

Date of Executive Licensing Panel: 12 April 2013

Centre details

Project Title	Developing criteria for estimating quality of stem cells derived from human embryos
Centre Name	Guys Hospital
Centre Number	0102
Research licence Number	R0133
Centre Address	Stem Cell and Embryology Research Laboratories, Assisted Conception Unit, 11th Floor Tower Wing, Guy's Hospital, London, SE1 9RT
Person Responsible	Dr Dusko Ilic
Licence Holder	Mr Yacoub Khalaf
Treatment centres donating to this research project	Lister Fertility Clinic (0006) Sussex Downs Fertility Centre (0015) Herts and Essex Fertility Centre (0030) BMI Chelsfield Park ACU (0086) The Woking Nuffield Hospital (0144) Chelsea and Westminster Hospital (0158) Salisbury Fertility Centre (0197) South East Fertility Clinic (0208)
Date Licence Issued	1 May 2011
Licence expiry date	30 April 2014
Additional conditions applied to this licence	None

Doc name: R0133 interim inspection
TRIM reference: 2013/001753

Contents

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 Human Fertilisation and Embryology (HF&E) Act 1990 (as amended) and the Code of Practice (CoP) and that progress is made towards achieving the stated aims of the project. The report summarises 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 (ELP) which makes the decision about the centre's licence.

Report to Executive Licensing Panel

Brief description of the centre and its licensing history:

Guy's Hospital has held this HFEA research licence since April 2002. The licence was last inspected on 23 November 2010 and a Research Licence Committee agreed to the renewal of the research licence in March 2011.

The Executive Licensing Panel agreed to a change of Person Responsible (PR) in April 2011, due to the retirement of the previous PR. The current PR has completed the HFEA Research PR Entry Programme.

Title of research project:

Developing criteria for estimating quality of stem cells derived from human embryos

Summary for licensing decision:

In considering overall compliance, the inspection team considers there is sufficient information drawn from documentation submitted by the centre prior to inspection and from observations and interviews conducted during the inspection visit to draw a conclusion on the continuation of the centre's licence.

The Executive Licensing Panel is asked to note that at the time of the inspection there was one critical area of non-compliance.

Since the inspection visit the PR has provided evidence that the recommendation has been fully implemented:

Critical area of concern:

- **The PR must ensure that embryos are not stored for longer than the consented storage period. The PR should ensure that this is clarified in standard operating procedures (SOPs) and that all staff are aware of this requirement. The PR should send revised copies of the relevant SOPs to the inspector.**

Recommendation to the Executive Licensing Panel:

The inspection team considers that overall there is sufficient information available to recommend the continuation of this centre's licence without additional conditions. In making this recommendation it is noted that the PR has responded to all recommendations made in this inspection report.

Summary of project

Lay summary of the research project:

Stem cells are unique cells that are able to copy themselves exactly and also specialise into new cell types. The most powerful human stem cells, termed human embryonic stem cells (hESC), can be isolated from the earliest stages of human development. They have great potential in: a) regenerative medicine, b) studying disease progression, c) the search for new drugs. At Guys Hospital, hESC lines are derived from embryos made available following IVF or from preimplantation genetic diagnosis (PGD) treatment cycles undertaken to avoid transmitting a known genetic disease.

(i) Lines with clinically relevant mutations:
So far 22 lines have been derived carrying clinically relevant genetic mutations derived from affected embryos following PGD. These include cystic fibrosis (4 lines: KCL-003, 021, 042, 043), Huntington's disease (7 lines: KCL-005, -008, -012, -013, -027, -028, -036), myotonic dystrophy type 1 (1 line: KCL-018), neurofibromatosis type 1 (2 lines: KCL-024, -025), spinal muscular atrophy type 1 (1 line: KCL-026), Von Hippel-Lindau cancer syndrome (3 lines: KCL-015, -016, -017), beta-thalassemia (1 lines: KCL-035), beta-thalassemia carrier (1 line: KCL-030), Wiskott-Aldrich syndrome and cystic fibrosis carrier (1 line: KCL-029), and Turner Syndrome (1 line: KCL-041).

(ii) Clinical grade lines:
The researchers have derived and characterised 8 clinical grade lines, which have been deposited into the UK Stem Cell Bank (UKSCB). Two lines, KCL-033 and KCL-034 were processed for further validation that is required for cells designated for use in therapy.

Objectives of the research:

The primary objective of the research is to adapt rapid throughput technology to perform comprehensive quantitative assessments requisite for the establishment of normal and disease-specific cell line identity.

This is a cross-disciplinary biotechnology approach that has not previously been applied to the study of either human embryonic stem cells (hESC) or induced pluripotent stem cells (iPSC), and which will significantly facilitate the use of these cells by researchers in academia and particularly by end-users in industry and the commercial sector.

Human embryonic stem cells not only differ from animal derived stem cells, but they also seem to be dissimilar from induced pluripotent cells (adult cells). Furthermore and most importantly, human cell lines may differ from each other, and individual clones derived from any one inner cell mass may also differ significantly. This requires specifically the use of human embryos if the origin of this variation in human stem cells is to be understood, and will

need to use embryonic stem cells that have features that can be well characterised. If the researchers are successful with this novel methodology and technology, its application will be made accessible to the international research community and commercial sector whilst retaining the IP rights in the UK.

To achieve this objective the researchers intend to:

- Optimise protocols for array comparative genomic hybridization to be able to identify chromosomal imbalance and submicroscopic copy number variants in hESC and iPSC.
- Develop methods for using automated fluorescence microscopy combined with single cell image analysis to quantitatively assess self-renewal capability.
- Generate robust protocols to use dynamic array integrated fluidic platforms to determine differentiation propensity.

This biotechnological approach will result in the UKSCB being supplied with lines with detailed and robust characterisation, which will facilitate and accelerate the banking process, accelerating the rate at which cells can be made available to end users. In addition, as the complete cell line identity profile will be made available with the cells through the UKSCB, the end users will be able to select the most appropriate line for their application, thus improving efficiency and streamlining the route to manufacturing therapeutics.

Donation and use of embryos:

In the period from 1 January 2012 to 31 December 2012, the centre reported the use of 8 fresh embryos and 20 frozen embryos.

Details of inspection findings

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
(Guidance note 29, 30, 31)

What the centre does well.

The renewal of research licence R0133 was granted by a Research Licence Committee on 22 March 2011.

The peer reviewer for the renewal application agreed that the use of human embryos is necessary and justified for the proposed research and that the same results could not be obtained with adult stem cells or induced pluripotent stem cells.

Evidence of approval by an ethics committee was provided at the last licence renewal.

The activities licensed under project R0133 are the creation, use, keeping and storage of embryos. The renewal of the licence was approved to allow research for the following designated purposes:

- 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)
- Increasing knowledge about the causes of congenital disease or congenital medical conditions
  HFE Act 1990 (as amended) Schedule 2 3A(2)(c)
- Promoting advances in the treatment of infertility
  HFE Act 1990 (as amended) Schedule 2 3A(2)(d)
- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
  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)

Specific stem cell lines requested by the UKSCB have been deposited in the bank (Research Licence Condition (RLC) R30).

Quality indicators have been established (RLC R64) and audits undertaken (RLC R65).

Written agreements have been established with third parties (RLC R78) and evaluations of these third parties have been undertaken (RLC R79). Three third party agreements were audited during the inspection and all three were compliant with RLC R81.

What they could do better.

Nothing noted.

Have respect for the special status of the embryo when conducting licensed activities
(Guidance note 15, 18, 22, 25, 26)

What the centre does well.

The centre has a documented procedure for ensuring that embryos do not develop beyond 14 days or the primitive streak has appeared (if earlier) (RLC R28). An audit of a sample of ten laboratory records performed in the course of the inspection confirmed compliance with this requirement.

Review of centre documentation and an audit of ten sets of records demonstrated that:

- Comprehensive records of the embryos used in the research project, from donation to the project through to disposal at the end of the research process are maintained (RLC R13).
- Embryos are used for the purposes authorised by this licence (RLC R5 and R23).
- Embryos are used within the consented storage period (RLC R39) except as detailed below.

The PR has ensured that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA (General Direction 0002 and RLC R13, R14 and R15).

What they could do better.

In one case three embryos were thawed and used for research four days outside the consented storage period (HF&E Act 1990 (as amended) Schedule 3, 8(1) and RLC R39).

Changes / improvements since the last inspection on 23 November 2010:

Area for improvement	Action required	Action taken as evidenced during this inspection
No improvements were required at the last inspection.		

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 and reference	Action required and timescale for action	PR Response	Executive Review
In one case three embryos were thawed and used for research four days outside the consented storage period ((HF&E Act 1990 (as amended) Schedule 3, 8(1) and RLC 39).	The PR must ensure that embryos are not stored for longer than the consented storage period. The PR should ensure that this is clarified in SOPs and that all staff are aware of this requirement. The PR should send revised copies of the relevant SOPs to the inspector. This recommendation should be implemented immediately.	In order to emphasise importance of following the rule that embryos should not be kept longer than the consented storage period, a new SOP has been written (Use of embryos donated for research) with clearly outlined responsibilities. The SOP has been effective since 15 Feb 2013	The SOP entitled 'Use of embryos donated for research' has been provided to the inspector. The SOP makes it clear that embryos should not be used after their consented storage period. No further action required.

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 and reference	Action required and timescale for action	PR Response	Executive Review
None noted.			

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 and reference	Action required and timescale for action	PR Response	Executive Review
None noted.			

Additional information from the Person Responsible

HFEA Executive Licensing Panel Meeting

12 April 2013

Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF

Minutes – Item 1

Centre 0102 – (Guys Hospital) – Interim Research Inspection Report

Members of the Panel:	Committee Secretary:
Juliet Tizzard – Head of Policy and Communications (Chair) Rachel Hopkins – HR Manager Ian Peacock – Analyst Programmer	Rebecca Loveys

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 has held a licence for research project R0133 since April 2002.

2. The Panel noted that the centre's current research licence was issued 1 May 2011 and is due to expire 30 April 2014.

3. The Panel noted the Project Title, 'Developing criteria for estimating quality of stem cells derived from human embryos'.

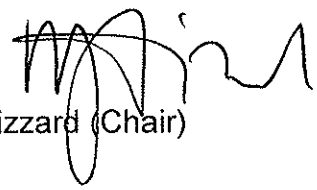
4. The Panel noted that for the year 2011 the centre reported 81 cycles of IUI with 17 pregnancies, which equates to a 21% clinical pregnancy rate and is in line with the national average.

5. The Panel noted that, during the inspection, the Inspectorate identified one critical area of non-compliance only, relating to embryos being stored beyond the consented storage period.

6. The Panel noted that the Person Responsible addressed this critical area of non-compliance quickly and to the satisfaction and recommendations of the inspectorate.

Decision

7. The Panel agreed to the Inspectorate's recommendation to continue the centre's licence with no additional conditions.

Signed: 
Juliet Tizzard (Chair)

Date: 18 April 2013