Human Fertilisation and Embryology Authority

Minutes of the Executive Licensing Panel

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

Minutes – item no. 3

Centre 0017 (Newcastle Fertility Centre at Life) – Interim Inspection Report – Research Project R0152

Members of the Panel:	Juliet Tizzard Director of Strategy & Corporate Affairs (Chair) Joanne Anton Policy Manager Paula Robinson Head of Business Planning
Members of the Executive in attendance:	Sam Hartley Head of Governance & Licensing Dee Knoyle Committee Secretary

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

The panel had before it:

- HFEA protocol for the conduct of meetings of the 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 the 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 the publication of Authority and committee papers

Consideration

1. The panel noted that research project R0152 is carried out at centre 0017, Newcastle Fertility Centre at Life research laboratory. The current research project entitled ‘Towards improving assisted reproductive technologies for the treatment of infertility and prevention of disease’ has been licensed by the HFEA since August 2004.

2. The panel noted that all licensed material used in the project is obtained from centre 0017, Newcastle Fertility Centre at Life treatment and storage centre which is located within the same unit and The Gateshead Fertility Unit (0170)

3. The panel noted that the current licence is due to expire on 31 July 2017.

4. The panel noted that at the time of the inspection on 26 February 2015, one major and one other area of non-compliance were identified.

5. The panel noted the Inspectorate's recommendation for the continuation of the centre’s research licence with no additional conditions.

Decision

6. The panel endorsed the Inspectorate's recommendation to continue the centre’s research licence, with no additional conditions.

Signed: Date: 3 June 2015

Juliet Tizzard (Chair)

Research Interim Inspection Report

Date of Inspection: 26 February 2015
Purpose of inspection: Interim inspection of a research licence
Length of inspection: 5 hours
Inspectors: Dr Douglas Gray (lead), Ms Lesley Brown

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 30/01/2015 and 26/02/2015.

Date of Executive Licensing Panel: 22 May 2015

Centre details

Project title	Towards improving assisted reproductive technologies for the treatment of infertility and prevention of disease.
Centre name	Newcastle Fertility Centre at LIFE
Centre number	0017
Research licence number	R0152
Centre address	Bioscience Centre, International Centre for Life, Times Square, Newcastle upon Tyne, NE1 4EP
Person Responsible (PR)	Dr Meena Choudhary
Licence Holder	Dr Mary Herbert
Treatment centres donating to this research project	Newcastle Fertility Centre at Life (0017), The Gateshead Fertility Unit (0170)
Date licence issued	01/08/2014
Licence expiry date	31/07/2017
Additional conditions applied to this licence	None

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 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 which makes the decision about the centre's licence.

Report to Executive Licensing Panel

Brief description of the centre and its licensing history:
The Newcastle Fertility Centre is based within the International Centre for Life. The research laboratory is located within the same unit as the treatment and storage centre. Research project R0152 has been licensed since August 2004.

The project is authorised for the following activities:

- Creation of embryos in vitro
- Keeping embryos
- Storage of embryos
- Using embryos

These activities are authorised for the following purposes:

- Increasing knowledge about serious disease or other serious medical conditions
- Developing treatments for serious disease or other serious medical conditions
- Increasing knowledge about the causes of any 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

The licence was last renewed in August 2014 following a desk based assessment. In November 2014 Dr Alison Murdoch stood down as the PR and Dr Meena Choudhary was appointed.

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 major non-compliances and one 'other' recommendation for improvement;

Major non-compliances:

- The PR should ensure that activities authorised by licence R0152 only take place on the premises specified on that licence.

'Other' recommendations for improvement:

- The PR should audit the database used to manage their bring-forward system against the terms of consent as specified in consent forms to assure that there are no errors.

All embryos donated to the project have been used for the objectives authorised by the licence to meet the defined statutory purposes.

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.

Summary of project

This section presents information submitted by the PR in the licence renewal application and the Research Information and Data Sheet for 2014.

Lay summary of the research project:

'The focus of our research is to extend the scope of assisted reproductive technologies (ART) to prevent transmission of mitochondrial DNA (mtDNA) disease and to improve outcomes of ART for the treatment of infertility. During the next three years, we propose to pursue the following aims.

(1) Develop new clinical treatments to minimise transmission of mtDNA mutations from a mother to her child. This part of the research programme will build on previous work in which we demonstrated that it is technically feasible to transfer nuclear genetic material, contained in pronuclei, between fertilised human eggs. We propose to further optimise and test the safety of pronuclear transfer between fertilised eggs. We will also test the efficacy of an alternative procedure known as meiosis II spindle transfer in which the nuclear genome is transferred between unfertilised eggs.

(2) Improve the outcome of infertility treatments through gaining a better understanding of the cellular and molecular events occurring during pre-implantation development in vitro, and to determine how these are affected by the routine laboratory procedures.

(3) Investigate the pathways leading to chromosomal abnormalities in eggs and embryos. We hope that these investigations will help us to better understand the mechanisms underlying chromosomal abnormalities in eggs of older women.'

Objectives of the research:

'Objective1. To develop new clinical treatments to minimise transmission of mtDNA mutations. Mutations in mtDNA can cause a range of fatal and debilitating diseases. Reports from our lab (Craven et al, 2010, Nature: 465) and others (Tachibana et al, 2013, Nature:493) indicate that inheritance of mtDNA can be uncoupled from inheritance of nuclear DNA by transplanting the nuclear genome between eggs. This can be done either before fertilisation by transplanting the meiosis II spindle (MST) and its associated chromosomes, or after fertilisation by transplanting the pronuclei (PNT) between fertilised eggs. The latter approach has been the major focus of our research to date. Our ongoing work aims to optimise PNT procedure and to test the efficacy of MST. Our primary objective is to maximise the production of good quality blastocysts and to perform a range of studies, including chromosomal analysis and gene expression studies, to compare PNT blastocysts with unmanipulated controls. We will also test the effect of PNT/MST on cell cycle and reprogramming events during the earliest stages of development. In accordance with the recommendations of the HFEA Expert Panel, we will generate ESC lines to compare those derived PNT/MST blastocysts with controls. These lines will also be used to investigate the fate of karyoplast-associated mtDNA. While our proof of concept work on PNT was conducted using abnormally fertilised eggs, these have a limited potential for onward development, and are therefore of limited value in our endeavours to further optimise and test the safety of PNT. Thus, progress towards clinical treatments requires a supply of oocytes donated and fertilised specifically for this research project. Where possible, we will use mouse zygotes to develop

and perform initial tests of experimental techniques. However, there are species differences and any meaningful tests of safety and efficacy require the use of human oocytes and zygotes.

Objective 2. To improve the outcome of infertility treatments through gaining a better understanding of the cellular and molecular events occurring during pre-implantation development in vitro, and to determine how these are affected by the routine laboratory procedures of assisted reproductive technologies. Recent advances in our understanding of how key developmental events are regulated during the pre-implantation period make it possible to perform more in depth analysis of embryo quality than was previously possible. We believe that the application of these advances to assess the effect of laboratory interventions will contribute to improved treatment outcomes. A primary focus of this part of our research is to optimise blastocyst vitrification with a view to maximising the efficiency of our blastocyst transfer programme. Our work to date indicates that the vitrification/warming procedures induce loss of cell viability in blastocysts but not in cleavage stage embryos. We therefore propose to test a number of modifications to blastocyst vitrification procedures. We also propose to further optimise the techniques of oocyte vitrification. While our results on oocyte survival are encouraging, the development of blastocysts from vitrified oocytes is variable between patients. It is not clear whether this is a consequence of biological or technical factors. We therefore propose to extend our studies on oocyte vitrification. This work will strengthen the evidence base for our own fertility preservation programme and will be valuable to the wider research and clinical community. Reliable methods for oocyte vitrification are also key to the success of the work outlined in Objective 1. The oocyte vitrification studies will require donation and fertilisation of oocytes specifically for research purposes. There is no realistic alternative to performing these experiments on human oocytes. To maximise the use of donated oocytes, we will design experiments in which oocytes included in this study can be used as controls for work outlined in Objective1.

Objective 3. Investigation of molecular and genetic events leading to formation of normal oocytes and embryos. This part of our research is focussed on understanding the mechanisms underlying meiotic chromosome segregation errors. Using mouse oocytes we have shown that female ageing is accompanied by depletion of the chromosome-associated protein complex known as cohesin (Lister et al, Current Biology, 2010). Cohesin is a conserved protein complex, which clamps sister chromatids together from the time of DNA replication until they segregate to daughter cells during cell division. Cohesin is required to maintain the unique chromosome structure required for normal segregation during the meiotic divisions. In this project, we will test the clinical significance of these findings by comparing cohesin levels between oocytes from young and older women. A greater understanding of the mechanistic basis underlying the association between female age and oocyte aneuploidy will provide insights into the possibility of developing intervention strategies to improve reproductive outcomes in older women. For these experiments we require immature oocytes (GV stage and MI oocytes) from consenting women undergoing ICSI treatment. These will be vitrified and stockpiled to facilitate the design of controlled experiments in which to perform direct comparison of levels of chromosome-associated cohesin in oocytes obtained from young and older women.'

Donation and use of embryos:

In the period from 1 January 2014 to 31 December 2014, the centre reported:

- the donation of 152 fresh embryos, of which 144 were used and 8 disposed before being used in research
- the donation of 183 frozen embryos, of which 124 were used and the remainder are in storage in addition to 227 embryos donated prior to 1 January 2013, and
- the creation of 114 embryos, all of which have been used;

Egg donors are also recruited at the centre in order for embryos to be created. From 2015 we no longer collect information relating to the number of eggs donated to research.

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.

At the last renewal, a peer reviewer agreed that the use of human embryos was necessary and justified for the proposed research.

Evidence of approval by an ethics committee was also provided at the last renewal of the licence. We reviewed evidence during our inspection that the ethics approval remained valid for the duration of the research licence.

What they could do better.

Nothing noted on this inspection.

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.

On inspection, a review of centre documentation and an audit of records of the usage of embryos in the project demonstrated that:

- Proper records of the storage of embryos in the research project are maintained.
- Robust procedures were in place to ensure proper records of the usage of embryos are maintained from donation to the project, usage in research through to disposal at the end of the research process (RLC R13).
- The researchers have a documented procedure for ensuring that embryos do not develop beyond 14 days post-fertilisation or the appearance of the primitive streak, whichever is earlier (RLC R28).
- Discussions with the PR provided assurance that all embryos donated to the project will only be used for the objectives authorised by the licence to meet the defined statutory purposes (RLC R5 and R23). This is facilitated by restricted access to embryos during storage and use, and supervision of research staff by the PR.
- A storage log is maintained which records the storage consent expiry dates for any embryos in storage for research purposes. All frozen embryos in storage were within their consented storage period (RLC R39).

An audit of donor records showed that:

- Effective consent for the use of the embryos in the research project had been documented by the gamete providers (RLC R18).
- The developmental stage of the embryos at the time of donation to research noted in the patient records concurred with that noted in the research usage log, assisting the

researchers in ensuring disposal before 14 days post-fertilisation (RLC R28).

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.

- The centre operates a 'bring-forward system' to help them identify when stored embryos are approaching the end of the period for which consent has been given. With staff at the centre, we reviewed the centre's log of stored embryos used to operate their bring-forward system. Two instances were identified in which the end of the storage period for which the donor had given their consent had been inaccurately recorded compared to their consent form (see recommendation 3). In both instances the embryos were still within the period of storage for which consent had been given. There is however a risk that errors of this type mean embryos could remain in storage beyond their consented period or the statutory storage period (whichever is less).

- Research licence condition R1 requires that the activities authorised by the licence must be carried out only on the premises specified on the licence. The PR informed us that 13 embryos donated to R0152 have been transferred to a different HFEA licensed research premises at centre 0246, the MRC National Institute of Medical Research. Here, the embryos were used in research primarily for the purposes of R0152. Therefore for these embryos, some activities authorised in R0152 have not been carried out on the premises specified on the licence (see recommendation 1).

  We have held further discussions with the PR, and with the PR of centre 0246. We are satisfied that together they considered the licence conditions. Advice was also sought from HFEA, before research activities authorised under R0152 took place on a different licensed premises. Following the inspection, the PR has provided assurance that no further embryos would be transferred to centre 0246 until centre 0246 have been granted a licence authorising the research activities.

  We have considered what regulatory actions are required with respect to HFEA's compliance and enforcement policy. It is important to note that embryos were only used for purposes that have been considered to be necessary and desirable by a Licence Committee; that the research was carried out on premises licensed for the conduct of human embryo research under the supervision of staff considered to be suitable to carry out research involving human embryos, and; fully in-line with the consent given by the gamete donors. We note that a member of the research team was advised by a member of the HFEA executive that it was permissible to transfer embryos to other licensed premises (which is the case). The HFEA executive failed to advise however that the requirements of standard licence condition R1 mean that it was not permissible for the transferred embryos to be used in research only licensed to take place at the premises of centre 0017. It is acknowledged that this misinformation led to the research being conducted on premises other than those licensed. Our recommendation takes these mitigating factors in consideration.

Changes & improvements since the last inspection

No recommendations for improvement were made at the last inspection, a desk-based assessment of a licence renewal application in 2014.

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
None			

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
1. Activities authorised by the licence have taken place on premises not specified on the licence. Research Licence Condition R1	Taking into consideration the mitigating factors noted in this report, we do not consider that a recommendation is necessary.	As highlighted in the report, HFEA advice was sought by us prior to transferring any embryos to the other HFEA licensed premise for genetic analyses in relation to the consented research project under licence RO152. Misinformation contributed to the mitigating factors but as assured, appropriate steps have been taken to have the other premise licensed to undertake relevant analyses on embryos created for our approved research project.	An application for a licence to carry out objectives specified in R0152 at premises 0246 was considered and granted by a licence committee on 20 April 2015. No further action is necessary.

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
2. Incorrect information has been recorded in the centre's bring-forward system that could have led to embryos being stored outside of the terms of consent given. CoP Guidance Note 17.7	The PR should audit the database used to review the processes for managing the bring-forward system to identify how errors in recording the terms of consent as specified in consent forms arose. The PR should provide a summary of the findings of this review including corrective actions and timescales for their implementation by 24 July 2015. All necessary corrections should be made to the records of consent identified in the course of the inspection.	Transcribing errors in recording end of storage period in 2 cases were identified during inspection though still within the valid storage period. This has been corrected in the excel database to reflect correct end of storage period after cross-checking with the valid consents in the notes. An audit has been undertaken with summary and recommendations (Attached). In brief, no further transcription errors were identified from all the stored frozen embryo sets. Corrective action: From immediate effect, an additional column has been added onto the Freeze Thaw spread sheet subtracting the expiry date of embryos stored from the freeze date, as a quick way of checking the expiry date of embryos.	We have reviewed the audit and corrective actions, and we consider sufficient steps have been taken to prevent similar occurrences. We have advised the PR to audit again after a number of new entries are made onto the spreadsheet to provide assurance that the corrective actions are effective.

Additional information from the Person Responsible
Minor amendment: On page 7,the period in donation of use of embryos should read 1st January 2014 (instead of 2013) to 31st December 2014 (instead of 2012). In the frozen embryo use & remaining in storage data, it should read prior to 1st January 2014 rather than 2013. We appreciate the support and advice from HFEA throughout the inspection and post inspection process. Executive Comment (21/04/2015): the above correction has been made.