Research Licence Renewal Report: Desk based assessment

Centre name:	**Hull IVF Unit**
Centre number:	**0021**
Research licence number:	**R0067/8/C**
Project title:	**Biochemistry of Early Human Embryos**
Date licence issued:	**1 February 2010**
Licence expiry date:	**31 January 2013**
Additional conditions of licence:	**None**
Person Responsible:	**Professor Henry Leese**
Licence Holder:	**Dr Roger Sturmey**
Inspector:	**Dr Andrew Leonard**
Date assessment completed:	**21 August 2012**
Research Licence Committee date:	**11 September 2012**

Purpose of report

The Human Fertilisation and Embryology Act 1990 (as amended) only permits research licences to be granted for a period of three years and, by law, research centres must have an inspection visit every two years. In September 2011, the Authority agreed to a revised compliance cycle for research centres. The Authority agreed research centres do not need to have an inspection visit prior to the renewal of a licence under the following circumstances:

- That the research will continue to be carried out on the same premises
- That no critical areas of concern were identified during the last inspection visit to the centre
- That the centre, where applicable, had complied with all of the recommendations identified during the last inspection visit
- That the centre has not had a 'grade A' incident since the last inspection visit
- That there had not been any material change in circumstances since the last inspection visit e.g. a change in the Person Responsible (PR)
- That the centre has provided the HFEA with data on embryo usage in a timely fashion.

The centre performing research project R0067 has met all of the above requirements.

Inspection details:

The report covers a desk based evaluation of the applications and supporting information and any other information received between 11 August 2011 and 22 August 2012.

Report to Research Licence Committee

Brief description of the centres and their licensing history:
The project, 'Biochemistry of Early Human Embryos' (R0067), was first licensed in 1995. The current licence is due to expire on 31 January 2013, having been last renewed for three years by a Research Licence Committee (RLC) on 18 November 2009.

The PR applied in July 2010 to change the licensed research premises from the University of York (centre 0062) to the Hull IVF Unit (centre 0021). This change was approved by the Executive Licensing Panel on 10 September 2010 such that centre 0021 is now a treatment and storage with research centre. The project at centre 0021 was last inspected on 11 August 2011. No non-compliances were found and no recommendations needed to be made.

The PR has now applied to renew the research licence from the 1 February 2013.

Variation to licence: None

Summary for licensing decision
In considering overall compliance, the inspection team considers that it has sufficient information to conclude that:

- The PR is suitable and has discharged his duty under section 17 of the HF&E Act 1990 (as amended). This conclusion is based on the centre's self assessment questionnaire (SAQ) and on evidence from the last inspection visit on 11 August 2011 which both indicate that there are no non-compliances associated with the research project.
- The premises are suitable. This conclusion is based on the centre's SAQ, the report of the last inspection on 11 August 2011 and on the plan of the research premises provided with the application, which show the premises to be unchanged from those previously inspected, which were compliant with HFEA requirements.
- The practices are suitable. This conclusion is based on the centre's SAQ, on the report of the last inspection visit on 11 August 2011, on the peer reviewer's comments and on the continued approval from East Yorkshire & North Lincolnshire Research Ethics Committee.
- The PR has submitted appropriately completed documentation in application for renewal of the licence.
- The centre has submitted fees to the HFEA in accordance with requirements

The RLC is asked to note that there are no critical or major areas of non-compliance, but that the inspector has made a recommendation to correct one 'other' area of non-compliance or poor practice.

'Other' areas of practice that require improvement:

- The PR should ensure that the annual 'Research information and data sheet' for the project is returned within the timescale discussed in General Direction 0002, i.e. by 31 January of the following year.

The licence application
The activities to be licensed are:

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

The PR has also indicated in the application that as part of the research project: RNA may be extracted from embryos and converted to cDNA to enable analysis of gene expression. Embryos may also be lysed and fixed to enable studies on DNA damage or intracellular metabolic components. Embryos may also be fixed and stained for cell counting and assessing the presence of proteins of interest and/or cellular organelles

None of the proposed activities are prohibited by the HF&E Act 1990 (as amended).

These research activities are considered necessary or desirable for the following purposes:

A. Increasing knowledge about serious diseases or other serious medical conditions
HF&E Act 1990 (as amended) Schedule 2 3A(2)(a)

> The reason for this, as stated by the PR, is: 'Through the course of our research we have made progress in elucidating the biochemical basis of sub-fertility and early embryo viability. For example, we have discovered links between the biochemical activity of early embryos and DNA damage. The work is now progressing and has begun to uncover a relationship between the metabolic activity of the early embryo in relation to metabolic characteristics of the mother. These ideas are based on animal studies performed in our research labs, which shows that when oocytes are exposed to increased levels of fatty acids there are significant and lasting effects on the metabolic and genetic regulation of the resulting embryo. Understanding how the nutritional status of the mother can 'programme' the embryo is important in understanding the concept of non-genetic hereditary disease, particularly in the context of metabolic disorders such as the so called "metabolic syndrome".'
> The reason for this, as stated by the Peer Reviewer is: 'The proposed studies will lead to a greater understanding of how maternal obesity effects embryo quality and its metabolism. These effects could have considerable implications for the health of the offspring, as proposed by the DOHaD hypothesis.' [DOHaD = Developmental Origins of Health and Disease]

B. Promoting advances in the treatment of infertility
HF&E Act 1990 (as amended) Schedule 2 3A(2)(d)

> The reason for this, as stated by the PR, is: 'In addition to discovering how the early embryo may be susceptible to sub-optimal metabolic conditions, the study of the metabolic activity of early embryos has led to the identification of a number of non-invasive markers of early embryo viability. For example, we have shown that the pattern by which an early embryo on day 2 of development consumes certain key metabolic substrates and produces others can predict the likelihood of whether that embryo will form a blastocyst, the degree of DNA damage and the likelihood of

implantation. By generating further data in this regard, the confidence in such assays to generate a translatable test of embryo viability will be increased. The development of such approaches should, improve success rates of ART and reduce the need for multiple embryo transfer.'

The reason for this, as stated by the Peer Reviewer is: 'The studies will result in the finding of non-invasive markers of embryo quality and perhaps provide specific indicators of the appropriate in vitro culture environment for the embryos of women suffering from obesity. They may also impact on PCOS and its treatment.' [PCOS = polycystic ovary syndrome]

C. Increasing knowledge about the development of embryos
HF&E Act 1990 (as amended) Schedule 2 3A(2)(h)

The reason for this, as stated by the PR, is: 'Early embryos produced in vitro as part of an ART procedure are exposed to conditions that by definition sub-optimal, compared to the natural in vivo environment. By determining the metabolic and biochemical function of early development in vitro we can improve knowledge of how development in vitro is regulated.

The reason for this, as stated by the Peer Reviewer is: 'By analysing embryos which are likely to have different metabolic profiles, we will learn more about how important specific metabolites are in normal embryos. We will learn how abnormal metabolism affects early embryonic gene expression.'

These three statutory purposes are the same as those for which the research project was licensed by the RLC in September 2009.

The peer reviewer has recommended approval of the research project's licence application.

Recommendation to the Research Licence Committee:
The inspector considers that overall there is sufficient information available to recommend the renewal of the licence for a period of three years without additional conditions.

Summary of the project

Lay summary of the research project:

This study will be the first to investigate the metabolism of embryos derived from overweight and obese women and those with a body mass index (BMI) in the healthy range. Strong evidence for an association between maternal obesity and reduced embryo quality comes from studies on domestic animals, where a high level of feeding prior to and during conception leads to adverse outcomes in pregnancy; observations which we have linked to the metabolism of the early embryo. This proposal seeks to test the hypothesis that embryo metabolism is associated with maternal obesity. The experimental methods to be used are mainly 'non-invasive'; they involve placing the surplus embryos individually in a micro-droplet of culture medium which does not harm the embryos in any way but allows us to study their biology and then replace them in a fresh culture droplet to monitor their development to the blastocyst stage - at which they would normally begin to implant in the uterus (womb). The experiments will measure key processes of embryo metabolism; how nutrients are taken up from the culture medium and used (i) to generate the energy which powers all cellular functions and (ii) to provide the building blocks for the proteins involved. Specifically, the project will measure the consumption of oxygen and nutrients including glucose and amino acids, the constituents of proteins. We know from our previous work that these profiles of nutrient consumption are directly related to the ability of early embryos to form a blastocyst in culture and to give rise to a pregnancy following embryo transfer. We will also measure the amount of 'fat' within the embryos since this may well be increased in obesity and compromise embryo health. The data will be related to the BMI of the patient, the aetiology of infertility, which will be established from routine clinical investigation including hormone profiles, egg number and quality, fertilisation rates, and embryo development. We will also compare the biological data on a patient's surplus embryos with the outcome of IVF treatment, i.e., the fate of the transferred sibling embryos. This may tell us whether embryo metabolism is characteristic of a given patient and relates to pregnancy outcome, especially the risk of miscarriage. Furthermore, whilst carrying out these studies, we will analyse our data to confirm a relationship between early embryo viability and the way in which the embryo metabolises nutrients from the medium in which it is grown. This will help us in our ultimate goal of discovering non-invasive markers of embryo viability.

Objectives of the research:

We feel that addressing the questions posed throughout this project will provide valuable information on the question 'what makes a good embryo'? Our hypothesis is that a good embryo needs to expend less energy rectifying damage to the genome, transcriptome and proteome. The research will also provide a number of markers of embryo health; at the molecular and cellular levels – against which improvements in IVF technologies may be tested. The specific objective is to determine the influence of maternal BMI on the metabolism of the embryo. Maternal overweight/obesity compromises reproductive health in terms of conception rates, miscarriage, pregnancy outcome and long term health. This proposal tests the hypothesis that these problems are due to a negative impact of obesity on embryo health. A range of established non-invasive, metabolic markers predictive of embryo viability will be applied to surplus human embryos arising from IVF. The data will be related to BMI, clinical background, and pregnancy outcome of sibling embryos to provide key information to women on the importance of achieving an appropriate BMI to maximise their chances of conception and ensure their offspring's health

Lay summary of the research undertaken since the inspection on 11 August 2011:
Recruitment of patients has been slower than anticipated due to significant improvements in cryopreservation techniques, leading to fewer embryos available for research. However, we have made progress in building our understanding of the way that day 5, 6 and 7 blastocysts consume and release amino acids into the embryo culture medium and how this relates to cavity expansion and embryo 'activity'. In this regard, we have collected a number of time-lapse images where the changes in blastocyst morphology are continually monitored. Analysis of stochastic changes in morphology is a promising tool for non-invasive embryo selection and we have been comparing such stochastic changes to metabolism of amino acids. These studies are ongoing. Furthermore, we have begun to collect spent medium from early embryos to analyse metabolism as a function of the BMI of the donor. We believe that the environment in which the oocyte and early embryo grows is shaped by the nutritional physiology of the mother, and alterations in the periconceptual environment can lead to changes in the metabolic regulation of the early embryo. Again, these studies are ongoing.

Peer Review Comments:
This application for research licence renewal was sent out for peer review and the reviewer recommended that the research licence should be renewed.

The Peer Reviewer provided statements, detailed in the 'Summary for licensing decision', in relation to the project addressing the statutory purposes (as defined in Schedule 2 3A (2) to the HF&E Act 1990 (as amended)) specified in the renewal application.

The Peer Reviewer considered the use of human embryos to be necessary because: 'Yes, it will provide significant insights into the effects of human obesity on human embryo development.'

The Peer Reviewer considered the number of embryos used in the last three years in the research project is justified because: 'Yes, they have made progress in assessing amino acid activity and the effects on embryo culture.'

The Peer Reviewer considered the number of embryos to be used in future in the project to be justified because: 'Yes. This number would allow thorough statistical analysis to be conducted.'

The Peer Reviewer considered the use of human embryos will address the statutory purposes because: 'The investigators require human embryos to determine how obesity affects embryo metabolism and quality. The question is specific to human obesity and reflects the subtle changes that need to be documented in human embryos against the specifics of an obese patient's condition.'

The Peer Reviewer considered the project's objectives will address the statutory purposes because: 'Yes, the objectives clearly state that they will determine whether obesity affects the metabolism of the embryo. They will employ the appropriate scientific tools to assess metabolism and compare this to the clinical profile of the patient.'

Donation and use of embryos:

The Research data and information form for 2011 provided by the centre indicated that between 1 September 2011 and 31 December 2011, 30 fresh embryos were donated, received, used and disposed of in the research project. A further 7 frozen embryos were donated to the project and remain in storage in this time. No embryos were used in the project in 2010 or between 1 January and 31 August 2011. This embryo usage is less than that proposed in the licence application in 2009 (250 fresh embryos per year). This is because of the research project's relocation from York University to Hull IVF, which stopped research activity between January 2010 and August 2011.

The renewal application proposes that the research project will use 250 fresh and 20 frozen embryos, and 50 failed to fertilise oocytes, per year for the next three years.

As discussed above, the peer reviewer considers that the past use of embryos in the project and the proposed future use are justified.

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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 Acts, 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 risk of causing harm to a patient, donor, embryo or to a child who may be born as a result of treatment services. A critical area of non-compliance requires immediate action to be taken by the PR.

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, embryo or to a child who may be born as a result of treatment services
- which indicates a major shortcoming from the statutory requirements;
- which indicates a failure of the PR to carry out his/her legal duties
- a combination of several “other” areas 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

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 statutory requirements or good practice.

Area of practice and reference	Action required and timescale for action	PR Response	Executive Review
The PR returned the 'Research information and data sheet' for 2011 which reports annual embryo usage, to the HFEA on 24 February 2012. This was after the date for submission stated in General Direction 0002 (31 January of the following year). Research licence condition R14 requires the PR to provide, in such form and at such intervals as it may specify in Directions, with such copies of or extracts from the records, or such other information, as the Directions may specify.	Going forward the PR should ensure that the 'Research information and data sheet' for the project is returned each year within the timescale required by General Direction 0002.	I apologise for not ensuring that the 'Research information and data sheet' for 2011 was returned by 31 January 2012. I will ensure that the data sheet is returned promptly in future.	30 August 2012: The PR's response indicates that this regulatory issue will be addressed. No further actions are required. Compliance with General Direction 0002 will be reviewed annually.

Additional information from the Person Responsible
I will make sure the Unit staff are aware of the need to return the data sheet in good time.

HFEA Research Licence Committee Meeting

11 September 2012

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

Minutes – Item 6

Centre 0021 (Hull IVF) - Renewal Inspection Report for Research Project R0067

Members of the Committee: Emily Jackson (lay) – Chair Andy Greenfield (professional) Sally Cheshire (lay) Neva Haites (professional)	Committee Secretary: Lauren Crawford Legal Adviser: Stephen Hocking, DAC Beachcroft LLP

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:

- Renewal Research – Desk-based Assessment report, 21August 2012
- Renewal Application form
- Self Assessment Questionnaire
- Anonymised Peer Review form
- Previous Committee Minutes

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)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Directions 0000 – 0012
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Background

1. Centre 0209 has been licensed for research activity since 2005. The current licence is due to expire on 31 January 2013, having been renewed by a Research Licence Committee in November 2009.

2. The research premises were previously located at the University of York (0062) an application to vary the research licence project was approved by the Executive Licensing Panel in September 2010.

3. The project R0067 at centre 0021 (Hull IVF) was last inspected on 11 August 2011. No non-compliances were found and no recommendations needed to be made.

Consideration

4. The Committee noted that this is a desk-based assessment of the research project and that the inspection team considers that it has sufficient information to conclude that:
   - The PR is suitable and has discharged his duty under section 17 of the HF&E Act 1990 (as amended). This conclusion is based on the centre's self assessment questionnaire (SAQ) and on evidence from the last inspection visit on 11 August 2011 which both indicate that there are no non-compliances associated with the research project.
   - The premises are suitable. This conclusion is based on the centre's SAQ, the report of the last inspection on 11 August 2011 and on the plan of the research premises provided with the application, which show the premises to be unchanged from those previously inspected, which were compliant with HFEA requirements.
   - The practices are suitable. This conclusion is based on the centre's SAQ, on the report of the last inspection visit on 11 August 2011, on the peer reviewer's comments and on the continued approval from East Yorkshire & North Lincolnshire Research Ethics Committee.
   - The PR has submitted appropriately completed documentation in application for renewal of the licence.
   - The centre has submitted fees to the HFEA in accordance with requirements.

5. The Committee noted that at the time the desk based assessment took place, 21 August 2012, there was one 'other' area of non-compliance that had been identified by the inspectorate that required improvement and that a recommendation had been made for this as follows:
   - The PR should ensure that the annual 'Research information and data sheet' for the project is returned within the timescale discussed in General Direction 0002, i.e. by 31 January of the following year.

6. 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 fee had been paid. The Committee noted that the application was made by the proposed Person Responsible ("PR") for Research.

7. 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 Inspector was satisfied the PR had satisfactorily completed the PR entry programme and is suitably qualified and experienced to undertake the role.

8. The Committee was satisfied that the premises to be licensed are suitable for the conduct of licensed activities as the Inspector confirmed that the premises were suitable and secure.

9. The Committee was satisfied that the licence application involved the authorisation of activities for the purpose of research.

10. The Committee was satisfied that the renewed licence would not apply to more than one project and that the activity of the licence, permitted under the Act, is for ' creation of embryos in vitro', 'keeping embryos', 'storage of embryos' and 'the use of embryos for research'.

11. The Committee was satisfied that the use of human embryos is necessary because the investigators require human embryos to determine how obesity affects embryo metabolism and quality. The question is specific to human obesity and reflects the subtle changes that need to be documented in human embryos against the specifics of an obese patient's condition.

12. The Committee noted the Peer Reviewer's support for the application and was satisfied that the activity to be licensed is necessary or desirable for the following purposes, specified in Schedule 2 paragraph 3A(2) to the Act, for the following reasons:

    - *Increasing knowledge about serious diseases or other serious medical conditions* (Schedule 2 paragraph 3A(2)(a) to the Act): The reason for this is: The proposed studies will lead to a greater understanding of how maternal obesity effects embryo quality and its metabolism. These effects could have considerable implications

for the health of the offspring, as proposed by the DOHaD hypothesis (DOHaD = Developmental Origins of Health and Disease)

- *Promoting advances in the treatment of infertility* (Schedule 2 paragraph 3A(2)(d) to the Act): The studies will result in the finding of non-invasive markers of embryo quality and perhaps provide specific indicators of the appropriate in vitro culture environment for the embryos of women suffering from obesity. They may also impact on PCOS and its treatment.' (PCOS = polycystic ovary syndrome)
- *Increasing knowledge about the development of embryos (Schedule 2 paragraph 3A(2)(h) to the Act):* The reason for this is: By analysing embryos which are likely to have different metabolic profiles, we will learn more about how important specific metabolites are in normal embryos. We will learn how abnormal metabolism affects early embryonic gene expression

13. The Committee was satisfied that the proposed use of embryos does not involve mixing sperm with the egg of an animal.

14. The Committee was satisfied that the inspector had previously seen the patient information and consent forms, and that these met the statutory requirements.

15. The Committee was satisfied that the research project had received the necessary approval from East Yorkshire & North Lincolnshire Research Ethics Committee.

16. The Committee noted the recommendation from the Inspectorate to renew the centre's research licence for a period of 3 years with no additional conditions.

Decision

17. The Committee agreed to renew the research licence for project (R0067) for a period of three years with no additional conditions.

18. The Committee urged the centre to implement the remaining recommendations within the agreed timeframe (31 January 2013) and reminded the centre of their duty to comply with General Direction 0002 in regards to the timely return of data and information submissions.

Signed: Date: 24/09/2012

Emily Jackson (Chair)