Licence Committee - minutes

Centre 0021 (Hull IVF Unit)

Renewal Research Licence – Research Project R0067

Thursday, 8 November 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Andy Greenfield (Chair) Kate Brian Anita Bharucha Ruth Wilde New Authority member – Gudrun Moore (Observed for induction)	
Members of the Executive	Catherine Burwood (acting Committee Secretary) Dee Knoyle (Observer) Julie Katsaros (Observer)	Senior Governance Manager Committee Officer HFEA Inspector (induction)
Legal Adviser	Graham Miles	Blake Morgan LLP
Specialist Adviser		
Observers		

Declarations of interest:

- Members of the committee declared that they had no conflicts of interest in relation to this item.

The committee had before it:

- 8th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members

The following papers were considered by the committee:

- Renewal desk based assessment
- Renewal application form
- Peer review
- Previous licensing minutes:
    - 17 November 2017 – interim inspection report
    - 5 November 2015 – renewal inspection report

1. Background

1.1. Hull IVF Unit, centre 0021, is licensed to provide treatment and storage services and is also licensed to undertake research project R0067: 'Biochemistry of early human embryos'.

1.2. The project was first licensed in 1995. The research licence was renewed on 1 February 2016 and is due to expire on 31 January 2019.

1.3. An interim inspection was carried out on 21 September 2017, prior to this recent renewal inspection, and there were no areas of practice that required improvement.

2. Consideration of application

Application

2.1. The committee noted that an application was submitted to renew the research licence for project R0067.

2.2. The committee noted that the application to renew the research licence was made by the Person Responsible (PR) for a period of three years.

2.3. The committee noted that the centre, in its application form, has applied for the following activities:

- keeping embryos
- use of embryos
- storage of embryos.

2.4. The committee noted that the proposed activities are to be licensed for the following purposes:

- Increasing knowledge about serious diseases or other serious medical conditions
- Promoting advances in the treatment of infertility
- Increasing knowledge about the development of embryos.

Inspection Process

2.5. The committee noted that a desk-based assessment took place on 1 October 2018 and this report covers the performance of the centre since the last inspection, findings from the desk-based assessment, including a review of appropriate documentation and communications received from the centre. The committee noted that, at the time of the inspection, no recommendations were made for improvement.

Peer Review

2.6. The committee noted that the Peer Reviewer was supportive of the project.

2.7. The committee noted that the Peer Reviewer indicated that they believed the following research purposes were relevant:

- Increasing knowledge about serious diseases or other serious medical conditions
- Increasing knowledge about the development of embryos.

Recommendation

2.8. The committee noted that the inspectorate recommends the renewal of the research licence for project R0067 for a period of three years, without additional conditions, with the above activities and purposes applied for by the PR.

3. Decision

3.1. The committee had regard to its decision tree.

Administrative Requirements

Supporting Information under General Direction 0008

Application

3.2. The committee was satisfied that the application was submitted in the form required and contained all the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fees had been paid.

Ethics Approval

3.3. The committee was satisfied that the research project has been approved by East Yorkshire & North Lincolnshire Ethics Committee. Evidence was provided by the PR that this approval remains active and covers the research activity described in the licence application.

Proposed Person responsible (PR) – Professor Henry Leese

3.4. The committee noted that the proposed PR, Professor Henry Leese, is willing to assume the responsibility of the role of PR.

Proposed Licence Holder (LH) – Dr Roger Sturmey

3.5. The committee noted that the proposed LH, Roger Sturmey, is willing to assume the responsibility of the role of LH.

Research Project

3.6. The committee was satisfied that the research licence would not apply to more than one research project.

Activities

3.7. The committee was satisfied with the suitability of the activities applied for:

- keeping embryos
- use of embryos
- storage of embryos.

Permitted Research Purposes

3.8. The committee was satisfied that the activities to be licensed are necessary or desirable for the following purposes, specified in paragraphs 3A(1) and 3A(2) of Schedule 2 of the HF&E Act 1990 (as amended):

- Increasing knowledge about serious diseases or other serious medical conditions

  The project will investigate the role of maternal health in early embryo biochemistry and health consequences for future offspring.

- Promoting advances in the treatment of infertility

  The project will extend our current understanding of the way in which the biochemical phenotype of an embryo can be modified by a variety of assisted reproductive technology (ART) practices, which consequently may affect fertility.

- Increasing knowledge about the development of embryos

  The project will increase knowledge of human embryonic development through its investigation of metabolism.

Prohibited Research Activities

3.9. The committee was satisfied that none of the proposed activities are prohibited by the HF&E Act 1990 (as amended).

3.10. The committee was satisfied that this is a research project and that no embryos used in the project would be implanted into a woman.

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

Use of Human Embryos

3.12. The committee was satisfied that the use of human embryos is necessary for the purposes of the research.

3.13. The focus of this project is human preimplantation embryonic development; mouse preimplantation embryos are different in many ways and the mouse maternal environment is also quite different.

3.14. The committee was satisfied that the proposed research project does not involve the derivation of human embryonic stem cell lines for human application or the genetic modification of embryos.

3.15. The committee was satisfied that no embryos would be used without obtaining proper consent for their use in research from patients.

Person Responsible (PR) – Professor Henry Leese

3.16. The committee was satisfied that the proposed PR possesses the required qualifications and experience and that the character of the proposed PR is such as is required for supervision of the licensed activities. It was further satisfied that the proposed PR will discharge his duties under section 17 of the HFE Act 1990 (as amended).

Proposed Licence Holder (LH) – Dr Roger Sturmey

3.17. The committee was satisfied that the proposed LH is suitable for the role.

Premises – Reproductive Medicine Research, Hull York Medical School, Women's and Children's Hospital, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ

3.18. The committee was satisfied that the premises and facilities are suitable for the conduct of the licensed activity applied for.

Licence

3.19. The committee agreed to renew the research licence for project R0067, at centre 0021, entitled 'Biochemistry of early human embryos', with no additional conditions for a period of three years with the following:

Activities:

- keeping embryos
- use of embryos
- storage of embryos.

For the following purposes:

- Increasing knowledge about serious diseases or other serious medical conditions
- Promoting advances in the treatment of infertility
- Increasing knowledge about the development of embryos.

3.20. The committee agreed that the centre's future renewal inspection report should be submitted to the Licence Committee for consideration.

4. Chair's signature

4.1. I confirm this is a true and accurate record of the meeting.

Signature

Name

Andy Greenfield

Date

3 December 2018

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 assessment, carried out to assess 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 the licence.

Date of assessment: 1 October 2018

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

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.

Inspectors: Dr Andrew Leonard

Date of Licence Committee: 8 November 2018

Centre Details:

Project title	Biochemistry of Early Human Embryos
Centre name	Hull IVF Unit
Centre number	0021
Research project number	R/0067/10/a
Centre address	Women's and Children's Hospital, Hull Royal Infirmary Anlaby Road, Hull, HU3 2JZ
Person Responsible (PR)	Henry Leese
Licence Holder (LH)	Roger Sturmey
Treatment centres donating to this research project	Hull IVF Unit only
Date licence issued	01/02/2016
Licence expiry date	31/01/2019
Additional conditions applied to this licence	None

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Section 1: Summary report

Brief description of the centre and its licensing history:

The Hull IVF Unit is licensed to provide treatment and storage services and is also licensed to undertake research project R0067: Biochemistry of early human embryos. This project seeks to evaluate changes in the media of cultured embryos resulting from their metabolism and to correlate those changes with embryo viability and potential for live birth, as well as with secondary factors such as patient health. The project was first licensed in 1995.

The research project was last inspected on 21 September 2017 when no non-compliances were found.

The research licence was renewed on 1 February 2016 and is due to expire on 31 January 2019. There are currently no additional conditions on the licence.

The executive considered the good compliance of this project at the last licence renewal and the absence of non compliances at the interim inspection on 21 September 2017. The executive noted that the project proposal in the renewal application form, was not significantly different from that at the last licence renewal. The inspection team had no concerns regarding the centre's self-assessment questionnaire (SAQ) and other information submitted in support of the application also raised no concerns. The executive therefore decided that it was proportionate to perform a desk-based assessment of the centre's renewal application.

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 Direction 0008, including evidence of ethics approval. Patient information and consent forms were also submitted and reviewed, and it was noted they have not changed significantly since the previous renewal application for this project
- the application has designated an individual to act as the 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:

- Keeping embryos
- Use of embryos
- Storage of embryos

Other activities, already undertaken in the project, are specified on the application form as:

- Metabolic studies - consumption and release of metabolites from individual embryos - glucose, lactate, pyruvate, amino acids.
- Timelapse studies

- Fixing of embryos for cell counts and allocation (blastocysts). Also measurement of endogenous reserves and biochemical analysis of nucleic acids.

The proposed research 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 activities specified above are required by the PR for the following purposes, as defined in Schedule 2 3A (1) and (2) of the HF&E Act 1990 (as amended):

- Increasing knowledge about serious diseases or other serious medical conditions
- Promoting advances in the treatment of infertility
- Increasing knowledge about the development of embryos

The PR states in 'objectives' in the application form, how the project will address these purposes, as follows:

- *Increasing knowledge about serious diseases or other serious medical conditions*: We will do this by studying how maternal ill health can programme alterations in early embryo biochemistry. We will measure a range of biochemical endpoints including markers of metabolic activity.
- *Promoting advances in the treatment of infertility:*
  Concerns have been raised about the impact of the ART process on short and long-term health risks to mother and offspring. Building on existing data, we will increase the evidence base on the way in which the biochemical phenotype of an embryo can be modified by ART practices. Examples include the method of ovarian stimulation, the gamete/ embryo culture conditions, the mode of fertilisation, and impact of cryopreservation techniques. We will also seek to understand the impact of the underlying cause of infertility on early embryos and distinguish this from the impact of ART practices by studying the biochemistry of embryos created from the gametes of fertile donors. Our overall experimental strategy will generate data of direct relevance to women undergoing ART and to those planning to conceive naturally. It is only by studying spare embryos arising from IVF that we can collect information on the physiology of the human preimplantation embryo.
- *Increasing knowledge about the development of embryos:*
  The methods used to measure embryo biochemistry of early embryos indicate the depletion of substrates that are parts of known metabolic pathways. We are now able to expand these data by studying directly the mitochondrial function of single preimplantation embryos. These methods have been developed in an animal model, and give information of biochemical function of early embryos in more detail than ever before. These include the proportion of energy that is 'wasted' (that is not used productively) as well as the real-time activity of the mitochondria within the embryos. This project will not use embryonic stem cells or human admixed embryos.

The peer reviewer has indicated that they believe the following purposes are relevant:

- *Increasing knowledge about serious diseases or other serious medical conditions*
- *Increasing knowledge about the development of embryos*

Because: 'The project is mainly to do with evaluating embryos in relation to their environment pre recovery. This may reflect serious disease of the mother and will contribute understanding to embryo development. The candidates consider this will

advance treatments in IVF…well maybe in the distant future but this is definitely secondary. It may advance our understanding of the role of BMI in infertility more quickly.'

Prohibited research activities:
The activities to be licensed are not prohibited by the HF&E Act 1990 (as amended) and do not involve 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 who has stated: 'this focus is on human preimplantation development; murine preimplantation embryos are different in many ways and the murine maternal environment is not comparable.'

The renewal application proposes the use of a maximum of 20 failed to fertilise 'embryos', 200 fresh embryos and 20 frozen embryos each year for the three year term of the proposed new licence.

The peer reviewer has stated regarding justification for the numbers of embryos to be use in research: 'As far as is possible. It is erroneous to think that an accurate estimate is possible. It will depend on a multitude of factors including nature of available patients/embryos, consenting, recovery rates etc and other laboratory variables.'

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

Premises:
The premises are suitable. This is based on information submitted with the application and the previous inspection visit in September 2017.

Recommendation:
The Licence Committee is asked to note that there are no areas of practice that require improvement.

The inspection team considers that, overall, there is sufficient information and evidence available to recommend 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:

- Keeping embryos
- Use of embryos
- Storage of embryos

For the following purposes:

- Increasing knowledge about serious diseases or other serious medical conditions
- Promoting advances in the treatment of infertility
- Increasing knowledge about the development of embryos

Section 2: Summary of the research project

This section summarises information submitted in the research licence application and from the Peer Reviewer.

Lay summary of the research project:

Why the project is being carried out: We know very little about the processes that form a human embryo and why some embryos turn out to be healthier than others. The purpose of our work is to carry out a detailed examination of the development of the early human embryo, particularly how it generates the energy it needs to grow. This knowledge will help optimise embryo culture and transfer procedures to enhance IVF success rates. A second area of increasing importance is how the environment in which early development occurs can influence the long-term health of the babies born. For example, a woman's body weight affects the quality of her eggs and embryos; a detailed understanding of which could increase the chances of a healthy pregnancy and a healthy baby.

What the research project aims to achieve: The first aim is to devise a simple, reliable method for embryo selection; the second is to discover whether the preconception environment, including maternal body weight can affect the health of eggs and early embryos. This information will enable couples trying for a baby naturally or through IVF to be provided with sound preconception advice.

What your research involves and why you need to use human embryos: The research uses highly sensitive laboratory tests, most of which are non-invasive, to study the biochemistry of individual human embryos, donated to research after treatment. The data can then be related to the ability of the embryos to develop successfully in culture. We do pilot work in the laboratory on animal embryos to confirm our approaches are feasible before conducting this essential research on spare human embryos.

How this will help you achieve your research aims The data will (i) provide reassurance that a non-invasive test to select single embryos for transfer is safe and effective such that clinical trials could safely be undertaken (ii) demonstrate the importance of the preconception environment in ensuring the health of embryos conceived via IVF, and the short and long-term health of the babies.

Objectives of the research:

We wish to illuminate understanding of the biochemistry of early human embryos. To achieve this, we will pursue the following objectives;

- Objective 1: Increasing knowledge about serious diseases or other serious medical conditions. We will do this by studying how maternal ill health can programme alterations in early embryo biochemistry. We will measure a range of biochemical endpoints including markers of metabolic activity.
- Objective 2: Promoting advances in the treatment of infertility. Concerns have been raised about the impact of the ART process on short and long-term health risks to mother and offspring. Building on existing data, we will increase the evidence base on the way in which the biochemical phenotype of an embryo can be modified by ART practices. Examples include the method of ovarian stimulation, the gamete/ embryo culture conditions, the mode of fertilisation, and impact of cryopreservation techniques. We will also seek to understand the impact of the underlying cause of infertility on early embryos and distinguish this from the impact of ART practices by studying the biochemistry of embryos created from the gametes of fertile donors.

Our overall experimental strategy will generate data of direct relevance to women undergoing ART and to those planning to conceive naturally. It is only by studying spare embryos arising from IVF that we can collect information on the physiology of the human preimplantation embryo.

- Objective 3: - Increasing knowledge about the development of embryos. The methods used to measure embryo biochemistry of early embryos indicate the depletion of substrates that are parts of known metabolic pathways. We are now able to expand these data by studying directly the mitochondrial function of single preimplantation embryos. These methods have been developed in an animal model, and give information of biochemical function of early embryos in more detail than ever before. These include the proportion of energy that is 'wasted' (that is not used productively) as well as the real-time activity of the mitochondria within the embryos. This project will not use embryonic stem cells or human admixed embryos.

Summary of the research undertaken to date:

Summary (from summary of progress in application form).
What we have shown so far: Using 888 embryos generously donated to our work so far (between 2011-2015; 808 embryos, 176 patients and in 2018; 80 embryos, 20 patients), we have shown that the biochemical processes that early embryos use to generate energy whilst it is in vitro, can be modified by a number of factors, including i) a woman's preconception body mass index; ii) the conditions in which embryos are cultured; iii) the choice of hormonal stimulation used to stimulate egg production; iv) whether embryos are frozen prior to transfer. We now wish to further understand how the embryo responds to environments imposed upon it to learn about the importance of the 'best start in life'.

Progress (from application form)
The research study of the biochemistry of early human embryos has been licenced since 1995, resulting in numerous publications and summarised in a recent review published by the group (Leese et al 2016). Our understanding of preimplantation embryo metabolism has advanced and we now have a good understanding of how metabolic events contribute to the development of the zygote into the blastocyst. We have identified indicative biomarkers of embryo health with which to improve the success of assisted conception technologies. The work and the results of the research continue to address the original objectives of the project – as listed;

1. Increasing knowledge about serious diseases or other serious medical conditions: It is increasingly clear that the origins of major serious noncommunicable diseases including cardiovascular disease, diabetes and metabolic syndrome may lie in the peri-conceptual period when the preimplantation embryo is particularly sensitive to environmentally induced perturbations. The results arising from activity as part of this licence have already made significant contribution to this understanding. The aim of our research is to fully understand the mechanisms by which the physiology and metabolism of the early human embryo respond to changes in maternal health and nutrition, as well as different IVF culture conditions, which can potentially influence ART outcomes and the susceptibility of the offspring to disease in later life. In the past 2-3 years we have continued to focus on the metabolic disruption that maternal overweight / obesity (OWOB) has on embryo development. We have clear evidence to suggest oocyte and embryo viability is compromised in OWOB (Leary et al 2015). • Lower oocyte diameters • Lower glucose utilisation • Altered amino acid turnover • Higher triglyceride content. Furthermore, the

addition of compounds such as L-Carnitine to the culture medium can influence the consumption of these metabolites (Leary et al 2016) and different ovarian stimulation regimes (Leary et al 2017) and culture techniques can also leave a lasting legacy on the metabolic phenotype (Leary et al 2016).

2. Promoting advances in the treatment of infertility: 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 - with the prospect of clinical application to improve embryo selection techniques. In earlier work we have shown correlative relationships between embryo biochemistry and levels of molecular damage, providing confidence in the biology underpinning the concept of metabolic assays as markers of embryo health. We will continue to explore the way in which components of treatment regimens might impact embryo biochemistry and subsequent outcome. For example, we have shown that differences exist in the metabolic function of embryos that have been cryopreserved compared to those that have not, and that superovulation regime used can also impact embryo metabolic activity (Leary et al 2017). We also see links between differences in the metabolism of embryos and the underlying cause of infertility (Leary et al 2015; Kean et al 2018). Understanding areas such as this provides vital data on how the process of ART and the cause of subfertility can be reflected/can alter embryo physiology.

3. Increasing knowledge about the development of embryos: Early embryos produced in vitro as part of an ART procedure are exposed to conditions that, by definition, are suboptimal compared to their natural in vivo environment. By determining the metabolic and biochemical function of early development in vitro we can improve knowledge of how such development is regulated. In more recent years, using a range of non-invasive methods to determine embryo metabolism, we have been able to show that embryos from overweight and obese patients show significant metabolic disruption. This data has been collected using non-invasive biochemical methods to analyse the composition of the embryo culture medium after a defined period of incubation. The depletion and/or appearance of a number of compounds are determined; these include glucose, lactate, pyruvate, and amino acids. At the conclusion of incubation, the embryos are discarded in ways that allow us to maximise the information that we can obtain from each individual embryo. Thus, embryos may be permeabilised and disaggregated to allow us to measure the amount of intracellular lipid, or may be fixed and stained with fluorescent dyes so that we can determine the allocation of cells in the blastocyst. In order to understand the importance of metabolic pathways in early development, we have added a range of biochemical agents to the culture medium to inhibit or activate a pathway of interest. This includes carnitine; an activator of fatty acid metabolism; and insulin; critical in the hormonal regulation of glucose metabolism. This approach means that we obtain the maximum amount of information from each individual precious human embryo donated for research.

Publications list

Kean S, Leary C, Cunningham T, Maguiness S (2018) Endometriosis is associated with reduced blastocyst formation rate. Human Fertility, 21:1, 52- 75, DOI: 10.1080/14647273.2018.1431510

Leary C, Leese H, Sturmey R (2015) Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Human Reproduction 30,1, p122-132.

Leary C, Leese H, Sturmey R (2016) Embryos from frozen IVF/ICSI cycles display different patterns of substrate utilisation to those of fresh cycles Human Fertility 19, 1 p75.

C.K. Leary, R.G. Sturmey (2016) Evaluation of preimplantation human embryo metabolism in embryos exposed to L-carnitine during in-vitro development. Fertil Steril 106, 3, Supp e357
Leary C, Sturmey R (2017) The effect of gonadotropin releasing hormone (GnRH) agonist and antagonists stimulation protocols on the viability and metabolism of human oocytes and early embryos. Human Reproduction 32, S1, p73.
Leese HJ, Guerif F, Allgar V, Brison DR, Lundin K, Sturmey RG. (2016) Biological optimization, the Goldilocks principle, and how much is lagom in the preimplantation embryo. Mol Reprod Dev. Sep;83(9):748-754. doi: 10.1002/mrd.22684.

Donation and use of embryos:
In 2017 the researchers used no fresh or frozen embryos. The research project subsequently commenced activity in 2018, according to the progress report, and 80 embryos have been used in research.

Peer review comments:
Considering the importance of the objectives of the project, the peer reviewer considered them to be:

> 'Quite important. Going back to the DoHaD [Developmental origin of health and disease] hypothesis it is clear that nutrients and other components of the maternal environment will affect the early embryo so this is a concept established in the literature for decades and known to be important. It is equally clear that IVF conditions can perturb this environment substantially. So the hypothesis is sound if not new. Results may be confounded by the multiple genetics of patients and their embryos in a diverse human population and the grave difficulties of identifying very small amounts of substances let alone differences in cohorts from different [BMI] environments when there are so many other variables.'

Considering whether the proposed research will address the project's objectives, the peer reviewer considered:

> 'Self-volunteered data on diet, alcohol and smoking etc are very likely to be inaccurate and since the number of embryos and patients contributing to different cohorts is likely to be small these may not form reliable criteria to measure against. The numbers do not allow comparison of fresh and frozen embryos which will be of different quality. The biochemical tests have been established by Prof Leese who has many publications on single embryo metabolism. This work will be reliable in terms of the technical measurement but may be confounded by the embryo material, since subtle or gross genetic anomalies contributing to the infertility will of course influence the outcome. The interaction between genes and environment is really a key issue and it would be good to extend the study beyond what has been done before on metabolism. One major issue is will they really have enough material to see subtle differences, with maternal BMI say, with so many other variables?
>
> 'Only some embryos will be collected at the end of assays for gene profiling which seems wasteful and perplexing: this kind of data is essential to understanding the results of non-invasive assays. The reason for not studying gene expression in all embryos (or if not this then protein/lipid etc distribution and expression by e.g. immunological means) at the completion of non-invasive assays is a mystery and a potential flaw.'

The peer reviewer agrees that the research project has made progress and addressed its defined purposes, based on the literature produced by the group. The peer reviewer also notes that the research group has ‘been publishing in this area for many years and are established in the field. Emeritus Prof Leese has an excellent reputation in this field.’

Section 3: Details of the inspection 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, CoP Guidance Note 22.

What the centre does well.

The SAQ and risk assessment of the project, provided by the PR in support of the application, and findings during previous inspections at the centre such as that in September 2017, provide good evidence that:

- Proper records of the storage of embryos in the research project have been maintained in the past, and will be maintained in the future.
- Robust procedures are in place to ensure proper records of the use of embryos are maintained from donation to the project, use in research through to disposal at the end of the research process, and that annual use is reported to the HFEA (General Direction 0002 and RLC R13, R14 and R15).
- 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 in the past have been, and in future will be, only used with the effective consent of the gamete providers and for the objectives authorised by the licence to meet the defined statutory purposes (RLC R5 and R23). This is facilitated by restricting access to embryos during storage and use, and supervision of research staff by the PR.

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 inspected against:

Information, counselling and consent; CoP Guidance Note 22, RLC R18, R19, R20, R21, R22. Consent for storage; CoP Guidance Note 22, RLC R31, R32, R33, R35, R36, R38, R39.

What the centre does well.

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

The SAQ and risk assessment of the project, provided by the PR in support of the application, and findings during previous inspections at the centre, provide good evidence 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 and R20).
- information is provided to patients by trained personnel in a manner and using terms that are easily understood (RLC R21). The competence of staff at the recruiting centre to provide information in this way, and to seek consent, has been assessed.
- 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

The SAQ and risk assessment of the project, provided by the PR in support of the application, and findings during previous inspections at the centre, provide good evidence that:

- Stored embryos are obtained only from HFEA licensed centres (RLC R32 and R33).
- The centre has effective processes for monitoring stored embryos and ensuring they remain within their consented storage period. All frozen embryos used in the research project have been used within their consented storage period (RLC R35, R36, R38 and R39).

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 inspected against:

Premises and facilities; RLC R10.

What the centre does well.

Premises and facilities

Based on the centre's SAQ and the last inspection visit in September 2017, the inspector is assured that the premises and facilities are secure, clean, well maintained and are suitable for carrying out the licensed activities (RLC R10). In addition, all of the equipment and materials used in licensed research activity are designated for the purpose and are appropriately maintained in order to minimise any hazard to patients and/or staff.

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 R3, R14, General Direction 0002.

What the centre does well.
The PR has provided all necessary information requested during this assessment within the required timescales (RLC R3).

Since the last inspection, the centre has submitted the annual research information and data sheet to the HFEA within the required timeframes (RLC R14 & General Direction 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.
The SAQ and risk assessment of the project, provided by the PR in support of the application, and findings during previous inspections at the centre, provide good evidence that processes are in place to detect, report to the HFEA and investigate adverse incidents (RLC R40).

The centre reported one incident to the HFEA in 2018. This was investigated appropriately by the centre and corrective and preventative actions were implemented to the satisfaction of the HFEA incidents team and the centre's inspector.

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 inspected 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 East Yorkshire & North Lincolnshire 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.

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; RLC R1, R3, R5, R6. The Person Responsible; HF&E Act 1990 (as amended) Section 16 & 17, RLC R8, R9.

What the centre does well.

Licensing

Information obtained at the last inspection in September 2017, a review of the SAQ and risk assessment of the project, provided by the PR in support of the application, confirm that all licensed research activities will be performed only at the licensed premises under the supervision of the PR (RLC R1, R2).

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 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. The inspection team considered that the PR has fulfilled his responsibilities under Section 17 of the HF&E Act 1990 (as amended).

What they could do better.
Nothing noted.

Section 4: Monitoring of the centre's performance

Following an interim inspection in September 2017, 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 require 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