Research Renewal Inspection Report

Date of Inspection: 26 June 2012
Purpose of inspection: Renewal of Research Licence
Length of inspection: 4 hours
Inspectors Andrew Leonard

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 25 August 2009 and 9 July 2012.

Date of Research Licence Committee: 11 September 2012.

Centre details

Project title	Development of a model to study implantation in the human
Centre name	Oxford Fertility Unit
Centre number	0035
Research licence number	R0111/1/b
Centre address	Institute for Reproductive Sciences, Oxford Business Park North, Oxford, OX4 2HW.
Person Responsible	Dr Karen Turner
Licence Holder	Professor Ian Sargent
Treatment centres donating to this project	0035
Date licence Issued	01/10/2009
Licence expiry date	31/08/2012
Additional conditions applied to this licence	None

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Purpose of the Inspection Report

The purpose of the inspection is to assess whether research using human embryos is carried out in compliance with the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended) and the Code of Practice (CoP) and that progress is made towards achieving the stated aims of the project. The report summarises the findings of the licence renewal 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 Research Licence Committee/Executive Licensing Panel which makes the decision about the centre's licence renewal application.

Report to Research Licence Committee

Brief description of the centre and its licensing history:

Centre 0035 is a treatment and storage with research centre. Research project R0111 was first licensed at the centre's current premises at the Institute for Reproductive Sciences on 1 October 2009. The project has however been licensed since 1 March 1998 at centre 0035's previous premises at the Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford (now centre 0311). The research licences for project R0111 at centres 0035 and 0311 both expire on 31 August 2012 and applications have been submitted to renew both licences. The licences have no additional conditions.

This report was originally presented for consideration by the Executive Licensing Panel (ELP) on the 25 July 2012. The Chair of the ELP considered however that the report was best considered by the Research Licence Committee on the 11 September 2012. The licence was due to expire on 31 August 2012 therefore the ELP on 10 August 2012 issued Special Directions to allow the research project to continue until 30 November 2012 while the renewal application is considered by the Research Licence Committee.

Variations to licence:

None

Title of the research project:

Development of a model to study implantation in the human

Summary for licensing decision

In considering overall compliance, the inspector considers that he has sufficient information drawn from the inspection visit and from documentation submitted by the centre and the peer reviewer, to conclude that:

- the PR is suitable and has discharged her duty under Section 17 of the HF&E Act 1990 (as amended).
- the premises are suitable
- the practices are suitable
- the centre has submitted appropriately completed documentation in application for renewal of their licence
- the centre has submitted fees to the HFEA in accordance with requirements

The inspector has made recommendations to correct two major areas of non-compliance and one 'other' area of non-compliance, which the PR has agreed to implement within the timescales defined in the report:

'Major' areas of non compliance:

- The PR should consider the written patient information ('*the embryos will be anonymous once they are transferred to the research laboratory')* and the process involving the transfer of patient identifying details to the researchers at centre 0035 via the 'Research Donation Sheet'. The PR should revise the written information and/or the process to ensure that the written information accurately describes the process (HF&E Act 1990 (as amended), Schedule 3, 3 (1)b).
- The written information provided to patients considering research donation of frozen embryos should be revised to include that counselling is available and should state how an appointment can be arranged (Research Licence Condition R18).

'Other' areas of practice that require improvement:

- The PR should ensure that the 'Research information and data sheet' for the project is returned within the timescale discussed in General Direction 0002

The Research Licence Committee is asked to endorse these recommendations and that they are implemented within the time limits specified in the report.

The licence application

The PR has applied for a research licence and has indicated that the following activities will be carried out under the auspices of the licence:

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

The creation of embryos in vitro for research purposes is not included because all embryos used in project R0111 are derived from the licensed treatment activities at centre 0035. No embryos are specifically created for the research project.

The PR has also indicated in the application form that embryos will be fixed at different stages of development prior to immunofluorescence labelling and also co-cultured with human endometrial cells to model implantation. Genetic testing may also be done in future on cells removed from the embryos as 'DNA composition may be important for evaluation of implantation potential'.

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

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

1) 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: 'The proposed studies will investigate factors involved in peri-implantation events including preimplantation embryo development, embryo secretions, embryo attachment and implantation. They therefore have a direct bearing on our understanding of embryo development and may reveal potential new treatments for infertility caused by failed implantation.'

The reason for this, as stated by the Peer Reviewer is: 'The project intends to investigate factors important for the process of implantation using an ex-vivo system'

2) Increasing knowledge about the causes of miscarriage (*HF&E Act 1990 (as amended) Schedule 2 3A(2)(e))*

The reason for this, as stated by the PR, is: 'The proposed studies will investigate factors involved in peri-implantation events including preimplantation embryo development, embryo secretions, embryo attachment and implantation. They therefore have a direct bearing on our understanding of embryo development and may reveal potential new treatments for infertility caused by failed implantation. As

miscarriage may be caused by poor implantation, these studies will be directly relevant.'

The reason for this, as stated by the Peer Reviewer is: 'The studies proposed here are focused on the peri-implantation stage of pregnancy and the process of implantation. It is anticipated that the knowledge gained will provide insight into problems with implantation, which are a major cause of miscarriage.'

3) 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: 'The proposed studies will investigate factors involved in peri-implantation events including preimplantation embryo development, embryo secretions, embryo attachment and implantation. They therefore have a direct bearing on our understanding of embryo development and may reveal potential new treatments for infertility caused by failed implantation.

The reason for this, as stated by the Peer Reviewer, is: 'Since this project focuses on the process of implantation, the embryos will be cultured for several days, including the time at which the early embryonic lineages are segregated. Analyzing the metabolic products of developing embryos is one of the components of this study. Another is monitoring the response of implanting embryos to exogenous factors.'

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

The patient information sheets and consent forms meet the statutory requirements, with two exceptions which are discussed in the report.

Recommendation to the Research Licence Committee:

The inspector considers that overall there is sufficient information available to recommend the renewal of this research licence for a period of three years without additional conditions.

Summary of project

Lay summary of the research project:

Despite significant advances in assisted reproduction technology over the last decade, pregnancy rates remain disappointingly low. While fertilisation is now achievable in most cycles, embryos which appear morphologically normal still fail to implant. The purpose of this project is to investigate the development of embryos before and during the implantation process and the factors which control these crucial events. To do this we are developing in vitro systems to specifically model how human embryos develop prior to implantation, how they initially attach to the endometrium and how they invade and interact with the different cell populations of the endometrium during implantation. In these models human embryos donated for research will be cultured to the blastocyst stage. Blastocyst invasion is studied by co-culturing blastocysts with endometrial stromal or epithelial cells or on microbiopsies of endometrial tissue. Trophoblast invasion is monitored by time lapse photography and immunofluorescence microscopy. By adding factors which either stimulate or suppress the actions of a range of molecules, we will determine their role in these processes. The ultimate aim is to develop new treatments which will improve blastocyst implantation and hence pregnancy rates in assisted reproduction.'

Objectives of the research:

1) Detection of molecules involved in the implantation process in pre-, peri- and postimplantation embryos.

2) The implantation models will be used to investigate aspects of human embryo implantation: Fresh embryos donated for research will be obtained from the Oxford Fertility Unit. For some experiments (pre-implantation development) embryos will be cultured to the blastocyst stage in the embryo research laboratory in the IRS facility. However, for other experiments (implantation model), embryos will be transported at the cleavage or blastocyst stages to the existing facility in the Nuffield Department of Obstetrics and Gynaecology (NDOG) and cultured. The reason for this is that the endometrial cells are cultured in the NDOG and the image analysis system used for these studies is also located there. Given the space limitations and the cost it is not possible to duplicate these facilities in the IRS.

Future Developments

1) The role of IL-33 and ST2 in maternal immune response to the implanting embryo. One of the causes of implantation failure could be an abnormal maternal immune response against the embryo. We are studying the role of the cytokine IL-33 and its receptor ST2 in this process. We have recently published work showing that levels of ST2 are significantly altered in pre-eclampsia [1] and that its source may be the placenta. We are now looking at IL-33 and ST2 in early pregnancy and our preliminary data suggest that both molecules are expressed by pre-implantation embryos. One aim of this study will be to map the expression of IL-33 and ST2 at different stages of embryo development and at the time of implantation. A second aim is to investigate the effect of adding IL-33 or ST2 to embryo culture to determine whether either affects embryo development and invasion, using our implantation model.

2) Novel molecular markers for human gametes and embryos competence. The purpose of this project is to develop new methods for determining embryo viability to enable the

selection of those with the highest implantation potential for transfer back to the mother. By doing this we hope to improve the pregnancy rate per cycle and thereby the cost effectiveness of the treatment. This study will utilize a new way to sample the blastocyst proteome by collecting fluid from the blastocoel during the vitrification process. The fluid will then be analysed by mass spectrometry and the levels of expression of molecules detected will be correlated with blastocyst morphology and subsequent development post thawing. Genetic assessment of the blastocysts will also be carried out using comparative genomic hybridization. Molecules identified in this initial study will then be analysed in the blastocoel fluid of blastocysts used for clinical treatment to determine whether there is any correlation with pregnancy success.

[1] Granne, I., Southcombe, J.H., Snider, J.V., Tannetta, D.S., Child, T., Redman, C.W.G. and Sargent, I.L. (2011) ST2 and IL-33 in pregnancy and pre-eclampsia. PLoS One Vol. 6 (9), e24463.'

Lay summary of the research undertaken since the last inspection on 25 August 2009

The application form states: 'The proposed studies are designed to determine molecules that are critical for early human development before and during the implantation process. These are both embryonic and maternal, and further knowledge of these will increase our understanding of the maternal- embryo dialogue that is likely to direct these developmental processes. The resource we have built up during the course of the last twenty years that allows us to construct and perform human embryo-endometrial co-cultures puts us in a unique position in being able to address questions of early human development events. Not only will the results of the proposed studies increase our knowledge of early human development, which would otherwise be impossible to achieve, but also contribute to the development of better treatments for infertility and improved IVF protocols.

The project's last annual embryo usage return stated: 'The purpose of this project is to investigate the development of embryos before and during the implantation process and the factors which control these crucial events using in vitro models. The ultimate aim is to develop new treatments which will improve blastocyst implantation and hence pregnancy rates in assisted reproduction.

'The main achievements have been:
1) We have shown that HLA-G and IL-33 (and its receptor ST2) are expressed by pre-implantation embryos and may be important in preventing the implanting embryo being rejected by the mother's immune system.
2) Using our implantation model, we have shown that heparin binding epidermal growth (tm-HB-EGF) and its receptor are involved in blastocyst attachment to the endometrium.
3) Using our endometrial stromal invasion model, we have shown that molecules called Rho GTPases are critical for blastocyst invasion and that GnRH, a drug given as part of IVF treatment, is not detrimental to implantation.
4) In collaboration with Professor Nick Macklon, our implantation model has been used to study the ability of human endometrial stromal cells to be able to sense the presence of poor quality embryos and thereby prevent them from implanting. This mechanism appears to be compromised in women who suffer from recurrent miscarriage, enabling poor quality embryos to implant.'

Peer Review Comments

The application for the renewal of this research project has been peer reviewed and the reviewer has recommended that the application is approved.

The Peer Reviewer provided statements, as detailed above 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: 'In order to understand the process of implantation and identify potential problem areas in human fertility it is essential to utilize the whole embryo in an environment as close to the human physiological condition as possible.'

The Peer Reviewer considered the number of embryos used in the last three years in the research project is justified because: 'The research has resulted in an impressive number of publications that will inform the scientific community and provide useful information that may help to understand infertility and provide foci for future therapeutic approaches.'

The Peer Reviewer considered the number of embryos to be used in future in the project to be justified because: 'The in vitro development of human embryos is of variable efficiency. In order to obtain sufficient numbers of embryos at the peri-implantation stage for statistically viable studies, it is necessary to begin with at least twice as many embryos to allow for a proportion of developmental failure. Each study will need to be replicated on several occasions for scientific integrity. Therefore, the proposed number of embryos to be used seems quite justified for this study.'

The Peer Reviewer considered the use of human embryos will address the statutory purposes because: Human embryos will be used to model implantation in an ex-vivo model system. The metabolic activity of the embryos will be monitored by collecting fluid from the cavities of blastocysts. The response of embryos during the implantation period to various added factors will be monitored with a view to establishing optimal conditions for successful implantation and embryo development.

The Peer Reviewer considered the projects objectives will address the statutory purposes because: 'The purpose of the research is to identify problems occurring during embryo implantation that may be responsible for in vivo implantation failure, with a view to devising strategies to overcome these problems. The objective is to make use of the established ex-vivo implantation system to investigate specific factors that can exacerbate or alleviate these problems.'

Donation and use of embryos

In the period from 1 January 2011 to 31 December 2011, the centre reported that 131 fresh and 133 frozen embryos were donated for use in the project. All of these embryos have been used in the project. Of the 131 fresh embryos used, 105 were subsequently disposed of while 25 were frozen for later re-analysis. All of the 133 frozen embryos used have been disposed of.

This embryo usage is less than that proposed in the licence application in 2009 (750 fresh and 250 frozen embryos per year). This is because donor recruitment has been less than

expected and because use of the embryos in some aspects of the project (e.g. implantation studies in co-culture) has not occurred due to staff changes.

The renewal application proposes that the centre will use 100 fresh and 400 frozen embryos in the project 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.

Details of 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 (HF&E Act 1990 (as amended), Schedule 2 (3) and Guidance note 22)

What the centre does well.

The research project has been provided with ethical approval from an appropriately constituted Research Ethics Committee operating under the National Research Ethics Service. Evidence was also provided to the inspector that a progress report to that committee was recently submitted and that the ethical approval is active until 31 December 2014.

The PR has documented in the licence application that the following activities will be carried out: Storage of embryos; Use of embryos in research; Keeping embryos. These proposed activities are not prohibited by the HF&E Act 1990 (as amended). The activities are considered by the PR necessary for the following statutory purposes defined in Schedule 2 3A (2) to the HFE Act 1990 (as amended):

- (d) promoting advances in the treatment of infertility,
- (e) increasing knowledge about the causes of miscarriage,
- (h) increasing knowledge about the development of embryos.

A peer review was obtained for this renewal application and is supportive of the licence renewal. In the opinion of the inspector, appropriate justifications that the activities to be licensed are necessary or desirable for the statutory purposes, have been provided by the PR and the peer reviewer, as discussed in detail in the 'Summary for Licensing Decision' on pages 3 – 5. The peer reviewer has also stated that the use of human embryos is necessary and that the proposed number of embryos to be used is justified, for reasons also provided in the 'Summary for Licensing Decision'.

What they could do better.

Nothing noted at 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.

Discussions with the PR, review of the centre's documented research procedures and embryo usage log, and inspection of the premises and equipment, indicated to the inspector that the special status of the human embryo is respected. This was evidenced by several observations:

1. The centre has processes, documented in standard operating procedures (SOPs), which prevent the use of embryos in activities other than those which are licensed (Research Licence Condition (RLC) R23). These procedures ensure that embryos

are used in a respectful manner for only the purposes specified in patients' consents (Schedule 3 to the HF&E Act (1990) as amended).

2. Research recruitment practices ensure that no money or other benefit is given to patients donating embryos to the project (RLC R24). Written information also states that patients will not directly benefit from their donation.
3. The transfer of fresh and frozen embryos to research is witnessed to ensure their correct identification and to confirm that research consents are present (Licence Condition T71). This check was seen to be documented in the records reviewed on inspection of seven patients who donated to the project in 2011-2012.
4. Removal of frozen embryos from dewars for research use is witnessed and recorded in patient records (Licence Condition T71). Consents for research are also verified to be in place before the embryos are removed from storage.
5. After the witnessed identity and consent check, embryos are transferred to research-designated incubator space. This transfer is logged on a 'Research Donation Sheet' affixed to the door of the incubator. Each embryo is subsequently uniquely identified using the research code and drop number, as required by RLC R26. The research code is also recorded on the 'Research Donation Sheet' to allow reversal of anonymisation if necessary.
6. Centre 0035 has practices which ensure the separation of research and clinical embryology roles, as required by RLC R27.
7. Research processing is documented for each embryo anonymously in an embryo research spreadsheet, stored on the centre's secure server. Research consented blastocysts have, throughout 2012, been used in the blastocoel sampling arm of the research project.
8. The research incubator space, the 'Research Donation Sheet' and the embryo research spreadsheet are reviewed daily, to prevent the culture of embryos beyond 14 days post-fertilisation. These measures ensure compliance with RLC R28.
9. Electronic card key locks are fitted to the doors controlling access to non-patient areas in centre 0035. These locks are accessible to licensed centre staff only. Experimental notes and records are kept on the centre's secure server or in a locked drawer in the clinical embryology office at centre 0035. These arrangements ensure that the security of the centre is appropriate for licensed activity.
10. The cryolaboratory at centre 0035 is used to store embryos for use in research as well as those for use in treatment. It was considered compliant with CoP requirements at the last HFEA inspection of the treatment and storage licence. It is fitted with fire, movement and temperature monitors linked to the building management system, which provides warnings to on-call staff in the event of dewar failure, fire or break-in.
11. There is appropriate equipment at centre 0035 for the project which is well maintained and serviced. It is noted that blastocoel biopsies are performed using an ICSI rig which is used for both treatment and research, however never at the same time so that treatment and research activities remain separated.
12. The PR ensures that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA, as is required by General Direction 0002.

What they could do better:

Nothing noted at this inspection

Give prospective and current patients and donors sufficient, accessible and up-to-date information to enable them to make informed decisions and ensure they have provided all relevant consents before carrying out any licensed activity (Guidance note 4)

What the centre does well.

The written information provided to patients considering the donation of their fresh or frozen embryos to this research project was reviewed. Both information sheets were considered compliant with RLC R19 since they contained information on:

- the nature of the research project;
- that the decision whether to donate will not affect their treatment in any way;
- that they can vary or withdraw the term of their consent until the point the embryos are used in research;
- whether the embryos will be reversibly or irreversibly anonymised, and the implications of this;
- whether any information will be fed back to them;
- how the research is funded.

Research embryo donors are recruited using documented information provision and consenting processes. All patients at centre 0035 are provided with written research information in the general information pack provided at the start of treatment and with verbal information at an open evening (RLC R19). The general information and the open evening discuss the availability of counselling for those considering consenting decisions (RLC R18). The patients sign consents to research if they so choose at consenting consultations with nursing staff two weeks or more after written information was provided (RLC R18). The fertility nurses and the research nurse are trained in information provision and in taking consent (RLC R21). Patients can also discuss the research with the project's Licence Holder whose contact details are included in the written information (RLC R22).

Frozen embryos can also be donated to research. Patients at centre 0035 with stored frozen embryos are annually asked to confirm arrangements for the forthcoming year, by sending them a consent form and a 'donating frozen embryos to research' information sheet (RLC R19). The consent form allows patients to consent to their embryos being: stored for a further year (if possible); allowed to perish; donated for use in treatment; or donated for use in research. The information sheet provides contact details for the Licence Holder from whom the patients can obtain further information (RLC R22).

Processes are in place to prevent a breach of patient consent to research (RLC R18). Prior to egg collection and just prior to the transfer of embryos to research, a patient's consent forms including consent to research are verified in the patient records by an embryologist and a witness. The PR confirmed that embryos would only be used in research when a consent has been documented, thus embryos can only be used in research approved by the licence for project R0111 (RLC R19 and R23).

Review of seven records on inspection from patients who donated to the project in 2011 or 2012 indicated that all seven contained consents for research appropriately completed by both gamete providers (RLC R18).

Embryos stored for treatment, if then consented for research, remain in the same dewar position until thawed for use in research. Research consented fresh embryos subjected to

blastocoel sampling may be subsequently frozen and stored in a research-designated area within a dewar. Cryopreserved research embryos are recorded in the embryo storage logs which are also used to record embryos stored for treatment. These logs are regularly reviewed by clinical embryology staff to ensure that no embryos are stored without consent (RLC R36 and R39). The researchers also note embryo storage consent expiry dates in the research records. These records are regularly reviewed to prevent storage of the embryos beyond their consented storage period (RLC R36 and R39).

What they could do better.

The transfer of embryos to research is logged on a 'Research Donation Sheet'. Specifically, the name of the embryo provider as well as other details is written on the sheet, which is available to the researchers. Each embryo is subsequently uniquely and anonymously identified using the research code and drop number. This is of concern because donors of fresh and frozen embryos are told in written information that: '*the embryos will be anonymous once they are transferred to the research laboratory.*' This phrase can be interpreted to describe the current situation, i.e. that the embryos are anonymised once (i.e soon after) they are transferred to research. The inspector notes however that the phrase can also be interpreted as meaning that no identifying information will be passed to the researchers, which is not the case given patient names are logged on the embryo donation sheet which is seen by the researchers. The accuracy of the written information provided to patients is therefore questionable and thus potentially non-compliant with HF&E Act 1990 (as amended), Schedule 3, 3 (1)b.

The provision of independent counselling for patients considering the decision to donate to research, is not specifically discussed in the information sheets provided to patients donating fresh or frozen embryos (RLC R18). Those consenting to the donation of fresh embryos to research are informed about the availability of counselling in other written information provided at the same time, as well as verbally by the fertility nurses. In contrast, patients consenting to the donation of frozen embryos are not provided with any other information and the decision is likely to be considered some years after the patients were last informed about the availability of counselling.

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**

(Guidance note 2, 12, 16, 17, 19, 23, 24, 27, 28)

What the centre does well.

The inspector was satisfied that research activities are carried out only on the premises specified on the licence and under the supervision of the PR (RLC R1). The research licence was approved in 2009 for the licensed premises at the Institute of Reproductive Sciences, Oxford Business Park North, Oxford, i.e. the premises of centre 0035. At this inspection, the PR stated that research is carried out at centre 0035 in the clinical embryology laboratory (room HG21), which contains an incubator with a research-designated shelf and an ICSI rig used to sample blastocoel fluid from blastocysts. The

cryolaboratory (HG26) is also used to store research consented embryos but the research laboratory (HG32) is not currently used for research activities. The PR explained that the research laboratory could not be equipped with a research-dedicated ICSI rig so an ICSI rig in the clinical laboratory has to be used to sample blastocoel fluid. To facilitate the research, the embryos enter the research pathway by being placed in research-designated incubator space in the clinical embryology laboratory, rather than being transferred to an incubator in the research laboratory as used to happen. Discussions with the PR indicate that research and clinical embryology activities at the centre remain separated (RLC R27).

From a review of research records and discussions with research staff, the inspector was satisfied that research donated embryos are only used in research activities specified on the licence (RLC R5). The PR has also implemented all the requirements in the report of the initial licensing inspection on 25 August 2009.

Information requested in support of the renewal application was provided in a timely manner (RLC R3 and R8e) and all members of the research team co-operated fully with the inspection (RLC R2 and R8b).

The centre has an incident reporting protocol compliant with HFEA requirements of which staff are aware (SLC R40).

The PR ensures that appropriate records of embryo usage are maintained which were available for review on inspection (RLC R13 and R15).

What they could do better.

The PR returned the 'Research information and data sheet for 2011' which reports annual embryo usage, after the required date for submission stated in General Direction 0002 (31 January in the following year).

Changes / improvements since the last inspection on 25 August 2009:

Area for improvement	Action required	Action taken as evidenced during this inspection
1) The document 'Research and training projects using surplus eggs and embryos; patient information sheet v.4, dated 01/08/09' will be the only information/consent sheet provided to patients consenting in Centre 0035 to the use of their fresh embryos in the proposed project. The form should state whether embryos will be reversibly or irreversibly anonymised and the implications of this when donating to research, to be compliant with CoP Standards S.8.3.2c. The information sheet and consent form will also need to be up-dated with the HFEA research number assigned to this proposed project. To comply with HFEA Code of Practice Guidance, the information sheet should also inform donors that: a) the research is experimental and any gametes and embryos used and created for the purposes of any project of research may not be transferred for treatment (G.5.13.1a); b) they may specify conditions subject to which their gametes or embryos may be used (G.5.13.1f).	It is accepted that these information requirements may be satisfied verbally by clinical staff. However, given that the patient information can be reviewed before a print run is ordered, it is recommended that these issues are included in the information sheet so that it contains all information required by HFEA guidance. It is also recommended that the consent form attached to the document, at consent point 5, is revised to not just state that consent can be withdrawn, but to include the mechanism for withdrawal.	The written information provided to patients considering the donation of fresh embryos to research project R0111 was reviewed by the inspector. It has been revised and was considered to be compliant with the requirements of RLC R19. No further action is necessary.
2) The document 'Frozen embryos to research.docv v.3, dated 02/03/09' will need revision as it will need to be up-dated with the HFEA research number assigned to this proposed project. The information sheet asks patients with further questions to contact the research nurse, however the proposed project (as well as R0111, R0143 and R0149) does not have an assigned research nurse. The PR should be mindful of CoP Standard S.8.4.2 'that a designated individual……is available to discuss the project of research….with the donors'. Contact details for such an individual are provided in 'Research and training projects using surplus eggs and	The PR should audit the information provided to patients at Centre 0035 with frozen embryos in storage and ensure it complies with HFEA CoP Standards and Guidance, notably S.8.3.1 and S.8.3.2 a-d and G.5.13.1 a-i.	The written information provided to patients considering the donation of frozen embryos to research project R0111 was reviewed by the inspector. It has been revised and was considered to be compliant with the requirements of RLC R19.

embryos; patient information sheet v.4' and the inspectorate recommend that these contact details are also included in Frozen embryos to research.docv v.3. The inspectorate note that the ability to withdraw consent is discussed in the information sheet, but recommend the mechanism for doing this, i.e. contact a member of the Centre staff, is included. The inspectorate also note that the corporate branding applied to 'Research and training projects using surplus eggs and embryos; patient information sheet v.4' has not been applied to 'Frozen embryos to research.docv v.3'. 'Frozen embryos to research.docv v.3' will be provided to patients who have already been supplied with previous versions of the research information form 'Research and training projects using surplus eggs and embryos', when they had their treatment. This may however have been some years before. At the very least, such patients will not have been provided with information discussed in point 1) above as being absent from 'Research and training projects using surplus eggs and embryos, version 4'.		Further action is necessary to ensure that the patient information discusses the availability of counselling to patients who are deciding whether to donate their frozen embryos to research.
3) The consent form associated with Frozen embryos to research.docv v.3' was also reviewed by the inspectorate. It allows varied consent to either of two projects (R0111 and R0149). It will need revision as needs to be up-dated with the HFEA research number assigned to this proposed project and the corporate branding applied to 'Research and training projects using surplus eggs and embryos; patient information sheet v.4' has not been applied. It was also noted that a review date of 10/08/09 was written on the document, but not in the document control footer, which states a last revision date of 05.07.07.	The research consent form provided to patients considering the donation of their frozen embryos needs to be revised.	The consent form used by patients donating frozen embryos to research was reviewed by the inspector. It has been revised and was considered to be suitable for use. No further action is necessary.
4) The patient information sheet 'Frozen embryos to research - External v.1, dated 05/07/07, 1 page)' is sent to patients with embryos in storage at Centre 0139. The form will need revision as it will need to be up-dated	The PR should audit the information provided to patients at Centre 0139 with	The PR informed the inspector that frozen embryos for use in research project R0111 have

with the HFEA research number assigned to this proposed project. Given the role of the proposed licensed research, this project number could be included together with R0111 in a single consent. The information sheet asks patients with further questions to contact the research nurse, however the proposed project does not have an assigned research nurse. The PR should be mindful of CoP Standard S.8.4.2 'that a designated individual……is available to discuss the project of research….with the donors'. Contact details for such an individual are provided in 'Research and training projects using surplus eggs and embryos; patient information sheet v.4' and the inspectorate recommend that these contact details are also included in Frozen embryos to research - External v.1. The inspectorate note that the ability to withdraw consent is discussed in the information sheet, but recommend the mechanism for doing this is included in the form. The inspectorate also note that the corporate branding applied to 'Research and training projects using surplus eggs and embryos; patient information sheet v.4' has not been applied to 'Frozen embryos to research.docv v.3'. It is not clear what other information regarding research patients at Centre 0139 are supplied with. It may be that they are, or have been, provided with Centre 0035's 'Research and training projects using surplus eggs and embryos' in its earlier or current version. In this case, the issues raised in point 4) and in point 1) would need to be addressed to bring the information provision into compliance with the requirements of HFEA Standards and Guidance. They may however receive no further information, in which case the information provided would be deficient in many areas.	frozen embryos in storage and ensure it complies with HFEA CoP Standards and Guidance, notably S.8.3.1 and S.8.3.2 a-d and G.5.13.1 a-i.	not been sourced from patients at centre 0139 since the last inspection, nor will be in the future. Frozen embryos for use in project R0111 are only recruited from patients at centre 0035. No action therefore needed to be taken regarding this recommendation
5) A single consent form was provided for use by patients with embryos in storage at Centre 0035 and 0139. Its use for patients at Centre 0035 has been discussed at point 3) above. When used for patients at Centre 0139, the issues raised at point 3) above still need to be addressed. In	The research consent form provided to patients at centre 0139 needs to be revised to be compliant with these issues.	Research project R0149 is no longer active and the PR informed the inspector that frozen embryos for use in

addition, the consent form requires further revision as it allows consent to project R0149 when patients have been provided no information on the project in patient information.		research project R0111 have not been sourced from patients at centre 0139 since the last inspection, nor will be in the future. Frozen embryos for use in project R0111 are only recruited from patients at centre 0035. No action therefore needed to be taken regarding this recommendation.

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, General 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
The transfer of embryos to research is logged on a 'Research Donation Sheet'. The name of the embryo provider as well as other details is written on the sheet, which is available to the researchers. Donors of fresh and frozen embryos are however told in written information that: '*the embryos will be anonymous once they are transferred to the research laboratory.*' This phrase can be interpreted to describe the current situation but also can be interpreted as meaning that no identifying information will be passed to the researchers, which is not the case. The accuracy of the written information is therefore potentially non-compliant with HF&E Act 1990 (as amended), Schedule 3, 3 (1)b.	The PR should consider the written patient information ('*the embryos will be anonymous once they are transferred to the research laboratory')* and the process involving the transfer of patient identifying details to the researchers at centre 0035. The PR should then either revise the written information and/or the process to ensure that the written information accurately describes that process. The recommendation should be implemented by 26 September 2012 and the inspector informed of the actions taken.	This section of the Patient Information is being re-written to reflect the true situation. The recommendation will be implemented before 10/08/12. It has already been done but awaits the return from leave of the Licence Holder for final discussion.	The inspector considers that the PR's response indicates that this regulatory issue will be addressed appropriately within the required timescales. Actions are still required and their implementation will be reviewed through on-going monitoring.

The provision of independent counselling is not discussed in the information sheet provided to patients considering the decision to donate their frozen embryos to research (RLC R18). Such patients are making this decision some time after they underwent treatment and were last informed about the availability of counselling when considering consenting decisions.	The patient information sheet provided to those considering research donation of frozen embryos should be revised to include that counselling is available, if required, and should state how an appointment can be arranged. The recommendation should be implemented by 26 September 2012.	The Patient Information is being revised to include this. The recommendation will be implemented before 10/08/12. It has already been done but awaits the return from leave of the Licence Holder for final discussion.	The inspector considers that the PR's response indicates that this regulatory issue will be addressed appropriately within the required timescales. Actions are still required and their implementation will be reviewed through on-going monitoring.

Other areas of practice that requires improvement

Other areas of practice that require improvement is any area of practice, which cannot be classified as either a critical or major area of non compliance, but which indicates a departure from good practice.

Area of practice and reference	Action required and timescale for action	PR Response	Executive Review
The PR returned the 'Research information and data sheet for 2011' which reports annual embryo usage, after the required date for submission stated in General Direction 0002 (31 January of the following year).	The PR should ensure that the 'Research information and data sheet' for the project is in future returned within the timescale discussed in General Direction 0002.	This will be done in future	The inspector considers that the PR's response indicates that this regulatory issue will be addressed appropriately. Compliance with this General Direction will be reviewed annually.

Additional information from the Person Responsible

HFEA Research Licence Committee Meeting

11 September 2012

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

Minutes – Item 2

Centre 0311 (Oxford Fertility Unit) - Renewal Inspection Report for Research Project R0111

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 Inspection report, 26 June 2012
- Renewal Application form
- Anonymised Peer Review form
- Previous Committee Minutes
- Revised Patient Information x 2
- Publications x 3

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 0035 is a treatment and storage with research centre. Research Project R0111 was first licensed at the centre's current premises in October 2009. However, the project has been licensed since 1 March 1998 at the previous premises (now centre 0311).

Consideration

2. The Committee noted that at the time the renewal inspection took place, 26 Jun 2012, there were two major and one other areas of non-compliance that had been identified by the inspectorate that required improvement and that recommendations had been made for each of these.

3. The Committee noted that the PR had provided evidence to the inspectorate that the two major areas of non-compliance recommendations have been addressed and changes implemented.

4. 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.

5. 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 her 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.

6. 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.

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

8. 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 'keeping embryos' 'storage of embryos' and 'the use of embryos for research'.

9. The Committee was satisfied that the use of human embryos is necessary because as stated by the Peer Reviewer 'In order to understand the process of implantation and identify potential problem areas in human fertility it is essential to utilize the whole of the embryo in an environment as close to the human physiological condition as possible'.

10. 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:

    - *Promoting advances in the treatment of infertility* (Schedule 2 paragraph 3A(2)(d) to the Act): The reason for this is: The project intends to investigate factors important for the process of implantation using an ex-vivo system
    - *Increasing knowledge about the causes of miscarriage* (Schedule 2 paragraph 3A(2)(e) to the Act): The reason for this is: The studies proposed here are focused on the peri-implantation stage of pregnancy and the process of implantation. It is anticipated that the knowledge gained will provide insight into problems with implantation, which are a major cause of miscarriage
    - *Increasing knowledge about the development of embryos (Schedule 2 paragraph 3A(2)(h) to the Act):* The reason for this is: Since this project focuses on the process of implantation, the embryos will be cultured for several days including the time at which the early embryonic lineages are segregated. Analyzing the metabolic products of developing embryo's is one of the components of this study. Another is monitoring the response of implanting embryos to exogenous factors.

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

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

13. The Committee was satisfied that the research project had received the necessary approval from National Research Ethics Service.

14. The Committee noted the recommendation from the Inspectorate to renew the centre's research licence for a period of 3 years without additional conditions.

Decision

15. The Committee agreed to renew the research licence for project (R0111) for a period of three years with no additional conditions.

16. The Committee urged the centre to implement the remaining recommendation regarding research information and data sheet returns and reminded the centre of its duty to comply with General Direction 0002.

Signed: Date: 24/09/2012

Emily Jackson (Chair)