New Research Licence Inspection Report

Project Title	Development of a model to study implantation in the human
Centre Name	Oxford Fertility Unit
Centre Number	0035
Research licence Number	To be assigned. This New Research Licence Application is to allow research associated with project R0111 to be continued on a second site
Centre Address	Centre 0035's proposed new premises at: Institute for Reproductive Sciences, Oxford Business Park North, Oxford, OX4 2HW
Treatment centres donating to this research project	0035 – Oxford Fertility Unit 0139 – Bath Assisted Conception Clinic
Inspection date	25th August 2009
Licence Committee Date	16th September 2009
Inspector(s)	Andrew Leonard Gill Walsh
Fee Paid - date	Fee paid
Person Responsible	Dr Karen Turner
Nominal Licensee	Prof Ian Sargent
Licence expiry date	New licence application

About the Inspection:
The purpose of the inspection is to ensure that research will be carried out in compliance with the HF&E Act 1990, Code of Practice, licence conditions and directions. The report is used to summarise the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the Licence Committee who makes the decision about the centre's new licence application. The report is also available to patients and the public following the Licence Committee meeting.

Brief Description of the Project

This new research licence application is to allow research associated with project R0111 to be continued on a second site, at the proposed new premises of the Oxford Fertility Unit (OFU; HFEA centre 0035), at the Institute for Reproductive Sciences, Oxford Business Park North, Oxford, OX4 2HW. A new treatment and storage licence application has been made by the Centre's PR for these new premises from 1st October 2009, to be considered by a HFEA Licence Committee on the 21st September 2009.

Project R0111 is currently housed within a research laboratory at Centre 0035's premises on level 4 of the Women's Centre, John Radcliffe Hospital, and in research laboratories within the Academic Department of Obstetrics and Gynaecology, Oxford University, on the floor below Centre 0035. When the OFU moves to its proposed new premises, project R0111 will continue at the Academic Department of Obstetrics and Gynaecology, Oxford University on level 3 of the John Radcliffe Hospital. This new research licence application is to allow work associated with project R0111 to be carried out at Centre 0035's new premises. Much of the application is therefore common to the recent renewal application for project R0111, approved by research licence committee on the 15th July 2009.

The new research licence application includes the usage in each year of the 3 year licence term 750 fresh embryos and 250 frozen embryos. This usage concurs with the proposed usage in project R0111. This is unsurprising because all embryos consented to the new research project will be cultured at the IRS then transported to researchers working on project R0111 at the JRH.

The lay summary for the project states:
'Despite significant advances in assisted reproduction technology over the last decade, pregnancy rates remain disappointingly low. While fertilization 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. We are therefore developing in vitro models to study factors which control pre-implantation development and how the human embryo attaches, invades and interacts with the different cell populations of the endometrium during implantation and the molecules which are involved in these processes. It is hoped that these studies will increase our understanding of the causes of poor implantation and implantation failure and may lead to new treatments for infertility and miscarriage.'

Summary for Licence Committee

This is a new Research Licence Application to allow research associated with project R0111 to continue on a second site, at the proposed new premises of the Oxford Fertility Unit (OFU; HFEA centre 0035), at the Institute for Reproductive Sciences (IRS), Oxford Business Park North, Oxford, OX4 2HW. A new treatment and storage licence application has been made for these new premises from 1st October 2009, to be considered by a HFEA Licence Committee on the 21st September 2009.

Project R0111 is currently housed within a research laboratory at Centre 0035's current premises on level 4 of the Women's Centre, John Radcliffe Hospital (JRH), and in research laboratories within the Academic Department of Obstetrics and Gynaecology, Oxford University, on the floor below Centre 0035 (Note that in the application this unit is sometimes referred as the Nuffield Department of Obstetrics and Gynaecology – NDOG; this has been corrected in this report). When the OFU moves to its proposed new premises at the IRS, project R0111 will continue at its current premises in the JRH. This new research licence application is to allow work associated with project R0111 to be carried out at Centre 0035's new premises in the IRS. The proposed work will principally involve culturing research donated embryos in a designated research incubator and laboratory, before they are transferred to project R0111 at the JRH for molecular characterisation and other experiments. As a research licence can not cover research on two premises, this new licence application has had to be made.

The researchers consider that research on the two sites will form a common project, i.e. R0111. Thus much of this application is identical to the recent renewal application for project R0111, approved by research licence committee on the 15th July 2009. Indeed the only differences are in the premises and equipment section for obvious reasons, and in the patient information and consenting sections, due to document revision.

This new research licence application includes research on human embryos and storage of licensed material as the licensed activities, as were also applied for in the recent renewal of project R0111. The new research licence application is requested for the same defined purposes as project R0111, i.e.: Promoting advances in the treatment of infertility; increasing knowledge about the causes of miscarriages; increasing knowledge about the development of embryos. The new research licence application includes the usage in each year of the 3 year licence term 750 fresh embryos and 250 frozen embryos. This usage concurs with the proposed usage in project R0111. This is unsurprising because all embryos consented to the new research project will be cultured at the IRS then transported to researchers working on project R0111 at the JRH.

The PR has informed the inspectorate that research procedures related to this new research licence application will be identical to those used in project R0111. Thus the inspectorate were satisfied that the research will be well organised and carried out in a professional manner which complies with the Code of Practice, 7th edition. The proposed research donation processes, consenting and scientific practices are the same as those used in project R0111. These were considered compliant at the renewal inspection at the current premises in May 2009 and would appear to be so now in this application.

Patient information and consent forms provided with this application were considered by the

inspectorate to be compliant in many ways with HFEA Code of Practice, however some revision is required as detailed in Section 4 of this report. This is notably in the patient information supplied to patients with embryos in storage, to ensure that information provided is compliant with HFEA Code of Practice, S.8.3.1 and S.8.3.2 a-d and G.5.13.1 a-i. Changes should be made before patients consent to donate to this project.

Peer review of this new research licence application was positive and recommended acceptance of the application in its present form.

The inspectorate recommend the granting of a new research licence to this project. Normally new research licences are granted for a one year term, however in this case, the inspectorate recommend the provision of a three year licence since the Centre have held several HFEA research licences, three of which are currently active, and are considered to be in nearly all aspects compliant with HFEA requirements. This new research licence should commence on 1st October 2009.

Proposed licence variations

None

Report of Inspection findings

1. **Organisation**

Desired Outcome: The research is well-organised and managed and complies with the requirements of the HFE Act.

Summary of findings from inspection
Evidence of:

- Leadership and management
- Staffing
- Funding
- Organisation of the centre
- Resource management
- Research governance

Staff

Principal investigators	2
Scientists	4
Laboratory technicians	0
Support staff (receptionists, record managers, quality and risk managers etc)	0

Highlighted areas of firm compliance
The treatment and storage and research licences at Centre 0035's current premises have different PRs and clinical and research practices are separated. The one area of close approach between clinical and research activities is that embryos in storage for treatment for which consent for research use is obtained, remain stored in the same dewar position until used in research. There are no research dewars for embryo storage. Removal of embryos from dewars for research use is appropriately witnessed and recorded in patient records. These arrangements will continue at the new premises if this new research licence application is approved. The proposed Person Responsible (PR) is a Consultant Embryologist and the Laboratory Manager at Centre 0035, while the proposed Nominal Licensee and another professor of reproductive medicine lead the research. The proposed PR and NL hold the same positions on project R0111. The proposed PR has been in post since before the current licence was issued and has completed the PR Entry Programme. The PR has extensive knowledge of the regulatory requirements of the HFEA and is an external advisor to the HFEA. Discussions with the PR indicated that the project will be well lead and managed, as has been previously observed at the renewal inspection of project R0111 The project appeared to be appropriately staffed, with 2 lead scientists and 4 scientists included as licensed personnel in the application. These staff are the same as are licensed for project R0111. Centre 0035 has a research nurse, but she has not been able to work on project R0111 since September 2008, and will not be working on the new project either due to funding limitations. The research nurse is however still employed at the Centre on other projects and can give advice and information if available. The research nurse post may be reactivated if funding becomes available.

The induction procedure for research staff follows the Oxford University requirements and was observed by the inspectorate at a research inspection in May 2009. Each element of induction requires sign-off such that a record of induction is prepared and placed in the staff record. The PR said that research staff training meets the requirements of Oxford University and involves attendance at conferences and internal and external training programmes. Weekly departmental seminars are also held and researchers are encouraged to attend.

Funding is in place for this project and project R0111 from The Medical Research Council and the Wellcome Trust. It does not cover all aspects of the research and further funds are being sought.

While a formal organisational chart is not present, nor is it a requirement, the PR has described an appropriate organisation structure for research. An appropriate staff list was provided in the application All research staff who will have access to licensed material are on the research licence and will also be placed on the new treatment and storage licence for the new premises.

A formal research meeting between the PR and all researchers is currently scheduled twice a year, at which research progress and all matters relating to project R0111 are discussed and minuted. The lead investigators and the researchers meet on a weekly basis. This provides an opportunity to cascade essential information; e-mail is also used for this purpose. These arrangements will remain in place to facilitate communication between the research team working under the new research licence covered by this application.

Contact between the researchers and clinical staff at Centre 0035, by email and telephone, is currently as frequent as required for effective coordination of embryo supply to project R0111. These arrangements will continue to coordinate embryo donation to the new research project covered by this application, then on to project R0111. Communication is facilitated by the PR being the Clinical Laboratory Manager at Centre 0035 and the NL being the Scientific Director, though neither has a role in consenting patients for research. The researchers provide seminars at all staff meetings at Centre 0035, as a means to feedback research progress to clinical staff. Regular emails and telephone calls are used to communicate with Centre 0139. These arrangements will continue as part of the new research project covered by this application.

The Academic Department of Obstetrics and Gynaecology, Oxford University, provides the management structure within which the research staff operate. The University supplies a full range of support services, e.g. health and safety, finance, personnel and facilities management.

Laboratory standard operating procedures (SOPs) related to embryo donation and culture were reviewed by the inspectorate at the renewal inspection of project R0111 in May 2009 and were considered fit for purpose. At this inspection the PR said that these protocols would also be used for the new research project, as the work involved in it is the same as in R0111. Indeed the new research licence is required to allow culture of research donated embryos in a dedicated research laboratory in the new premises, before transfer to the Academic Department of Obstetrics and Gynaecology, Level 3, JRH for experimentation associated with project R0111. The PR also said that SOPs related to embryo donation and culture have already been reviewed to determine whether changes were required due to the move to new

premises. Few changes were necessary and these have all been made. SOPs related to downstream laboratory analyses on the proposed research project were recently considered as part of the renewal of project R0111. The principal investigators considered the SOPs were suitable for the analysis they wished to perform and were updated as required if technique development occurred.

The Centre has a procedure for reporting adverse incidents to the HFEA. This was reviewed at the renewal inspection for project R0111 and was considered appropriate. This procedure will also be used in the new centre premises research laboratory to ensure effective incident reporting occurs.

Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in by this inspection
All covered

2. Premises and equipment

Desired Outcome: The premises and equipment are safe, secure and suitable for their purpose.

Summary of findings from inspection:

- Suitability of premises
- Storage facilities
- Safety of equipment
- Servicing and maintenance of equipment

Highlighted areas of firm compliance
Centre 0035's new premises comprise a renovated two storey business unit of *ca.* 2400 m^2 floor area. The building, the Institute of Reproductive Science, is a collaboration between the University of Oxford, Oxford Fertility Unit and Reprogenetics (a company providing a genetic analysis service to the fertility sector). Thus 30% of the space is allocated to a reproductive sciences post-graduate teaching facility, 65% is allocated for Centre 0035 to provide licensed treatment services and 5% to the Reprogenetics laboratories. The premises were inspected soon after being handed over by the contractors and were therefore unequipped. This research licence application applies to the dedicated research laboratory (room HG32) and the cryolaboratory (HG26) within the new Centre 0035 premises. The cryolaboratory will be used to store embryos for use in treatment as well as in the new research project. Embryos being stored for treatment, if consented for research use, will remain in the same dewar position until thawed for use in research. This practice is the same as that used by the Centre at its current premises. The cryolaboratory was assessed on inspection of the new treatment and storage licence application for the new premises and was found to be compliant with HFEA requirements. Conditions were attached to this assessment in that the inspectorate required the PR to confirm to the HFEA by 30th September that the low level oxygen monitors, the facilities monitoring system and the liquid nitrogen storage vessel and autofiller manifold had been tested and certificated as being in full working order. The dedicated research laboratory is approximately 5 x 5 metres. Plans for its equipment were discussed with the research PR, who outlined that the room was to be equipped by the end of September 2009 with work benching, and a research dedicated incubator and air flow cabinet IVF workstation. The research laboratory will allow research donated embryos to be moved from the clinical IVF laboratories into a research environment as soon as possible after donation. Once there, they will be cultured until ready for transfer to the Academic Department of Obstetrics and Gynaecology, Level 3 and 4, JRH, for use in projects R0111, R0143 and R0149. This new research licence application covers the use of the research laboratory for culturing embryos for use in project R0111. Both the cryolaboratory and the research laboratory have electronic card key activated locks, by which access will be restricted to research personnel. Both rooms are fitted with fire, movement and temperature detector/monitors, which are integrated into the complex building management system installed at the new premises. This system will summons assistance in the event of fire or break-in and will also log all person who access the rooms. Dewars in the cryolaboratory will also be monitored by the facilities management system which will provide warnings to on-call staff in the event of dewar failure.

A documented system for equipment maintenance/servicing is in place at the new premises; the Clinical Laboratory Manager is the designated person responsible for the maintenance of equipment. On the last 2 inspections of project R0111, all equipment sampled was within servicing intervals and servicing documentation was available. All electrical equipment had been subjected to portable appliance testing. These working practices will continue at the new premises to ensure all equipment used in the proposed new project is safe and well maintained.

The research laboratory and cryolaboratory will be risk assessed before the start of licensed activities and then annually by Centre 0035 staff. All research procedures to be used on the proposed project have been risk assessed.

The research laboratory and cryolaboratory will be cleaned by the same contractor who will be cleaning the clinical IVF laboratories. The contractor is committed to providing named cleaners to the premises, thus the cleaning team of 5 persons will be stable and known to Centre staff and educated regarding the materials to use for cleaning and hazards in their workplace.

After inspection of the research premises and discussions with the PR, the inspectorate consider that the proposed research premises and equipment seemed appropriate and should provide a safe, clean and secure environment in which to pursue this research project.

Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in by this inspection
All covered

3. Donation of material

Desired outcome: Donors are recruited appropriately and any research carried out on their embryos is in accordance with their consent.

Summary of findings from inspection:

- Recruitment of donors
- Ensuring prospective donors have access to further guidance
- Ensuring prospective donors have time to consider donation properly
- Ensuring patient consent is not breached
- Donor and patient records
- Prevention of coercion of prospective donors

Highlighted areas of firm compliance
Embryo donors are recruited to the Centre's three licensed research projects (R0111, R0143 and R0149) by a common research donor recruitment procedure at Centre 0035 and also from the Bath Assisted Conception Clinic (Centre 0139). Currently, fresh embryo donors are recruited at Centre 0035 to three licensed research projects (R0143, R0143 and R0149) by a common research donor recruitment procedure which will also be used for the proposed project. All couples are provided research information with their treatment information at an initial orientation open evening. HFEA consent forms are signed at a consenting consultation some time afterwards, and general consent to research is taken on the HFEA treatment consent form if patients are interested. This practice will change slightly at the new premises as the new HFEA treatment consent form does not contain a general consent to research, rather it allows a patient to provide consent to allow the Centre to inform them about research donation opportunities. Thus if such consent is provided, research information will be discussed, if required, and research consents taken by nursing staff. If further information or time to consider is required, a further consultation is arranged at which research will be discussed and consent taken if patients so wish. The Centre's research consent form is detailed and allows them to specify the projects to which they consent to donate. Research consents are normally collected before the start of treatment and well before egg collection. Cryopreserved donated embryos from Centres 0035 and 0139 are also used. Patients with frozen embryos are annually asked to confirm storage arrangements for the forthcoming year. If they express an interest in donating to research they are sent a 'donating frozen embryos to research' information sheet and a consent form. The consent forms are signed by the patients and returned to their Centre. These recruitment procedures will remain in place after the move to new premises and be used for recruitment to the proposed new research project. Defined processes are in place to prevent a breach of patients' research consent and, according to the PR, will remain so after the move to new premises. Prior to egg collection, patient notes are reviewed for all consents including those for research and a note taken of research consented patients. After transfer of the best one or two embryos, the Centre has a specific procedure which defines the quality of embryos frozen for treatment; any remaining embryos are available for research. At this point research consents are verified in the patient notes, then checked again and witnessed by another clinical embryologist. These procedures for verifying consents will remain in place after the move to new premises.

Research consented embryos will be transferred to anonymised dishes then passed to the research laboratory with an affidavit from the clinical embryologists detailing the consents applying, and placed in culture. The research donation will be logged by the clinical embryologists in a book, kept in the clinical laboratory, detailing: anonymised research code; patient name; centre number; projects consented to; date of donation to research; developmental stage with length in culture post-fertilisation). After delivery to the research laboratory, the embryos will be allocated to a research project, depending on the consents provided and on which researchers are available, and transferred back to the Academic Department of Obstetrics and Gynaecology, JRH, for use in projects R0111 or R0143.

Cryopreserved embryos consented for the proposed research project, will be rapidly used after consent is provided, normally within days. Thus research storage audits are not planned however all storage dewars are audited two-yearly to comply with the treatment and storage licence conditions. Currently, research consented embryos in storage remain catalogued within the treatment and storage dewar logs and subject to the bring-forward system used in the clinical embryology laboratories to prevent storage beyond the consented storage period. If research-consented embryos approach the end of their consented storage, the clinical embryologists inform the researchers who arrange for their thaw and use in research. These practices will continue if this new research project licence is approved.

A research culture sheet labelled with the research number and culture dish location will be maintained for each embryo, on which daily observations and culture activities will be recorded. Culture sheets will remain in the licensed culture laboratory at all times.

The donation procedures currently used by the centre would seem to prevent the possibility of coercion of research donors and no complaints have been received regarding this issue. No evidence was observed to indicate that the Centre offer inducements to donate.

Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in by this inspection
All covered

4. Patient information and consents

Desired outcome: Patients are provided with appropriate information which allows them to give informed consent.

Summary of findings from inspection:

- Patient information
- Consent forms
- Patient information for projects deriving embryonic stem cells
- Consent forms for projects deriving embryonic stem cells

Results of consent audit
A consent audit was not performed on this new research licence application inspection. At the recent renewal inspection for project R0111 in May 2009, consenting procedures and documentation in patient records was reviewed. This indicated that, in the opinion of the inspectorate, consenting at Centre 0035 was robust and compliant with HFEA Code of Practice requirements.
Highlighted areas of firm compliance
The new patient research information/consent form for research at Centre 0035 (Research and training projects using surplus eggs and embryos; PIS v.4, dated 01/08/09, 5 pages) was reviewed by the inspectorate. It describes all the projects available at Centre 0035 and collects patient consents for the use of fresh embryos in projects R0111, R0143 and R0149. This document will also be used to inform patients regarding the proposed research project, which in essence will feed embryos into project R0111. These patient information and consent forms were well presented and generally compliant with Code of Practice requirements regarding information provided to research donors, however some minor issues of content are raised below at point 1. The information had been recently reviewed by the Centre and reflected the change to new premises. The research information/consent forms provided to patients with frozen embryos at Centre 0035 (Frozen embryos to research.docv v.3, dated 02/03/09, 1 page) was also reviewed by the inspectorate. This document is less detailed than the information provided to patients regarding fresh embryo donation, however patients provided with it should have already received an earlier version of 'Research and training projects using surplus eggs and embryos' before treatment. Taken together, the information provided by both documents to these patients fulfils most HFEA requirements, the exception being discussed below in issues for consideration at point 2) and 3). The research information/consent form provided to patients with frozen embryos at Centre 0139 (Frozen embryos to research - External v.1, dated 02/03/09) was also reviewed. This document contains little detail except for a description of research project R0111, and requires revision, as discussed below at point 4) and 5).
Issues for consideration
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. Given the role of the proposed licensed research, this project number could be included with R0111 in a single consent.

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.

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. 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 (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 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 patient 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'. 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.

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.

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 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. The PR should audit the information provided to patients at Centre 0139 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.

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 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.

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Executive recommendations for Licence Committee

The Licence Committee is asked to endorse the recommendation that the PR ensures that patient information is audited and revised to be compliant with the research information requirements of the HFEA Code of Practice, 7th edition. This assessment should be completed and any revisions made, before patients are consent for donation to this project.

Areas not covered in by this inspection

All covered

5. Scientific practice, Development of a model to study implantation in the human

Desired outcome: Research is carried out in accordance with licence conditions and makes progress towards achieving stated aims

Summary of:

- Peer review

Summary
The proposed licensed research activities include research on human embryos and storage of licensed material. Downstream analytical methods to be used include: PCR analysis of gene expression in embryos from early cleavage stage to blastocyst; High resolution immunohistochemical analysis after fixation; Transfection of siRNA and/or dominant-negative mutant cDNAs into the trophectoderm of peri-implantation blastocysts for gene knockdown. The research licence is requested for: Promoting advances in the treatment of infertility; increasing knowledge about the causes of miscarriages; increasing knowledge about the development of embryos. The proposed licence is almost identical to the application made for renewal of research project R0111, inspected at Centre 0035 in May 2009. This is because the proposed licence is to allow culture of research donated embryos at the new IRS premises for Centre 0035, before they are transported to the old JRH premises for experimental use in project R0111. In the future, some experimentation relevant to project R0111 will be performed on embryos under the proposed research licence at Centre 0035's new premises; there are however no immediate plans for this. **Usage and expected usage in next year**: The proposed project estimates it will use 750 fresh and 250 frozen embryos per year for the three year term of the licence. These usage estimates were also provided in the renewal application for project R0111 in May 2009. It is foreseen that embryos used in the proposed project will then be used in project R0111.
Summary of audit of stored and biopsied material
No licensed materials were in store on the day of inspection so no audit was performed.
Project objectives
The main objectives of the research are identical to those in R0111 namely: 1) Detection of molecules involved in the implantation process in pre-, peri- and post-implantation embryos with special reference to HLA-G and the factors which control its expression. 2) The solid phase, 2-D and 3-D models will be used to investigate aspects of human embryo implantation: Fresh embryos donated for research will be obtained from the Oxford Fertility Unit in the new IRS building. For some experiments (pre-implantation development) embryos will be cultured to the blastocyst stage in the new embryo research laboratory in the IRS facility under the new research licence. However, for other experiments (implantation model), embryos will be cultured under the proposed research licence for a short time before being transported at the cleavage or blastocyst stages to the existing facility in the Academic Department of Obstetrics and Gynaecology, JRH, and cultured under the R0111 licence. The reason for this is that the

endometrial cells are cultured in the JRH site 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 new research premises

Research proposal

Abstract

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. Molecules believed to be involved in blastocyst attachment are studied either by coupling them to glass slides or expressing them as cell surface molecules in cell lines. Blastocyst attachment to the slides or cells is then determined. 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.

Proposed work

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In these models human embryos donated for research will be cultured to the blastocyst stage. Molecules believed to be involved in blastocyst attachment are studied either by coupling them to glass slides or expressing them as cell surface molecules in cell lines. Blastocyst attachment to the slides or cells is then determined. 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.

Background

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. We are therefore developing in vitro models to study factors which control pre-implantation development and how the human embryo attaches, invades and interacts with the different cell populations of the endometrium during implantation and the molecules which are involved in these processes. This is an ongoing research study which currently operates under the Research Licence R0111.

The development of these models has progressed at different levels. Firstly, studies are being carried out to look at the expression of molecules thought to be involved in implantation in pre and peri-implantation embryos. Secondly, the dissection of molecular events involved in implantation is being investigated by studying the interactions between embryos and defined molecules in vitro and thirdly, we are studying the interaction between blastocysts and purified populations of endometrial stromal and epithelial cells in the presence or absence of specific receptor agonists/antagonists. The different cellular and molecular events involved in implantation are also being studied in 3-dimensional models comprising i) human endometrial epithelial and stromal cells and extracellular matrix that imitates the architecture of the normal endometrium, and ii) microbiopsies of endometrial tissue.

The main achievements have been:

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

Pre-implantation embryos express a range of molecules that may be involved in the implantation process. Documentation of both their pattern and levels of expression throughout embryo development to the blastocyst stage are essential to our understanding of their potential roles. To develop the necessary techniques for these studies we have focussed on one particular molecule, HLA-G, with which we have extensive experience.

a) HLA-G

Human leukocyte antigen G (HLA-G) is a virtually non-polymorphic HLA class I gene expressed by the implanting embryo, which is believed to play a key role in maternal immune tolerance of the fetus. In addition to its effects on T cells, it is now known that both decidual macrophages and natural killer (NK) cells express specific receptors for HLA-G and that binding of these receptors may trigger the release of a range of cytokines involved in implantation and angiogenesis. HLA-G mRNA can be alternatively spliced into six principal transcripts, which encode four membrane bound isoforms (G1, G2, G3, G4) and two soluble isoforms (G5 and G6). There has been a growing interest in HLA-G expression by human embryos as there have are reports suggesting that the levels of soluble HLA-G secreted into the culture medium by an IVF embryo could be used as a diagnostic marker of its potential to implant. However, not all studies support this finding [1]. Our previous work on this project has shown that the percentage of embryos expressing each HLA-G isoform mRNA increased with developmental stage but, contrary to expectation, soluble HLAG5 mRNA was not detected in single 2-8 cell embryos and was only expressed by 20% of morulae and blastocysts [2]. This is at a much lower frequency than the reports of the detection of soluble HLA-G protein. This disparity between mRNA and protein may be due to the HLA-G protein in the embryo being produced from maternal oocyte mRNA stores prior to embryonic genome activation and brings into question the measurement of soluble HLA-G for clinical evaluation of embryo quality.

b) Measurement of soluble HLA-G in IVF embryo culture medium

The Oxford Fertility Unit is part of a European Network of Excellence on Embryo Implantation Control (EMBIC), which, amongst many other projects, has investigated whether there is a correlation between soluble HLA-G expression and embryo quality in vitro. In only one of the three centres involved was a significant correlation between the presence of sHLA-G and successful implantation found [3]. Furthermore, it was apparent that the numbers of sHLA-G positive embryos and the levels of sHLA-G they produced were dependent of the culture media and conditions use in each IVF Unit. Overall these results do not support the idea that sHLA-G is as yet a reliable marker for selecting the best embryos to transfer in IVF.

c) Maternal factors which may upregulate HLA-G expression during implantation

Although measurement of sHLA-G in embryo culture supernatants may not yet be a reliable method of selecting the best embryos for transfer, HLA-G expression is still very likely to play an important role in blastocyst implantation. An important question is how factors (growth factors and cytokines) produced by the endometrium might upregulate embryo HLA-G expression and thereby improve implantation. In particular LIF, IFNκ, progesterone, IL-10 and, more recently, galectin-1 have been reported to upregulate HLA-G on trophoblast. Our aim is therefore to investigate the effect of these factors on HLA-G expression by human blastocysts. The ultimate aim would be to use these factors clinically to improve blastocyst implantation.

2) In Vitro models to study the molecular basis of implantation

a) Models to study the attachment phase of implantation

In this study, we showed that the membrane bound heparin binding epidermal growth (tm-HB-EGF) is expressed on the lumenal surface of the human endometrial epithelium at the time of implantation and that the its receptor (ErbB4) is expressed on the trophectoderm of human peri-implantation blastocysts, suggesting that HBEGF/ ErbB4 interaction could be involved in embryo attachment. To investigate this functionally HB-EGF was coupled to glass slides and expressed in Chinese hamster ovary cells. Significantly more embryos bound to HB-EGF than controls [4]. These data clearly suggest a role for HB-EGF in implantation and the techniques developed are applicable to the investigation of a range of molecules in these processes.

b) An in vitro model for stromal invasion during blastocyst implantation

A model for studying the invasion of endometrial stromal cells by human blastocysts has been established. Single hatched human blastocysts are cultured until day 9 on stromal cells prepared from endometrial samples from women undergoing hysterectomy layer. Blastocysts attach to the stromal cell and exhibit trophoblast spreading and outgrowth onto, and invasion into, the stromal cell layer [5]. These experiments have demonstrated the significant potential of this model for the study of the trophoblast invasion phase of the implantation process.

c) A *3D model for implantation*

We have also established a three-dimensional model for investigating implantation of the human embryo. Human peri-implantation blastocysts are placed on 3-D cultures of human endometrial stromal cells in an extracellular matrix gel overlayed with a layer of endometrial epithelial cells. The embryos are then allowed to implant for 24- 72 hours. This allows us to prepare thin sections of implantation sites and will enable us to investigate the expression of a number of different molecules in each embryo experiment, thus resulting in a very efficient use of embryos. We have so far determined the expression of extracellular matrix receptors,

integrins, in trophoblast and stroma of implanting blastocysts.

3) Studies using the in vitro model for stromal invasion during blastocyst implantation
The blastocyst/stromal cell invasion assay has been used to investigate the function of the Rho GTPAase family of signalling molecules and the effect of gonadotrophin (GnRH) analogues in embryo trophoblast spreading and invasion.

a) Rho GTPases and implantation
We have demonstrated that specific endometrial stromal cell Rhos are critical for trophoblast invasion. By inhibiting Rac1 and RhoA expression in stromal cells by the use of RNAi, we showed that Rac1 is essential for migration of stromal cells that occurs to allow the embryo to invade, and that RhoA inhibits this activity [6]. We hypothesise that the balanced activity of these molecules regulates and controls trophoblast invasion of the extracellular matrix of the endometrial stroma. We also demonstrated that factors that regulate Rac1 are inhibited adjacent to the invading embryo, further suggesting that the embryo itself signals locally to the stroma to facilitate invasion.

b) The effect of GnRH analogues on implantation
It has been suggested previously in the literature that GnRH analogues used in infertility treatment inhibit implantation. We have used the in vitro model to investigate the potential effect of GnRH analogues on embryo invasion into the stroma. We demonstrated that the presence in the co-cultures of the GnRH analogues cetrotide or buserilin did not affect the ability of the embryo to invade or the extent of invasion. We were thus able to show that, at least in vitro, these molecules do not affect this stage of implantation [7].

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Main objectives, methods and disposal
The main objectives of the research are identical to those in R0111 namely:

1) Detection of molecules involved in the implantation process in pre-, peri- and post-implantation embryos with special reference to HLA-G and the factors which control its expression.
2) The solid phase, 2-D and 3-D models will be used to investigate aspects of human embryo implantation:
Fresh embryos donated for research will be obtained from the Oxford Fertility Unit in the new IRS building. For some experiments (pre-implantation development) embryos will be cultured to the blastocyst stage in the new embryo research laboratory in the IRS facility under the new research licence. However, for other experiments (implantation model), embryos will be cultured under the proposed research licence for a short time before being transported at the cleavage or blastocyst stages to the existing facility in the Academic Department of Obstetrics and Gynaecology, JRH, and cultured under the R0111 licence. The reason for this is that the endometrial cells are cultured in the JRH site 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 new research premises

Future Developments
1) Maternal factors which may upregulate HLA-G expression during implantation
Although measurement of sHLA-G in embryo culture supernatants may not yet be a reliable method of selecting the best embryos for transfer, HLA-G expression is still very likely to play an important role in blastocyst implantation. An important question is how factors (growth factors and cytokines) produced by the endometrium might upregulate embryo HLA-G expression and thereby improve implantation. To study this we are initially using two models; human trophoblast (choriocarcinoma) cell lines and bovine embryos. Recently, we have looked at the effect of Galectin 1, an immunoregulatory molecule which plays a pivotal role in materno-fetal tolerance in the mouse, and shown that it significantly upregulates HLA-G protein expression on JEG3 cells, as measured by flow cytometry. It is proposed to study the changes in expression of the 6 different HLA-G mRNA isoforms using real-time PCR, and in particular the effect of Galectin-1 on sHLA-G. The effect of Galectin-1 on bovine embryo development and MHC expression will be studied in collaboration with Dr Trudee Fair at University College as a prelude to studying its effects on human embryos, once all of the techniques are established. Human embryos will then be cultured in the presence or absence of different concentrations of galectin-1up to day 9. At the end of the culture the embryos will be fixed in paraformaldehyde and the expression of HLA-G determined by immunofluorescence staining, or treated with lysis buffer to extract mRNA for real time PCR to identify the levels of expression of the different HLA-G isoform mRNAs.

2) The solid phase, 2-D and 3- D models for human embryo implantation will be used to investigate:-
i) the function of adhesion- related and EGF family molecules in implantation.
ii) the effect of procedures and drugs used in ART on the capacity of embryos to invade the endometrial stroma
iii) the fate of early human stem cells in the peri- and post implantation embryo in vitro

The endometrial cell-blastocyst co-culture models will also be used to identify genes that are modulated in response to the implanting human blastocyst in vitro. This has been achieved by co-culturing peri-implantation human blastocysts and endometrial epithelial or stromal cells for 24-48 hours. The RNA from both the blastocysts dissected from the cultures at the end of the experiment, and the endometrial cell layer, cultured either alone or together, has been amplified and subjected to hybridisation with three types of either cDNA or oligo arrays. We have identified a number of potential candidates that are induced in response to the blastocyst. We are now validating some of these molecules by real time RT-PCR and have begun to extend these validation studies to protein analyses. These experiments are particularly important since it has not been possible previously to study in the human genes that are modulated by the blastocyst, but such cross talk is likely to be very important in implantation, as shown in the mouse.

The 3- D models are beginning to yield data showing expression of members of the EGF family and integrins, complementing our work on these molecules in solid phase end cell-embryo co-culture systems.

Methods

We have now established robust and highly reproducible methods for culturing embryos to the blastocyst stage and performing experimental models of human embryo implantation. These are now routinely used in our laboratory. We will continue to use all three models: i) solid phase testing single or mixtures of molecules; ii) 2- D testing interaction of embryos with endometrial epithelial and stromal cell; and iii) 3- D allowing us to dissect the cellular and molecular events that mediate progression of the embryo through the implantation process. The co-cultures will be monitored for between 8- 12 days pc and then fixed in either acetone or paraformaldehyde and assessed. Other embryos will be disposed of after fixation in alcohol.

The expression of candidate molecules or differentiation markers will be achieved by high resolution fluorescence and image analyses techniques together with real time PCR. The function of specific molecules will be tested by specific inhibitors, transfection of the trophoblast and endometrial cells with fluorescently- labelled cDNAs or RNAi in the co-cultures.

Summary

The proposed studies are designed to determine molecules that are critical for early human development during the implantation process. These are both embryonic and maternal, and further our 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 fifteen 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.

Peer review comments (if applicable)

The peer reviewer used a renewal application peer review form, submitted on 24/08/2009. It was however clear that they considered that they had enough information available in the

application to recommend acceptance in its current form.

The peer reviewer concurred with the applicants in that the research complied with the following defined purposes: Promoting advances in the treatment of infertility; increasing knowledge about the causes of miscarriages; increasing knowledge about the development of embryos

Regarding the justification for the project, the reviewer stated:
'This group is involved in ongoing research at another centre, and this application is a request to expand the project to a new facility. The research has been very fruitful so far, resulting in several substantial publications. The use of discarded human embryos is justified for this research, and it is very likely that the findings of this research will lead to treatments/embryos selection criteria that may improve the chances of implantation, thereby increasing the number of successful pregnancies arising from IVF treatment.'

The peer reviewer also added:
'This application is presented by a group that has an excellent track record in the field and is currently involved in productive research of this nature. However, the application would benefit from more careful proof reading. In addition, I wonder if the applicants are aware that there is a duplicated section towards the end of Appendix D, where they describe Project A?'

The inspectorate believe that this latter comment has been made because the peer reviewer has assumed duplication of the information supplied to patients with embryos in storage, whereas there are two sets of information for such patients, one set for patients at Centre 0035 (Frozen embryos to research.docv v.3, dated 02/03/09, 1 page) and one set for patients at Centre 0139 (Frozen embryos to research - External v.1, dated 05/07/07, 1 page).

Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered on this inspection
All areas covered

Report compiled by:

Name	Andrew Leonard
Designation	HFEA inspector
Date	4th September 2009

Appendix A: Centre Staff interviewed

PR

Appendix B: Licence history

None. New licence application

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number 0035

Name of PR Dr Karen Turner

Date of Inspection 25th August 2009

Date of Response By email on 8th September 2009

Please state any comments regarding the inspection and actions you have taken or are planning to take following the inspection with time scales

The amendments to the patient information sheets/consent forms requested will be made as soon as possible and no further patients will be recruited until this has been done.

2. Correction of factual inaccuracies

Please let us know of any factual corrections that you believe need to be made (NB we will make any alterations to the report where there are factual inaccuracies. Any other comments about the inspection report will be appended to the report).

There were no factual inaccuracies in the report

HFEA Research Licence Committee Meeting

16 September 2009

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 1

Oxford Fertility Unit (0035; R0111) – New Licence to allow project R0111 at Centre (0035) to be carried on in new premises

Members of the Committee:	Committee Secretary:
Emily Jackson (lay) – Chair Richard Harries (lay) Hossam Abdalla (clinician)	Kristen Veblen Legal Adviser: Stephen Hocking, Beachcroft
Apologies: David Archard (lay) Lesley Regan (clinician)	

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:

- papers for licence committee (112 pages)
- one tabled paper (2 pages)

The Committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings
- 7th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- HFEA (Licence Committees and Appeals) Regulations 1991 (SI 1991/1889)
- Decision Trees for Granting and Renewing Licences and Considering Requests to Vary a Licence; and
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.

1. The Committee considered the papers, which included the new licence inspection report, the application form with ethical approval, staff

curriculum vitae, peer review, patient information and consent forms and relevant publications. Additionally, the Committee noted that a response to the report from the Person Responsible (PR) had been tabled.

2. The Committee noted that the inspection had taken place on 25 August 2009 and that, in the PR's response, she had undertaken to make all of the necessary amendments to the patient information that had been outlined in the report. Further the Committee noted in her response that the PR had committed to recruit no further patients until the patient information was fully compliant.

3. Additionally, the Committee noted that on the form titled, "Patient Consent to Research: Research and training projects using surplus eggs and embyros" point 5 should qualify the statement that "consent may be withdrawn at any time" with the statement that this is only possible until the embryos had been used in research, as was the case in the third paragraph of the patient consent to research form titled 'Derivation of human embryonic stem cell lines'.

4. The Committee also wished to draw the Centre's attention to repetition of the "Study A – Development of a model to study implantation in the human (COREC 04.Q1606/44, HFEA R0111)" in the patient information sheet regarding the donating of frozen embryos to research.

<u>The Committee's Decision</u>

5. The Committee identified the activities to be authorised by a licence as storage of embryos and use of donated embryos for research. The Committee agreed that they were satisfied that these activities were not prohibited under the HFE Act 1990 (as amended).

6. The Committee decided that these activities were necessary and desirable for the following purposes:
   - Promoting advances in the treatment of infertility
     HFE Act 1990 (as amended) 2 3(2)(a)
   - increasing knowledge about the causes of miscarriage
     HFE Act 2001 2 3(2)(c)
   - increasing knowledge about the development of embryos
     HFE (Research Purposes) Regulations 2001 2(a)

7. The Committee decided that it was satisfied that the proposed use of embryos was necessary and desirable for the purposes of this research. In making this decision, the committee took into account that in order to

understand failures in implantation of human embryos it was necessary to use human embryos, as animal embryos dd not behave in the same way.

8. The Committee noted that, with the changes the PR had undertaken to make, as well as the two amendments outlined above, it considered itself satisfied that the patient forms were fit for purpose. Additionally, the Committee again noted and commended the PR's commitment not to recruit any further patients until the forms were fully compliant.

9. The Committee considered itself satisfied that it was appropriate to grant a licence, noting that the appropriate fee had been paid.

10. The Committee agreed that it was satisfied as to the character, qualifications and experience of the Nominal Licensee. Also, the Committee agreed that it was satisfied as to the character, qualifications and experience of the Person Responsible as required for the supervision of the activities to be discharged under Section 17 of the HFE Act 1990 (as amended).

11. Further, based on the evaluation of the inspectorate, the Committee agreed that it was satisfied that the premises for which the Licence was to be granted were suitable for the activities outlined.

12. The Committee considered that usually a one year licence would be given for a new research project. However, the Committee considered that in this case, and with the recommendation of the inspectorate, a three year licence would be more appropriate, considering that this project was, in fact, a continuation of an existing project at different premises, and that none of the reasons usually given for granting a one year licence applied in this case. The Committee also noted that the licence for the other part of this project, conducted in different premises, would expire on 31 August 2012.

13. In the interest of efficiency and to reduce the regulatory burden on the clinic, the Committee decided to grant this licence for a period of 2 years and 11 months, with no additional conditions, so that the course of the related licences would now run concurrently, and be subject to renewal inspections and licence committee consideration at the same time.

14. The Committee requested that in future matters related to these related licences be brought to the same meeting of the Committee.

Signed..... Date 25.9.09

Emily Jackson (Chair)