Research Licence Interim Inspection Report

Project Title	Human Gamete Interaction and Signalling
Centre Name	Institute of Biomedical Research, Birmingham University
Centre Number	0209
Research licence Number	R0173
Centre Address	Institute for Biomedical Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT
Treatment centres donating to this research project	0119, ACU, Birmingham Women's Hospital
Inspection date	18th July 2008
Licence Committee Date	16th September 2008
Inspector(s)	Andrew Leonard; Janet Kirkland
Fee Paid - date	Fee paid
Person Responsible	Dr Jackson Kirkman Brown
Nominal Licensee	Dr Sue Avery
Licence expiry date	31st December 2009

About the Inspection:
The purpose of the inspection is to ensure that research is carried out in compliance with the HF&E Act 1990, Code of Practice, licence conditions and directions and that progress is made towards achieving the stated aims of the project.

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 licence renewal application. The report is also available to patients and the public following the Licence Committee meeting.

This report covers the period between 1 August 2007 and 18 July 2008.

Brief Description of the Projects

Project: **R0173: Human Gamete Interaction and Signalling**
Licensed since: 1st January 2006

The lay summary of the project is as follows:

As a human sperm approaches the egg it undergoes an event called acrosome reaction (AR), which is thought to be a pre-requisite for successful fertilisation. In the body or in-vitro (in IVF treatment) this is thought to be induced by interaction with proteins of the zona pellucida (ZP), a sticky coat surrounding the egg. Despite the crucial role of AR in fertilisation, the technical and logistic difficulties of undertaking experimental work have been such that almost nothing is known about what happens as a sperm moves through the outer egg coats.

In this project we will employ advanced fluorescent imaging (microscopy) techniques to examine in detail the events occurring as human sperm and egg interact, particularly with reference to concentrations of calcium which we know form a vital part of the signalling that occurs. The data we hope to generate will give new insight into the very early events occurring in fertilisation which, once we know and understand should allow the development of new diagnostic and treatment regimes

Research activities	Research on human embryos	✓
	Storage of licensed material	✓
	Creation of embryos for research	✓
	Derivation of human embryonic stem cells	
	Cell nuclear replacement	

Summary for Licence Committee

The interim inspection was of Project R0173, Human Gamete Interaction and Signalling, which has held a research licence since 1st January 2006 which is due to expire on 31st December 2009. The research licence is needed because the project investigates the early interaction of sperm and oocytes and molecular mechanisms within the two cells which support the resulting acrosome reaction. Thus the possibility exists that an embryo will be created. To date on this project, work has been carried out which has not involved licensed activities in that experiments have focussed on the responses in sperm and investigations have used oocytes enucleated by cytoplasmic removal, and sperm derived from research donors. Neither of these materials is considered HFEA-licensable however the centre effectively treats them as licensed material in their working practices.

No oocytes enucleated or otherwise have however been used in project R0173 this year as other non-licensible experiments were performed which will inform the design of the licensed experiments in the future. In addition, there has been no research nurse at Centre 0119 for most of the last year, hence recruitment of oocyte donors was suspended. A new research nurse will be appointed in September 2008 and usage in the next year is projected at 50 fresh immature oocytes and 30 failed to fertilise oocytes.

The researchers have appropriate experience and are well qualified to continue the programme of research. The premises and equipment are also appropriate and procedures are in place to ensure that patients are treated respectfully. Small improvements can be made in developing procedures to ensure patient consents are not breached and that patient information, research governance and the donation to research procedure, comply with the Code of Practice 7th edition, specifically:

- A procedure for reporting serious adverse events to HFEA should be developed to ensure compliance with General Licence Condition A.4.1 and Code of Practice, 7th edition, Standards S.9.4.1 and S.9.4.2.
- The inspection team were informed by the PR that non-minuted meetings between the PR and researchers occur weekly. The inspectorate recommends that these meetings are minuted and that minutes are stored for later reference.
- It is not clearly defined in centre procedures when oocytes are entering the research programme. The point of transfer to research and the process by which this occurs, needs to be clearly documented and should include witnessed verification that valid research consent is in place and anonymisation of the material, at the time of transfer to research. At present, oocytes are taken into research and enucleated, but research consents are only verified by the clinical embryologists and the sample anonymised on transfer of enucleated oocytes to the researchers. The research PR signs in the patient records that research consent is in place prior to egg collection but consent must be verified when the oocytes pass into research in case consents have been withdrawn. Thus the need to clearly define the point at which the oocytes enter the research pathway and ensure consents are checked and the donated materials anonymised at that point of transfer to the researchers.
- The research PR has a role as the Director of Research and Development at the Centre

for Human Reproductive Sciences in Centre 0119, and some of the other researchers attend that unit. The research PR has contact with the patients during their pre-treatment orientation, informing them regarding the IVF process and research at the centre in their first information session. The research PR and his research assistant consent patients for non-licensed research projects, and have had training with the local Trust on consent taking. It is important that the research PR and his research assistants only provide information to patients about the HFEA licensed research projects, but do not have a role in obtaining consent from patients for donation to them. Consent taking should be performed by staff at Centre 0119 including the research nurse. It is recognised by the inspectorate that the absence of the Research Nurse is one reason why research donation to project R0173 has stopped in the last year and consider that this indicates that the PR is mindful of these issues.

- Licence Committee should note that the patient information and consent forms provide for a patient to consent to supply 1 or 2 'good' oocytes, but only if 12 - 15 or >15 oocytes, respectively, are collected. This is considered by the centre, as clearly discussed in patient information, to have only a minimal impact on the potential success rate of a fresh cycle, but it may affect the number of embryos available for freezing.
- Patient information does not provide contact details for somebody independent of the research with whom patients can discuss donation. It also does not inform patients that they can see a counsellor to discuss the implications if they choose to donate, as required by Code of Practice, 7th Edition, G.6.7.2 (a). This information should be added to the information sheet or provided verbally to the patients.
- Patient information discusses the provision for patients to vary or withdraw their consent up to the point that oocytes are passed over to the researchers (specified as at egg collection), as required by Code of Practice, 7th Edition, S.8.3.1 and G.5.13.1 (g). It says that this can be achieved by asking a member of centre staff and that they should make sure that the staff member notes their withdrawal of consent and signs it. It is recommended that the information provides contact details for a named individual through whom this can be achieved, as well as relating that it can be discussed with a member of staff.

The inspectorate recommend continuation of the research licence for project R0173.

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 R0173

Principal investigator	Dr Jackson Kirkman Brown
Scientists	1 Lecturer; 2 post-doctoral research fellows; 3 PhD students
Collaborators	0
Support staff (receptionists, record managers, quality and risk managers etc)	Quality Manager from Centre 0119 Staff at centre 0119 recruit patients to the research project

Highlighted areas of firm compliance
The research premises of Centre 0209 comprise a laboratory (approximately 5 by 6 meters) within the Institute of Biomedical Research, a research-dedicated building which is part of the University of Birmingham School of Medicine. The Institute is approximately 300 meters from the Assisted Conception Unit, Birmingham Women's Hospital (*i.e.* Centre 0119, the donating centre to project R0173). The facilities and staff within the Institute are part of the University of Birmingham, which provides health and safety, human resources, financial management, training and other infrastructural support. The Person Responsible (PR) is a Senior Lecturer within the School of Medicine with many years of research experience, and also the Director of Research and Development at the Centre for Human Reproductive Sciences in Centre 0119. The PR is the project head and has been PR since its inception on 1st January 2006. The PR shows an understanding of the regulatory requirements of the HFEA. The PR is not the PR of a Treatment and Storage Licence and has completed the PR entry programme. The Nominal Licensee is the PR of the treatment and storage activities at Centre 0119 and has a role in coordinating between the research project and Centre 0119 but no role in carrying out the research. The researchers are well organised and have clear lines of communication and control. All research staff are employed by the University of Birmingham and on recruitment undergo induction through the university for health and safety, fire safety, occupational health etc. They also undergo a local induction course which covers the laboratory and HFEA-regulated work, and the activities of Centre 0119. Induction is signed off in staff personnel files, which are stored in a locked cupboard in the PR's office in the Centre for Human Reproductive Sciences in Centre 0119. The PR said that staff training meets the requirements of funding

bodies and the university and involves attendance at conferences, seminars and internal and external training programmes. Continual professional development (CPD) is also recorded in the staff personnel files stored in the PR's office in Centre 0119.

The research group is funded by the Medical Research Council, Wellcome Trust and Infertility Research Trust. The licensed research is currently not specifically funded and work is carried out using spare funding from these other sources. The PR informed the inspectorate that there is enough funding to last at least to the end of the current research licence and that further grant applications will be made.

Resource management and project coordination is achieved through weekly meetings between the PR and researchers. These are not minuted but email records of interactions were available. Minuted meetings are held between the researchers and the embryologists and nurses of Centre 0119. A dedicated research nurse is normally employed at centre 0119; this post is currently vacant however a candidate is expected to be in place by mid-September 2008. Research data is reported back to Centre 0119 in research seminars by the PR and other researchers, twice annually. A research day is held annually at Centre 0119 at which all research carried out by the Centre for Human Reproductive Sciences is showcased.

Laboratory standard operating procedures (SOPs) are available for staff in an electronic central folder on a university maintained computer server, accessible to specified users on the university computer network. The PR considered the SOPs include all required laboratory methods. The SOPs are updated and added to as required.

Issues for consideration

- A procedure for reporting serious adverse events to HFEA should be developed to ensure compliance with General Licence Condition A.4.1 and Code of Practice, 7th edition, Standards S.9.4.1 and S.9.4.2.
- The inspection team were informed by the PR that non-minuted meetings between the PR and researchers occur weekly. The inspectorate recommends that these meetings are minuted and that minutes are stored for later reference.

Executive recommendations for Licence Committee

The Licence Committee is asked to endorse the recommendations made in relation to the areas for consideration cited above.

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
The laboratory which comprises Centre 0209 is locked on a card key system, access being restricted to licensed personnel only. Oocytes (enucleated by cytoplasmic removal and thus non-licensible) are used on the day of donation and no long-term frozen storage facilities for licensed material are present. The laboratory was appropriately equipped, with a dedicated incubator, two air flow cabinets and two specialised microscopes with micromanipulation and microinjection equipment allowing vital observation of ion currents in oocytes/sperm using ion binding fluorescent dyes. Multiple wavelength channels can be monitored allowing several ion currents to be observed simultaneously within a sperm or oocyte, and data stored electronically. The PR considers that the researchers have all equipment they require for the project. The university ensures the research premises are cleaned and maintained. All apparatus is on service contracts organised centrally within the Institute by a specified person, the divisional technical manager (KW), and the PR considers that all equipment is well maintained. It was noted that the portable appliance testing (PAT) certificates were more than one year old but communication with KW after the inspection indicated that testing was compliant with the University of Birmingham protocol for PAT certification. The premises are risk assessed and randomly inspected by university health and safety staff. The university Biological Safety Officer also inspects the premises on a biennial cycle. The laboratory was inspected by the Health and Safety Executive when they visited the University of Birmingham last year and found to be compliant with their requirements.
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
Work on this project has been suspended for more than 12 months due to the absence of the research nurse, who was on sick leave and then resigned, and because the research goals of the PR were aimed at collecting more data in non-licensed experiments to inform the design of future experiments using licensed material. Donors are recruited from Centre 0119 by the research nurse and as discussed above, one will be appointed by the end September 2008. Recruitment will be carried out as it has been in the past. Specifically, written and verbal information regarding the research project is given when the patients attend an information session (the clinical group meeting) to introduce them to the clinic. They are given a tour of the laboratories and clinical facilities at Centre 0119, and briefed by the research PR in his role within Centre 0119 about IVF treatment and research projects. They are advised that research donation will not have any influence on their clinical treatment. Patients have been investigated by the referring clinics by this stage so can sign some clinical consents and the HFEA registration forms at the end of the session. Patients also indicate whether they are interested in research donation on a tick box in their clinical consent forms but are told by the research PR that this is not a commitment. The suitability of those indicating interest in research donation is assessed on the basis of medical records and those considered suitable are provided further information, which gives details of a person to whom they can address additional questions. The patients next attend a consultation during which they sign specific HFEA treatment consent forms and discuss their treatment plan, after which they can discuss research consent with the research nurse or a researcher. Patients then undergo down-regulation and attend for ultrasound scanning, after which they discuss research consent in the counselling room with the research nurse, or a researcher, and sign consent forms if they choose to donate to research. The research PR said that the researchers used to discuss research consenting with patients have attended local Trust training for consenting patients. He also said that 80% of patients express interest in research donation at the initial information session, and 40% of patients sign consent forms during a scanning day consultation. He considers it a positive sign that so many consent, but is equally positive about the 40% drop out as it suggests that information and time for consideration are allowing patients to make a fully informed decision, which may be negative in some cases. Research consent is obtained before the treatment cycle is started, i.e. long before egg collection, but several weeks after information is first supplied. Patients are also provided with multiple opportunities to obtain further information about the research. Given these points

it would appear that consent is informed and there is enough time for it to be well considered. The inspectorate consider patient information is balanced and non-coercive and note that no patient complaints have been received on this issue.

Prior to egg collection, patient records are signed by the research PR to indicate whether they contain a valid and complete research consent form. This signature is removed if a patient withdraws consent and staff at Centre 0119 know to discuss consent withdrawals with the research PR immediately, and to note such withdrawal in the patient records. In the clinical laboratory, research consented patients who fulfil the research donation criteria are pinpointed and the clinical embryologists call the researchers to warn of an imminent donation. If donation of a 'good' oocyte has been consented, it is selected by the clinical embryologist on the day of collection. 'Failed to fertilise' oocytes are provided after fertilisation checks have been performed by the clinical embryologists.

Donated oocytes are logged, anonymised and processed (e.g. enucleated by cytoplasmic removal) in Centre 0119 by the clinical embryologists. They are then transferred to the researchers along with a handover sheet detailing the research consent provided, this being witnessed on the handover sheet. Oocytes are then transferred from Centre 0119 to the research centre in a portable incubator. They are immediately placed in an incubator in the research premises, for short term (< 2 hours) culture before use in experiments.

The researchers see no patient identifying information after anonymisation, nor does such information leave Centre 0119. Experimental notes and data are documented on computer hard-drives and laboratory notebooks in Centre 0209, oocytes being referenced by their anonymised research code. Experimental notes and records are kept within the research premises. When records are no longer required, they are stored in a locked cupboard in the PR's office in the Centre for Human Reproductive Sciences in Centre 0119.

Issues for consideration

- It is not clearly defined in centre procedures when oocytes are entering the research programme. The point of transfer to research and the process by which this occurs, needs to be clearly documented and should include witnessed verification that valid research consent is in place and anonymisation of the material, at the time of transfer to research. At present, oocytes are taken into research and enucleated, but research consents are only verified by the clinical embryologists and the sample anonymised on transfer of enucleated oocytes to the researchers. The research PR signs in the patient records that research consent is in place prior to egg collection but consent must be verified when the oocytes pass into research in case consents have been withdrawn. Thus the need to clearly define the point at which the oocytes enter the research pathway and ensure consents are checked and the donated materials anonymised at the point of transfer to the researchers.
- The research PR has a role as the Director of Research and Development at the Centre for Human Reproductive Sciences in Centre 0119, and some of the other researchers attend that unit. The research PR has contact with the patients during their pre-treatment orientation, informing them regarding the IVF process and research at the centre in their first information session. The research PR and his research assistant consent patients for non-licensed research projects, and have had training with the local Trust on consent taking. It is important that the research PR and his research assistants

only provide information to patients about the HFEA licensed research projects, but do not have a role in obtaining consent from patients for donation to them. Consent taking should be performed by staff at Centre 0119 including the research nurse. It is recognised by the inspectorate that the absence of the Research Nurse is one reason why research donation to project R0173 has stopped in the last year and consider that this indicates that the PR is mindful of these issues.
Executive recommendations for Licence Committee
The Licence Committee is asked to endorse the recommendations made in relation to the areas for consideration cited above.
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

Highlighted areas of firm compliance
Recently revised patient information and consent forms for project R0173 were assessed by the inspectorate. They were compliant with the Code of Practice, 7th edition, except where noted below.
Issues for consideration
• The patient information and consent forms clearly explain that 'failed to fertilise' oocytes will be used in project R0173 and that these are of no use in treatment and therefore would not affect it. The information and consent forms also provide the facility for a patient to consent to supply 1 or 2 'good' oocytes, but only if 12 - 15 or >15 oocytes, respectively, are collected. This is considered by the centre, as discussed in patient information, to have only a minimal impact on the potential success rate of a fresh cycle, but the information clearly states that it may affect the number of embryos available for freezing. • Patient information does not provide contact details for somebody independent of the research with whom patients can discuss donation. It also does not inform patients that they can see a counsellor to discuss the implications if they choose to donate, as required by Code of Practice, 7th Edition, G.6.7.2 (a). This information should be added to the information sheet or provided verbally to the patients. • Patient information discusses the provision for patients to vary or withdraw their consent up to the point that oocytes are passed over to the researchers (specified as at egg collection), as required by Code of Practice, 7th Edition, S.8.3.1 and G.5.13.1 (g). It says that this can be achieved by asking a member of centre staff and that they should make sure that the staff member notes their withdrawal of consent and signs it. It is recommended that the information provides contact details for a named individual through whom this can be achieved, as well as relating that it can be discussed with a member of staff.
Executive recommendations for Licence Committee
The Licence Committee is asked to endorse the recommendations made in relation to the areas for consideration cited above.
Areas not covered in by this inspection
All covered

5. Scientific practice R0173, Human Gamete Interaction and Signalling

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

Summary of:

- Peer review

Summary

Licence granted for the purposes of:

The project was originally licensed under purposes laid down in Schedule 2 of the Human Fertilisation and Embryology Act 1990;

3(2)(a) to promote advances in the treatment of infertility

And 3(2)(d) developing more effective techniques of contraception

Usage in last year:

Most recent data for a 12 month period: From 15/07/2007 to 15/07/2007

Eggs	**Fresh**	**Failed to fertilise**	**Frozen**
Total number received	0	0	0
Total number used	0	0	0

Oocyte manipulation is carried out in the licensed laboratory (i.e. Centre 0209). All oocytes used on the project since its inception, have been enucleated by cytoplasmic removal within Centre 0119 on donation to the research project. Furthermore no oocytes have been transferred to the project in the last year, as indicated above. This is because the project has lacked a research nurse for most of the last year, though this post will be filled by September 2008. More importantly, the researchers consider they have strategically focussed upon the capture of important data from experiments that will inform the design and execution of licensed experiments, but have not themselves used licensed material this year. These experiments have used enucleated oocytes collected and stored frozen before this inspection year (ie 1 August 2007 and 18 July 2008), and have focussed on questions around sperm motility and zona proteomics. When these data are assembled and analysed they, alongside improved imaging equipment (the Centre have just been awarded £350000 for a new imaging system) will allow more effectively use of fresh whole oocytes in licensed work.

The research PR considers that when enucleated by cytoplasmic removal, the oocytes constitute non-licensible material as fertilisation through interaction with a sperm is impossible in the absence of oocyte genetic material. They are however effectively treated as if licensed. For example, the Centre has a procedure and working practices which ensure that all material is non-viable after experiments, before its subsequent storage, analysis or disposal. This is witnessed contemporaneously in most cases, albeit if experiments run into the early hours, witnessing is performed the following morning.

Estimated usage in the next year:

Material	Expected usage
Fresh Eggs (all immature)	50
Frozen Eggs	0
Failed to Fertilise Eggs	30
Fresh Embryos	0
Frozen Embryos	0

Summary of audit of stored and biopsied material

No licensed materials are stored

Renewed project objectives

The objective of this proposal is unchanged, ie to elucidate the events that occur during human sperm and egg interaction at a cellular and molecular level.

Aims

These aims are not mutually exclusive and many may be accomplished at once in single experiments:

1. Characterisation of the Ca^{2+} responses and other physiological status changes in human spermatozoa in response to zona-enclosed human oocytes.
2. Characterisation of the Ca^{2+} responses, motility and other physiological changes induced in human sperm by cumulus oophorus interaction and penetration.
3. Characterisation of any focal or global signalling events generated in cumulus cells due to interaction or presence of human spermatozoa.
4. Precise monitoring of the human fertilisation event and understanding of how any calcium signalling events occurring within the sperm may relate to those initiated in the oocyte.
5. Examination of whether signals initiated in the periphery of the cumulus, possibly induced by interaction with spermatozoa, propagate to the oocyte itself.
6. Accurate examination of the early fertilisation events in the fresh human oocyte.

Methods

The methods to be used are as described in the original proposal. In addition however, we may use commercially available IVM media and appropriate techniques to study immature oocytes that are consented under this project.

Using IVM to deliver more mature embryos to this project (see 8.1.2) will enable a wider range of research and also provide valuable data and experience for researchers and embryologists in this emerging field.

Summary of research undertaken

A) How the work undertaken relates to the objectives.

It is thought that many cases of infertility relate to as yet unknown causes to do with the interaction and recognition of gametes. Although some work has been done in the mouse, this is a poor model for the human, as many of the proteins shown to be important in the

mouse fertilisation system do not exist in humans. Hence to properly understand the events underlying human fertilisation it is critical to examine them with human cells.

Upon being ovulated the human oocyte is surrounded by a large mass of steroid producing cells (the cumulus oophorus). Work already undertaken in our laboratory has carefully examined the effects of the major steroid produced by this system (progesterone) upon human sperm and their calcium signalling. However, to further understand the events occurring as the sperm penetrates through the cumulus mass we need to examine the living and complex system.

It is also important to resolve whether acrosome reaction, a prerequisite for fertilisation, occurs as cells pass through the cumulus or when they reach the zona glycoprotein coat of the egg. The site of this event will help us more clearly identify the likely major agonist and whether the role of other agonists is to remove sperm by making them respond 'too early'.

We are in a unique situation where we can combine experience and expertise in calcium imaging within male human gametes with an accurate examination of how they interact with the oocyte. A further advantage is that with dual-labelling of the gametes we also hope to be able to examine whether contact with sperm induces signalling events within the cumulus, that pass to the oocyte signalling imminent fertilisation. Or whether as the egg is fertilised signals propagate back out through the cumulus - as potentially this may also act to prevent polyspermy.

B) Research undertaken to date.
We have identified that human cumulus produces nitric oxide as well as progesterone, that this nitric oxide can nitrosylate proteins within human sperm and that exposures at these levels to human sperm affect sperm motility and calcium signalling.

Current MRC funding is enabling us to capture, analyse and characterise sperm motility in three dimensions.

Proteomic work has demonstrated that humans have four zona proteins not three as in the mouse model, and we have started to be able to assess the glycosylation sites upon these proteins (work alongside Professor Ann Dell FRS, Imperial).

C) Results
See above

D) If progress was slower than anticipated, the reasons for this.
Progress on constituent parts of the research project has been rapid however we have as yet not performed experiments using licensed material. This is because further progress is required to effectively characterise proteins involved in sperm-zona interaction. Only then can experiments involving the creation of embryos, i.e. licensable activity, be undertaken in which variables will be limited and controlled such that effective conclusions can be drawn from the results. This will ensure that best use is made of available licensed material.

We envisage that in the near future we will be able to generate far better and more detailed data in our experiments. This has meant that in the last year, deferral of experiments creating embryos was desirable.

E) Publications which have arisen from work under the licence. We have a number of publications which will inform the licensable work but these did not involve working under the licence.
Peer review comments (if applicable)
Peer review was not required for this interim inspection.
Issues for consideration
NONE
Executive recommendations for Licence Committee
NONE
Areas not covered on this inspection
NONE

Report compiled by:

Name Andrew Leonard

Designation HFEA inspector

Date 10th August 2008

Appendix A: Centre Staff interviewed

PR and 2 researchers

Appendix B: Licence history

Licence	Status	Type	Active From	Expiry Date
R0173/1/a	Active	Research Project	01/01/2006	31/12/2009

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number 0119

Name of PR Jackson Kirkman-Brown

Date of Inspection 18th July 2008

Date of Response 15th August 2008

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

I will take action as follows:

- We are currently drafting a procedure for reporting serious adverse incidents and will have this in place before commencing further work. All persons working in the research laboratories will sign to confirm they have read and understood this procedure.
- When appropriate team meetings will be minuted and a record of this kept.
- Oocytes will enter the research program at the stage they are no longer for patient treatment. This will normally be after the fertilisation check, except when fresh oocytes are going to be consented and used. The embryologist performing the egg collection will therefore provide final confirmation from theatre, after checking the notes, that the couple have not withdrawn from the research project. After performing this check they will pass a confirmation slip, witnessed within theatre, with patient details and anonymisation code back to the laboratory. At this stage the oocytes will be deemed to have final clearance to enter the research pathway when appropriate.
- We will continue to maintain separation of research and clinical treatment.
- As the patient information is already professionally printed it is difficult to change at this stage. Hence, a separate slip with this key information will be provided to the patient. All patients already receive information about our independent counselling service but we will ensure this option is re-highlighted during the consent procedure.
- We have a clear box on our patient record sheet in theatre where consent is noted. We will ensure SOPs highlight that withdrawal of consent is noted here as well as on the main consent form. As stated above both will be inspected and witnessed at oocyte retrieval.

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).

Licence Committee Meeting

15 October 2008
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 6

Birmingham Women's Hospital (0119)
Interim Inspection

Members of the Committee:	In Attendance:
Anna Carragher, Lay Member – Chair	Chris O'Toole, Head of Research Regulation
Emily Jackson, Lay Member	Claudia Lally, Committee Secretary
Richard Harries, Lay Member	
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary	Providing Legal Advice to the Committee: Mary Timms, Field Fisher Waterhouse Solicitors

Conflicts 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 (35 pages)
- one tabled paper: email from the Person Responsible (2 pages)

1. The papers for this item were presented by Andrew Leonard, HFEA Inspector. Dr Leonard informed the Committee that this centre is medium sized and provides approximately 520 licensed treatment cycles per year. Dr Leonard reported that the centre has been proactive in the development and implementation of a quality management system and in the use of appropriate key performance indicators to monitor its activities. In addition, the centre's premises and the information it provides to patients were found to be appropriate. However, improvements were required in the following areas:
   - the organisational chart
   - third party agreements
   - staff communications
   - reviews of documents and procedures
   - witnessing
   - documentation of training and assessment of competency
   - validation of key processes

2. Dr Leonard summarised the response to the inspection report from the Person Responsible, which was appended to the report at page 31. He stated that the Person Responsible had responded very positivity to the inspection and to recommendations of the inspection team. Dr Leonard tabled an email from the Person Responsible, dated 14 October, which provided an update on staffing arrangements at the centre in response to the findings of the report.

3. The Committee considered the report and the responses by the Person Responsible. It considered the email from the Person Responsible describing the steps which are being taken to address the staffing issues. In particular, the Committee noted that a full time embryologist started in September. It also noted, with some concern, that the deficit in number of clinical staff described in the inspection report will not be addressed until next June, though there will be some level of cover arrangement until then. The Committee asked that the Executive closely monitor the staffing situation at the centre over the next few months. In addition, the Committee asked that the centre conduct a review to determine whether the current level of activity is safely supported by the current level of staffing and other resources. The results of the review should then be communicated to the Executive.

4. The Committee asked that the centre informs the Executive when Health Professions Council (HPC) registration for the clinical embryologist has been confirmed.

5. The Committee noted the response to the inspection by the Person Responsible and decided that the centre's licence should continue with no additional conditions. It asked that the Executive report the matter back to a Licence Committee if there are concerns that insufficient progress is being made in relation to the staffing issues or in relation to the activity review.

Signed..Anna Carragher..... Date..29.10.08.....
Anna Carragher (Chair)