Research Licence Interim Inspection Report

Project Title	Investigation into the role of sperm PLCzeta in human oocyte activation
Centre Name	IVF Wales
Centre Number	0049
Research licence Number	R0161
Centre Address	Department of Obstetrics and Gynaecology School of Medicine, Cardiff University, Heath Park, Cardiff, Wales CF14 4XN
Treatment centres donating to this research project	0049
Inspection date	26th March 2009
Licence Committee Date	20th May 2009
Inspector(s)	Andrew Leonard Wil Lenton
Fee Paid - date	Fee paid
Person Responsible	Professor Karl Swann
Nominal Licensee	Nazar Amso
Licence expiry date	31/12/2009

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 4th March 2008 and 26th March 2009.

Brief Description of the Project

R0161, **Investigation into the role of sperm PLCzeta in human oocyte activation**

Lay Summary (no changes from last inspection)
At fertilisation the sperm stimulates the egg to begin cell divisions and development. Studies in animals have suggested that the way the sperm does this is by introducing a special protein into the egg during the process of sperm-egg fusion. This protein is called PLCzeta. In our studies, we have injected messenger RNA for this protein into eggs that have failed to fertilise during IVF or ICSI. The RNA is then translated into PLCzeta protein within the egg. We have shown that this treatment can stimulate unfertilised human eggs to begin development. The biochemical effects of this protein inside the egg mimic those induced by the sperm at fertilisation. These results show us that PLCzeta can mimic the stimulatory effect of a sperm on egg development. This supports our proposal that the presence of PLCzeta in sperm is essential for normal fertilisation and development to take place. After injecting PLCzeta we found that some embryos could develop in culture up to blastocyst stage. Since these embryos were not fertilised by a sperm they are termed parthenogenic. Such parthenogenic embryos are not viable and cannot develop much further. However, the generation of parthenogenic blastocysts from unused eggs may be useful in future as a source of embryonic stem cells that would not require the use of viable human embryos.

		R0161
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 R0161, Investigation into the role of sperm PLCzeta in human oocyte activation. Project R0161, previously R0147, has had a research licence to use oocytes to develop parthenogenic embryos since September 2003. The project uses failed to fertilise oocytes and oocytes harvested during follicle reduction in over-stimulated intrauterine insemination (IUI) patients, all sourced from IVF Wales (HFEA centre 0049). Expression of the sperm protein PLCzeta in human oocytes stimulates their activation and parthenogenic development as pseudo-embryos up to the blastocyst stage. Further development can not occur due to the absence of male genetic material.

The current licence is due to expire on 31 December 2009. The project's objectives are:

i) to establish the effectiveness of PLCzeta in causing Ca^{2+} oscillations in human oocytes
ii) to establish the potential and optimal concentration of PLCzeta that is required to stimulate efficient preimplantation development of human oocytes
iii) to establish the relationship between the pattern of Ca^{2+} oscillations generated in human oocytes by PLCzeta and the degree of subsequent preimplantation development
iv) to investigate if non-invasive image analysis can be used monitor Ca^{2+} oscillations in activating human oocytes.

The fourth objective is new and results from the proposed use of Digital Particle Image Velocimetry (DPIV) to investigate oocyte cytoplasmic flow responses to PLCzeta.

Research carried out under the project licence has indicated that different patterns of Ca^{2+} oscillations are generated in human oocytes and that the pattern of oscillation depends upon the amount of PLCzeta protein expressed after injection of PLCzeta cRNA into the oocytes. Oocyte activation and embryo development also depend upon the expression level of PLCzeta; either too little or too much PLCzeta expression is not consistent with embryo development. Development to the blastocyst stage is only seen when PLCzeta expression in the oocyte is within a relatively narrow range. These observations are consistent with similar studies carried out with human PLCzeta luciferase in mouse oocytes (Yu et al. Human Reproduction. (2007) 23, 365-373).

No work has occurred on the project since the last inspection in March 2008 due to:
a) The researchers wish to inject PLCzeta protein into oocytes and this requires the development of an expression system for recombinant active PLCzeta. Several groups worldwide are attempting this but have yet to be successful due to the protein's toxicity in the expression systems used. The PR described how work on this goal is progressing in a local collaborator's laboratory and the development of novel expression strategies.
b) The length of time it has taken to raise funding and to source, install and commission the microscope system with which to perform DPIV analysis. The system is now in place and validation testing, using mouse oocytes injected with PLCzeta cRNA, has just been completed.

Research on the project is expected to start again in April 2009.* Usage in the next year is projected at 50 fresh oocytes and 200 failed to fertilise oocytes

The research is licensed for 'the creation of human embryos' to 'promote advances in the treatment of infertility' (*Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a))* and 'to

increase knowledge about the development of embryos' (*Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)).*

The researchers have appropriate experience and are well qualified to continue the programme of research. The proposed premises and equipment are appropriate and procedures are in place to ensure that patients are treated respectfully and their consent is not breached. The donation to research procedure complies with the Code of Practice, 7th edition. The inspectorate observed that the PR had taken appropriate and timely action regarding the breaches, non-compliances and recommendations made in the report on the inspection of the project on March 2008.

Regulatory issues identified by the inspectorate were:

1) One of the scientists on the project is also an embryologist at the donating centre (IVF Wales). The PR must ensure separation between treatment and research activities to comply with Standard S.8.4.1 'Where embryos are used in research, the Centre shall ensure that clinical and research roles are separated, so that individuals involved in advising patients regarding clinical decisions about their licensed treatment, are not involved in the research project to which patients are considering donating embryos'. This issue was discussed with the PR during the inspection and he considered that separation between research and treatment was achieved. For example, the nurses at the donating centre take all patient consents for research and the embryologist has no role in the process. It is recommended that the PR liaise with the Head of Laboratory at the donating centre and the scientist/embryologist, to ensure laboratory practices are compliant with S.8.4.1.

2) The inspectorate consider the consent form does not specifically state that the patients are consenting to the donation of their oocytes, whether they be failed to fertilise during IVF processing or derived from follicular reduction during IUI treatment, to be used in Research Project R0161. The PR should ensure that the consent form and patient information state specifically what the patients are consenting to.

No regulatory concerns were observed by the inspectorate on this interim inspection and they recommend continuation of the research licence for project R0161.

*The PR informed the Executive on 23rd April 2009 that recruitment has restarted

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 R0161

Principal investigator	Professor Karl Swann
Scientists	3
Collaborators	1
Support staff (receptionists, record managers, quality and risk managers etc)	Staff at centre 0049 recruit patients to the research project

Highlighted areas of firm compliance
The research centre is on the 5th floor of the University Hospital Wales within a zone of the building assigned to academic departments from the Cardiff University Medical School. The zone provides facilities for multiple research groups. The facilities and staff in this zone are part of Cardiff University, which provides Health and Safety, Human Resources and other support to the licensed centre. Oocytes are donated to the project from IVF Wales (HFEA centre 0049) which is based on the 1st floor of the same hospital. The PR is the Project Head, has been PR since 2003 and has completed the PR entry programme. The PR showed an understanding of HFEA regulatory requirements and is not the PR of a Treatment and Storage Licence. The PR is a professor of Cardiff University with many years of research experience. The PR advised the HFEA before inspection of the recruitment of two further scientists to the project and supplied their CVs. One is a clinician, not associated with treatment at centre 0049, and one an embryologist at centre 0049 who has a research doctorate from the laboratory in which the research is performed. Both will function as scientists on the project. The PR assured the inspectorate that the embryologist will have no role in patient consenting at centre 0049 (only nurses obtain research consents from patients) but may provide information regarding the research to patients on request. The Head of Embryology at Centre 0049 is on the research licence and has a role in coordinating between the project and Centre 0049 and providing research information to patients, but no role in carrying out the research. Resource management and project coordination is achieved through meetings between the

PR and research workers, held as required. Meetings are also held with the embryologists and nurses of Centre 0049. Minutes were seen of these meetings. Research data is reported back to Centre 0049 in research seminars by the PR. Research progress is also included in articles in the IVF Wales patient's newsletter.

The PR liaises with his collaborator at Cardiff University Medical School regularly about the project and is in daily contact. Collaboration is also required with groups in Oxford and Cambridge Universities; this is achieved by email and visits. A joint grant application to the Wellcome Trust was submitted last year and proved successful, indicating these communication pathways operate effectively.

The project is funded by elements of grants from the BBSRC and the Wellcome Trust, the latter having been awarded in 2008.

Experiments undertaken are monitored via a computer database kept by the PR. Experiments and their results are also documented in laboratory notebooks kept within the licensed premises. Research activities are controlled by written procedures, previously reviewed by the inspectorate, which ensure a consistent approach and that patient consent is collected appropriately. The centre has an incident reporting procedure which is compliant with the Code of Practice, 7th edition.

Issues for consideration

1) One of the scientists on the project is also an embryologist at the donating centre (IVF Wales). The PR must ensure separation between treatment and research activities to comply with Standard S.8.4.1 'Where embryos are used in research, the Centre shall ensure that clinical and research roles are separated, so that individuals involved in advising patients regarding clinical decisions about their licensed treatment, are not involved in the research project to which patients are considering donating embryos'. This issue was discussed with the PR during the inspection and he considered that separation between research and treatment was achieved. For example, the nurses at the donating centre take all patient consents for research and the embryologist has no role in the process. It is recommended that the PR liaise with the Head of Laboratory at the donating centre and the scientist/embryologist, to ensure laboratory practices are compliant with S.8.4.1.

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
Manipulation of oocytes is carried out in two licensed laboratories within a medical school zone of the University Hospital of Wales. The facilities and staff in this zone are part of Cardiff University Medical School, who provide Health and Safety support. The laboratories are secure and restricted to licensed personnel. Licensed material only leaves the premises when non-viable (e.g. after fixation for staining and cell counting). Project records are stored in one licensed laboratory (laboratory books) and also in the PR's office (computer spreadsheet database) which is also part of the licensed premises. This office was also secure and is locked when unoccupied. Oocytes donated to research are transferred from Centre 0049 to the research centre in a portable incubator by the researchers. A dedicated incubator is used for short term culture of oocytes/parthenogenic embryos. No long-term storage facilities are required as material is processed from fresh to a non-viable state within 6 days of receipt; viable licensed material is not subjected to long term storage. The laboratories were appropriately equipped, with a dedicated incubator and two specialised microscopes with micromanipulation and microinjection equipment, one in each laboratory. One of these microscopes has recently been upgraded with dual fluorescence and differential interference contrast (DIC) optics and specialised digital recording capabilities, to enable DPIV analysis of oocyte cytoplasmic movements to be performed. Apparatus is on service contracts in general, however the microscopes and micromanipulation and microinjection equipment are serviced and repaired by the PR, who has considerable experience of this equipment; the PR considers that they can service and repair the equipment more effectively and at lower cost than external service engineers. All equipment had been subjected to portable appliance testing (PAT) for electrical safety, a requirement of the last inspection report.
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
If a patient consents, oocytes which fail to fertilise during IVF/ICSI treatment, or are recovered from follicular reduction during IUI treatment, are donated to research. The donating centre considers oocytes to have failed to fertilise if no signs of fertilisation are apparent after overnight incubation with sperm, then again on inspection in the early afternoon following the day of insemination. This definition varies from the HFEA definition, which requires no signs of fertilisation 48 hours after insemination. Thus the material used in the research project may potentially be embryonic, albeit abnormally slow in fertilising, which is one reason why the HFEA licence is required. Work has been suspended since the last inspection in March 2008 due to problems with the production and supply of recombinant PLCzeta and the financing, sourcing and commissioning of the required microscope system with which to perform DPIV analysis. Research recruitment will start again in April 2009 as the microscope system has now been installed and commissioned. The procedures for donation noted on the last inspection in 2008 remain unchanged and the PR has ensured that transfer of oocytes from Centre 0049 to the research laboratory can be easily accomplished. Donors are recruited from Centre 0049 by the nursing staff. Written and verbal information regarding the research project is given to patients either by the Head of Laboratory, when they attend a patient information seminar, or by nursing staff at the patients' first consultation. At the next visit several weeks later, the nurses explain the research information if required, and assist the patients in completing the treatment consent forms and the research consent if they decide to donate to research. At subsequent visits a checklist is used to check if patients are aware of the project and if they would like to donate to research. Further information can be obtained by patients on request from either the Nominal Licensee of the research project (a consultant at Centre 0049), the Head of Laboratory, the scientist/embryologist or from a scientist in the Medical School whose contact details are on the patient information sheet. Research consent is obtained before the treatment cycle is started, i.e. long before egg collection, but several weeks after information is first supplied. Thus patients have adequate time in which to make their decision and to obtain further information. These features also limit the possibility of coercion. Patient information is also balanced and non-coercive and no patient complaints have been received regarding coercion. The staff of IVF Wales are professional and patient feedback suggests sensitive to their patients needs and respectful of their dignity.

Prior to transfer to the researchers, the embryologist releasing the oocytes checks that research consent has been signed by the patients and signs to this effect in a 'research donated oocytes' log held within Centre 0049. The embryologist also notes in the log the anonymised number by which the oocytes are henceforth identified and patient details. The receiving researcher signs for receipt and verifies the oocyte identifier and that research consent was confirmed by the embryologist. The oocytes are then transferred from the clinical laboratory to the research laboratory in a portable incubator by the researchers. No patient identifying information is transferred to the research centre. On arrival in the laboratory the oocytes are cultured in the incubator while they are logged onto the computer spreadsheet database. They are then used in imaging experiments within 1-2 hours, the experiments lasting for a maximum of 24 hours, though oocytes may be cultured for a further maximum of 5 days to assess their developmental potential.

Issues for consideration

None

Executive recommendations for Licence Committee

None

Areas not covered in by this inspection

Consents in patient records for research donation were not checked during this inspection since no activity has occurred since the last inspection. At the last inspection, consents were seen to be in order in the three sets of patient records inspected.

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
Patient information and consent forms for project R0161 were reviewed by the inspectorate. The PR has updated the consent forms and information to account for many of the issues raised in the report of the March 2008 inspection. The documents were compliant with the Code of Practice, 7th edition, except for the issues raised below. Improvements include the naming of a scientist, with contact details, who can provide information to patients independent of the researchers; up-to-date review reflected in document control footers; use of the donating centre's new name; provision of a mechanism for withdrawal of consent and advice to patients about it; and deletion of the provision for a researcher to be provided with a copy of the consent form. The consent for research is checked by nursing staff and embryologists several times during the treatment cycle before oocytes are donated to research; a checklist ensures the consent is checked again by the embryologist at the time of research donation.
Issues for consideration
The inspectorate consider the consent form does not specifically state that the patients are consenting to the donation of their oocytes to be used in Research Project R0161, whether they have failed to fertilise during IVF processing or are derived from follicular reduction during IUI treatment. The PR should ensure that the consent form and patient information state precisely what the patients are consenting to donate.
Executive recommendations for Licence Committee
That the Licence Committee require the PR to review patient information and the consent form to ensure it states precisely what the patients are consenting to donate.
Areas not covered in by this inspection
All covered

5. Scientific practice: R0161, **Investigation into the role of sperm PLCzeta in human oocyte activation**

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 under the purposes laid down in the Human Fertilisation & Embryology (Research Purposes) Regulations 2001;
2(2)(a) increasing knowledge about the development of embryos

Usage and expected usage in next year:
Most recent data for the period 04/03/2008 to 24/03/2009

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

No embryos have been supplied to the project, fresh or frozen, and none (except parthenogenic) created in this time period.

The PR stated in the progress report:
'One new aspect of the work that we had planned to start involved the analysis of differential interference contrast (DIC) images of eggs using Digital Particle Image Velocimetry (DPIV) as a way to monitor Ca2+ oscillations. We secured some funding from the Wellcome Trust for this work in the summer of 2008. Unfortunately, we had to wait until January 2009 to have the microscope installed and fully configured for this type of experiment. This system was tested using PLCzeta injected mouse oocytes and shown to be effective in monitoring Ca2+ changes with DPIV. We have now started to recruit patients to donate oocytes for experiments of this type.'

The PR related on inspection that recruitment is expected to commence again in mid-April 2009.[1]

The PR also stated in the progress report:
'We also still intend to inject recombinant human PLCzeta protein in human eggs to test its effectiveness in activating development. Progress has been slow in making an active recombinant PLCzeta protein. It should be noted that PLCzeta is an unstable protein and no laboratory in the world has yet achieved an effective means for generating human PLCzeta

[1] *The PR informed the Executive on 23rd April 2009 that recruitment has restarted

protein. We have started testing mouse recombinant PLCzeta in mouse eggs.'

Estimated usage in the next year:

Material	Expected usage
Fresh Eggs*	50
Frozen Eggs	0
Failed to Fertilise Eggs	200
Fresh Embryos	0
Frozen Embryos	0

Summary of audit of stored and biopsied material

No licensed materials are stored

Renewed project objectives

The research project has imaged human oocytes with photon imaging cameras using luminescence and fluorescence probes to assess calcium oscillations in response to PLCzeta cRNA injection. In future, the Centre plan to image oocytes with a cooled CCD high resolution camera system that can simultaneously record both fluorescence images (to measure intracellular Ca^{2+} oscillations) and differential interference contrast (DIC) images, which will be analysed for cytoplasmic flow using DPIV. The centre have recently completed the installation and commissioning of the required imaging equipment. The centre will carry out experiments involving PLCzeta cRNA and protein injection into human oocytes, and will analyse Ca^{2+} oscillations, cytoplasmic flow and pseudo-embryonic development for up to 6 days post-injection. PLCzeta protein injection experiments are needed to confirm the research projects observations made using PLCzeta cRNA injection. There is potential for DPIV measurement of oocyte cytoplasmic flow to evolve into methodology applied routinely in an IVF laboratory to assess oocyte 'fitness' in a non-invasive manner.

Renewed objectives

The PR stated in the progress report, 'The overall objectives are the same (see below). However, the studies of DPIV probably deserve a separate mention as a generic fourth objective.

i) to establish the effectiveness of PLCzeta in causing Ca2+ oscillations in human oocytes.
ii) to establish the potential and optimal concentration of PLCzeta that is required to stimulate efficient preimplantation development of human oocytes, and
iii) to establish the relationship between the pattern of Ca2+ oscillations generated in human oocytes by PLCzeta and the degree of subsequent preimplantation development.
iv) to investigate if non-invasive image analysis can be used monitor Ca2+ oscillations in activating human oocytes.'

One reason for recording both intracellular Ca^{2+} and DIC images of oocytes is that there is evidence in mouse oocytes that Ca^{2+} increases are accompanied by slight movements in the ooplasm (spasm). If this occurs in human oocytes it will provide a non-invasive way of assessing whether Ca^{2+} changes are occurring in human oocytes and how the ooplasm is

responding. These potential cytoplasmic movements will be correlated with other oocyte activation events, such as pronuclear formation and cleavage. This work will help to achieve objectives iii) and iv) and will be performed in collaboration with groups at Oxford and Cambridge Universities.

Summary of research undertaken

The PR stated in the progress report

How the work undertaken relates to the objectives.
We shall shortly be measuring PLCzeta induced Ca^{2+} oscillations in oocytes alongside analysis of differential interference contrast (DIC) images. The DIC will be analysed for cytoplasmic movement. The work to be undertaken will allow us to monitor Ca^{2+} oscillations in human oocyte in a non-invasive manner. This will allow us to establish the relationship between Ca^{2+} oscillations and later embryo development.

Research undertaken to date.
This has been described in previous reports. No activity has taken place since the last review.'

Results
N/A

If progress was slower than anticipated, the reasons for this.
One new aspect of the work that we had planned to start involved the analysis of DIC images of eggs using Digital Particle Image Velocimetry (DPIV) as a way to monitor Ca2+ oscillations. We secured some funding from the Wellcome Trust for this work in the summer of 2008. Unfortunately, we had to wait until January 2009 to have the microscope installed and fully configured for this type of experiment. This system was tested using PLCzeta injected mouse oocytes and shown to be effective in monitoring Ca2+ changes with DPIV. We have now started to recruit patients to donate oocytes for experiments of this type.

If work originally proposed was not carried out, the reason for this.
As explained above the work on DPIV analysis of Ca2+ oscillations had a delayed start, but is likely to start very soon.

We also still intend to inject recombinant human PLCzeta protein in human eggs to test its effectiveness in activating development. Progress has been slow in making an active recombinant PLCzeta protein. It should be noted that PLCzeta is an unstable protein and no laboratory in the world has yet achieved an effective means for generating human PLCzeta protein. We have started testing mouse recombinant PLCzeta in mouse eggs.

Please list references to any publications which have arisen from work under the licence.
None

Peer review comments (if applicable)

Peer review was not required for this interim inspection. Peer review at last renewal (ie in 2006) can be summarised thus:

The embryos are produced in this project by parthenogenesis, i.e. in the absence of a male gamete. They have limited developmental competence and can not develop into a foetus. *The project specifically looks at the earliest events in the process of oocyte activation and as such require the production of embryos in vitro. The potential results are very important and will increase understanding of the mechanisms of fertilization, reasons for failed fertilization and methods of generating stem cells from parthenogenically activated eggs.* *Plans for future work are a continuation of a long term programme of work by this group involving the use of techniques that have been established in animal models but which must be applied to human oocytes to answer the specific questions addressed by the project.* *This application represents a continuation of a programme of research that has produced some significant advances in the field of fertilization and activation, fully justifying previous use of human gametes with every reason to expect that it will produce further valuable data.*
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered on this inspection
None

Report compiled by:

Name Dr. Andrew Leonard

Designation HFEA inspector

Date 14th APRIL 2009

Appendix A: Centre Staff interviewed

PR and NL

Appendix B: Licence history

Licence	Status	Type	Active From	Expiry Date
R0161/2/a	Active	Research Project	01/01/2006	31/12/2009
R0161/1/a	Expired	Research Project	10/01/2005	31/12/2006
R0147/1/a	Expired	Research Project	30/09/2003	31/08/2004

The research project number changed as the project moved to centre 0049 in November 2004.

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number 0049

Name of PR Prof Karl Swann

Date of Inspection 26th March 2009

Date of Response 27th March 2009

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

I have discussed the issue of potential conflict of interest with regards to Karen Campbell being involved in the research project as well as being an embryologist in IVF Wales. This discussion has been noted in a follow up email that is archived.

The patient consent form has been modified to say that 'I (we) agree to donate my (our) oocytes for the above study'. The new form will be distributed to the clinic.

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).

On page 7 of the report it states that the new fluorescence imaging microscope has Hoffman contrast, but it actually has differential interference contrast (DIC) optics. *[now corrected in the report, AJL]*

HFEA Research Licence Committee Meeting
20 May 2009

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 3

IVF Wales (0049; R0161) – Interim report

Members of the Committee:	Committee Secretary:
Emily Jackson (lay) – Chair Richard Harries (lay) Neva Haites (geneticist) Hossam Abdalla (clinician) David Archard (lay)	Kristen Veblen Legal Adviser: Sarah Ellson, Field Fisher Waterhouse

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 (23 pages)
- no tabled papers.

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 Tree for Application for a Research Licence
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21st January 2009.

1. The Committee considered the report of the interim inspection and the response of the Person Responsible (PR).

2. The Committee noted that this project is investigating the role of sperm PLCzeta in human ooctye activation and the potential of the findings for the production of embryonic stem cells that would not require the use of viable human embryos.

3. The Committee considered whether there was sufficient separation between treatment and research activities to comply with Standard S.8.4.1 and noted that consent is taken by nurses at the donating centre, not the embryologist. The Committee further noted that the response of the PR addressed this matter.

4. The Legal Adviser confirmed that while the Code of Practice required separation it did not prescribe how this was to be achieved. The Committee agreed that it had been satisfied that there was sufficient separation.

5. The Committee further considered the content of the information given on the consent form for patients and the response from the PR concerning this issue. The Committee agreed that the response of the PR did not fully address the concerns raised in the inspection, particularly whether the patient is consenting to the donation of oocytes that have failed to fertilise during the IVF or are derived from follicular reduction during IUI treatment.

6. The Committee requested that the inspector follow up with the PR to ensure that the revised consent form referred to in the PR's response meets the concerns raised in the inspection.

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

7. The Committee decided that the licence should continue with no additional conditions.

Signed..... Date 29.5.09.
Emily Jackson (Chair)