Research Licence Inspection Report

1. Project Title Research Licence Number Person Responsible Nominal Licensee Inspection type Licence expiry date	**Improving methods for pre-implantation genetic diagnosis of inherited genetic disease and predicting embryo quality** R0075 Peter Braude Yacoub Khalaf Renewal 31 August 2009
Centre Number	0102
Centre Name	Guy's Hospital
Centre Address	Stem Cell and Embryology Research Laboratories Assisted Conception Unit, Guy's and St Thomas' Hospital NHS Trust, 11th Floor Tower Wing, Guy's Hospital St Thomas Street London SE1 9RT
Treatment centres donating to these research projects	Assisted Conception Unit Guy's Hospital (0102) The Woking Nuffield Hospital (0144) Bourn Hall (0100) Kings College London (0109)
Inspection date	26th February 2009
Licence Committee Date	20th May 2009
Inspector(s)	Miss Sarah Hopper Mrs Ellie Suthers

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 6th February 2008 and 27th February 2009.

Brief Description of the Projects

Project **R0075** entitled "**Improving methods for pre-implantation genetic diagnosis of inherited genetic disease and predicting embryo quality**" has been licensed since 1994.

The lay summary of the project is as follows:
Preimplantation genetic diagnosis (PGD) is a reproductive option for couples at substantial risk of conceiving a pregnancy affected with a known genetic disease who wish to avoid the emotional burden associated with an affected child, termination of pregnancy or recurrent miscarriages. PGD has been offered as a service at Guy's and St Thomas' for over ten years, and it is now the busiest and most successful unit in the country. PGD has been used for single gene diseases such as cystic fibrosis, for diseases which only affect males by selecting female embryos, and for couples with chromosome rearrangements. For single gene diseases, one cell is removed from a 3-day old embryo and tested for the mutation. A separate PGD test has to be developed for every different mutation, requiring substantial resources not always available in state-run medicine. In addition, these tests are technically difficult and very sensitive to contamination with non-embryo DNA.

Over the duration of our previous licence, we developed a new technique at Guy's, Preimplantation Genetic Haplotyping (PGH) which improves the reliability of single cell genetic testing and enables it to be extended to a wide range of diseases. It has also allowed us to move away from sexing embryos as a means of avoiding some genetic disease as we can use PGH to detect and distinguish unaffected males in addition to unaffected or carrier females. We intend to work over the next three years, further developing this approach for a wider range of genetic disorders, and to see whether we can extend the approach to include tests for some serious or lethal chromosomal trisomies such as Edward, Patau and Down syndrome. Further research will look at effect of mosaicism on diagnosis, and the impact of mitochondrial function during early development.

They are currently licensed under the following purposes:

- Developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation
  Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(e)

- Increasing knowledge about serious disease
  Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(b)

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

Changes/ improvements since last inspection

Since the last inspection a new research facility has been built on the 11th floor of the Tower Wing, Guy's Hospital. The new premises were inspected on the 5th June 2008 and the licence varied to reflect the new address of the premises on the 18th June 2008. The new research facility comprises of two dedicated research laboratories situated within the new assisted conception unit. New equipment has also been bought for use in the new laboratories.

There have been no significant staff changes since the last inspection.

Additional licence conditions and recommendations and actions taken by centre since last inspection

Additional Licence Condition	N/A
A	

Recommendations	**Action Taken**
An SOP should be created for the induction of new staff as required by CoP Standard S.6.6.3 and S.6.2.7. N.B The Committee endorsed this recommendation and asked that the SOP be submitted to the Executive by 12th May 2008.	This policy was not submitted to the Executive by 12th May 2008 but evidence that it is in place was seen at this inspection. A Trust and local induction policy, which was seen to have been in place since 2005 and has been reviewed on an annual basis, is stored on the main quality management system database. This included Trust requirements: mandatory training (annual) local induction and requirements. Local requirements included having read and understood local policies and procedures: the Code of Practice (7th Edition): Alerts and adverse incident policies (seen to include the HFEA reporting requirements) The quality manager confirmed that researchers are included in this induction process.

Summary for Licence Committee

Overall the inspectorate was satisfied that the centre demonstrated compliance with regulatory requirements for: the security of premises, procedures for recruitment of donors and the research governance framework.

However, two issues were raised on inspection:

1. It was noted that the documented protocol which outlines procedures to be taken to ensure that embryos used are not cultured past 14 days does not relate to this research project.

2. During the inspection it was found that in the past year licensed research work has been conducted in premises no longer licensed for that activity. Due to delays in building work the PR had not commenced research work in the premises which had been granted a licence by Licence Committee in June 2008. Instead, work had continued in the previously licensed premises, on the fourth floor of the same building. This is a breach of Section 12 of the Human Fertilisation and Embryology Act which states that "The following shall be conditions of every licence granted under this Act- that the activities authorised by the licence shall be carried on only on the premises to which the licence relates and under the supervision of the person responsible". The PR stated that as a contingency measure, in the event that they experienced technical problems on the 11th floor, he had maintained the laboratories on the 4th floor. The PR informed the inspectorate that he took steps to ensure that at no time any embryos were at risk and so continued to use the licensed treatment and storage assisted conception unit (centre 0102), to which their previously licensed research laboratory area is attached and functioning, for research purposes.

This breach has already been considered by a Licence Committee on the 11th March 2009 who considered that that there had been a breach of section 12 (1) (a) and requested that this breach be recorded in the licence history for the centre. In considering any action to take in relation to the breach, the Committee had regard to the misunderstanding about the operational date of the most recent variation of the licence and the fact that the licence ceased to apply to the 4th floor with immediate effect. The Committee also took into account the reassurances of the Person Responsible in relation to the research work undertaken and his admission that he should have anticipated the technical problems encountered and taken the precaution of licensing both floors. The Committee further noted the centre's good history of regulatory compliance, and on these grounds decided to take no further regulatory action on this occasion. However, the Committee agreed that the breach may be taken into account in future in the event of any future breach of regulatory requirements. An application to vary the centre's licence to include premises on the 4th and 11th floor of the building was also considered as this Committee meeting. The Committee concluded that the 4th and 11th floors could not be regarded as premises in different places given that they were floors within the same building on the same site. The Committee was also satisfied that the floors represented discrete areas within the building to which inspectors could gain access and that it was appropriate to vary the licences for the research projects with immediate effect, to state that the licences cover "ACU premises on the 4th and 11th floors, Tower Wing, Guy's Hospital".

The PR has applied for the licence to be renewed for a period of three years and for it to be

varied to include the creation of embryos in vitro. The PR has proposed that the licence be renewed under the following purposes:

- Promoting advances in the treatment of infertility *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)*
- Increasing knowledge about the causes of congenital disease *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(b)*
- Increasing knowledge about the causes of miscarriages *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(c)*
- Developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(e)*
- Increasing knowledge about the development of embryos *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)*
- Increasing knowledge about serious disease *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(b)*
- Enabling any such knowledge to be applied in developing treatments for serious disease *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(c)*

A peer reviewer considering the application recommended that the application be accepted without any changes.

The executive support this application and recommend that the licence be renewed without additional conditions. Subject to the agreement of the peer reviewer it is also recommended that the licence be varied to include creation of embryos.

Proposed licence variations

The PR has applied for the licence to be varied to include the following activity:

- creation of embryos *in vitro*

The PR's rationale for this variation is that where donor consent is in place they wish to use unfertilised eggs (this would include eggs which have not fertilised following IVF/ICSI or eggs which were not used because they were immature at the time of ICSI) to create embryos for use within the research project. The HFEA Executive are currently awaiting comments from the Peer Reviewer on this additional activity.

Breaches of the Act, Standard Licence Conditions or Code of Practice:

The table below sets out matters which the Inspection Team considers may constitute breaches of the Act, Standard Licence Conditions and/or the Code of Practice, and their recommended improvement actions and timescales. The weight to be attached to any breach of the Act, Standard Licence Conditions or Code of Practice is a matter for the Licence Committee;-

Breach	Action required	Time scale
Licensed research work on project R0075 has been conducted on the premises which are not licensed for research. Section 12 of the Human Fertilisation and Embryology Act states that The following shall be conditions of every licence granted under this Act- that the activities authorised by the licence shall be carried on only on the premises to which the licence relates and under the supervision of the person responsible.	The PR must ensure that licensed work is only conducted on appropriately licensed premises.	With immediate effect

Non-Compliance

Area for improvement	Action required	Time scale
Staff explained that there is a procedure in place to ensure embryos are not cultured beyond 14 days. However, the procedure as documented in the transfer of embryos to a research licence protocol specifically relates to practices to be followed in the other research project conducted at the centre (R0133).	It is recommended that the procedure to be followed for this research project be documented to ensure that embryos are not cultured beyond 14 days.	With immediate effect.

Recommendations

Area for improvement	Action required	Time scale
None noted		

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:

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

Staff R0075*

Principal investigator	Professor Peter Braude
Scientists	1
Laboratory technicians	
Research nurse	0.2 WTE research nurse
Support staff (receptionists, record managers, quality and risk managers etc)	

Highlighted areas of firm compliance
The PR who has managed this project since its inception in 1994 has completed the HFEA PR entry programme. The PhD student who is working on elements of this project has relevant and valuable embryology experience and has had access to continuing professional education. Evidence of the various courses and training sessions attended by the student was provided during the inspection. R0075 is funded by the Guy's and St Thomas' Charity and in part by grants from the Medical Research Council. The project has received renewed ethical approval from a properly constituted ethics committee. Meetings between the research staff are held. A record is maintained of these meetings and evidence of five formal meetings which took place in the past year was provided during the inspection. The quality management system in place for the licensed treatment and storage activities at this centre also supports the research activities. Documents submitted before and during the inspection had evidence of version control. The inspectorate was informed that research staff follow the assisted conception's unit incident handling policy. A copy of this policy was seen on inspection and was seen to meet

HFEA requirements with regard to reporting timelines. Progress reports have been submitted in accordance with the timelines outlined in General Direction D2006/4. The PR has put into place all requirements outlined at the last inspection: a staff induction policy is in place and a copy of this was provided to the inspectorate.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

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

Highlighted areas of firm compliance
At the time of inspection, the building work on the new premises had not been completed and pieces of equipment to be used on this project had not yet been installed. However, the research laboratories were inspected and were seen to be secure with access restricted to authorised personnel using a swipe card system. The room which will be used as the cryostore was seen to be fitted with low oxygen sensors and an alarm system. This room was also secured via the swipe card system. Records relating to research which contain patient information are stored in lockable administration offices which are situated in a restricted area of the assisted conception unit. The research team reported that they will have the necessary equipment required to undertake their stated objectives. Key equipment used in the research project will be connected to a system which will continuously monitor environmental parameters. Maintenance records and equipment logs were seen to be up to date and complete on the centres electronic quality management system. The centre has begun to validate its equipment following the Association of Clinical Embryologists (ACE) guidance. A completed validation form was seen for one of the centres class II hoods. Staff explained that there is a plan in place to validate all existing and new equipment as part of the transfer to the new facility.
Issues for consideration
The current licence for this research projects lists the 11th floor, Tower Wing, Guy's Hospital, St Thomas Street, London, SE1 9RT as the licensed premises. This licence was granted on the 18th June 2008 in response to an application made by the PR to reflect new premises, which would encompass the new assisted conception unit[1] and the research laboratories.

[1] The application for treatment and storage licence was considered by a licence committee on the 25th June 2008. The Committee agreed to vary the centre's licence to reflect the new address which would cover both the 4th and the 11th floor of the building (the premises being named as Assisted Conception Unit Guy's and St Thomas Hospital NHS Trust, Guy's Hospital). The Committee asked that no licence be issued to the centre (and thus no patient treatment be commenced under the terms of the licence) until the Executive has received confirmation that all the recommendations have been complied with. This confirmation has not been received and therefore treatment and storage activities have continued to be conducted in the original premises on the 4th floor under licence L0102/14/a.

During the inspection it was found that licensed research work on project R0075 has been conducted on the original and now unlicensed premises on the 4th floor during the past year[2]. Research records were reviewed which indicated that work on this project had been taking place since June 2008 but on inspection of the laboratories on the 11th floor it was clear that the required equipment to do this work was not in place. Embryos stored for future use in research were also seen to be stored on the 4th floor.

This issue was raised with the PR, who was reminded that licensed activities may only be conducted on licensed premises. To act otherwise is a breach of Section 12 (a) of the HFE Act (1990) which states: The following shall be conditions of every licence granted under this Act- that the activities authorised by the licence shall be carried on only on the premises to which the licence relates and under the supervision of the person responsible.

The PR was also asked to submit an incident report to the HFEA about this breach. This was received on the 11th March 2009.

The PR explained that he and his team have experienced significant and unanticipated delays in moving to the new licensed premises on the 11th floor. The PR stated that as a contingency measure, in the event that they experienced technical problems on the 11th floor, as has happened recently, he maintained the laboratories on the 4th floor. The PR informed the inspectorate that he took steps to ensure that at no time any embryos were at risk and so continued to use the licensed treatment and storage assisted conception unit (centre 0102), to which their previously licensed research laboratory area is attached and functioning, for research purposes. However, the PR acknowledges that they should have taken the precaution of licensing both premises to anticipate any such delay.

Executive recommendations for Licence Committee

The Licence Committee are asked to note that on inspection a breach of Section 12 (1a) was found. This section of the Act states: The following shall be conditions of every licence granted under this Act--(a) [except to the extent that the activities authorised by the licence fall within paragraph (aa), that those activities] shall be carried on only on the premises to which the licence relates and under the supervision of the person responsible.

This breach has already been considered by a Licence Committee on the 11th March 2009. The Committee noted the centre's good history of regulatory compliance, and on these grounds decided to take no further regulatory action on this occasion. However, they also noted that the breach may be taken into account in future in the event of any future breach of regulatory requirements.

Areas not covered in this inspection

None

[2] Unlicensed for research work.

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
- Prevention of coercion of prospective donors

Highlighted areas of firm compliance
Embryo donation to both projects is coordinated by a 0.2 WTE research nurse who has responsibility for donor centre coordination and support: embryo collection: verification of donor consent; documentation completion and embryo collection from the donor centres. The research nurse is employed by the Guys and St Thomas' NHS Foundation Trust which is reimbursed by the MRC for her time devoted to the individual MRC funded research project. Her remit it is to ensure all donated material is compliant with regulation and professional guidelines not the specific needs of the individual research projects. The research nurse explained that at the time of clinical consultation the clinical doctor will approach the potential donor about the concept of donating to research and provide them with written information and consent forms to take away to be completed and signed in their own time. If the potential donors want further information they can talk to the research nurse at any time. The inspectorate saw a checklist which is used at the time of this consultation which contains research requirements. A completed checklist was seen in a set of patient healthcare records. Information about how donors can withdraw consent is made available on the research consent form and in patient information material. No evidence of coercion of prospective donors was seen from a review of returned HFEA patient questionnaires submitted by patients at centre 0102. Consent for use of embryos in research is checked, witnessed and documented before embryos are actually used in the project. Evidence of this check was seen in all four research records audited by the inspection team. A documented standard operating procedure is in place which outlines the steps to be taken when transferring embryos from the clinical sphere to the research project. A copy of this procedure was reviewed by the inspectorate and seen to include a reminder to staff that embryos generated from donor eggs/sperm cannot be used in research unless the donor has also given consent. A documented procedure is also in place which describes the process for transferring embryos donated to research by patients at other units. Both protocols are supported by a detailed flow chart which outlines the processes involved. Donated material is given an individual and unique identifier for use in research; therefore

once it has been transferred for use in the research the material is anonymous. Use of this unique identifier was seen in the laboratory log books maintained by the research team. Researchers receive information regarding the expiry date of stored embryos. This information was seen to be clearly documented on the transfer sheets provided to the research team.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

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
- Donor and patient records

Highlighted areas of firm compliance
The patient information was considered by the inspectorate to be clear and lay intelligible. It is in accordance with the requirements of Standard Licence conditions and the 7th Code of Practice. It was noted during the audit of records, that in the past a specific written consent to this research project, was not consistently completed. However, more recently completed consent to research forms were of a specific nature. The PR is reminded of Code of Practice Standard 8.3.2 which states that before donors give their consent to the use of their gametes and/or embryos in a research project they are given oral information, supported by written material, which confirms: (a) the specific research project, including tests that may be performed on embryos or cells derived from the embryos as part of the licensed research project. Although there is not requirement that the consent form is to a specific research project, the PR should consider how he can satisfy himself that the appropriate information has been given prior to donation, particularly as donors are recruited from a variety of treatment centres.
Summary of audit of patient records
Four sets of records from patients who donated embryos to this project were reviewed and were seen to contain valid consent forms. Witnessing of the transfer of embryos to research was documented appropriately in all of the records reviewed. The transfer of embryos to research is witnessed, with the operator and witness signing to confirm have completed appropriate consents to research. The audit of donor records also revealed that the witnessing mechanisms in place prevented the use of embryos where consent from both gamete providers was not evident.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

5. Scientific practice

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

Summary of:

- Use of material
- Progress in achieving aims and objectives
- Standard operating procedures
- Minimisation of material loss and wastage
- Peer review

Use of material
Twenty eight fresh embryos have been supplied for this project in the last year and thirteen of these were suitable for inclusion in the project. In total two hundred and fifty eight frozen embryos have been supplied to the project in the last year and one hundred and one of these have been used so far. All the fresh embryos donated to this project were donated by patients receiving treatment at the Assisted Conception Unit Guy's Hospital (centre 0102). The frozen embryos have been supplied by four different licensed treatment and storage centres: Assisted Conception Unit Guy's Hospital, Woking Assisted Conception Unit, King's Fertility Clinic and Bourn Hall Fertility Clinic. The PR plans that 150 fresh embryos and 150 frozen embryos will be used within this project in the next 12 months.
Project objectives
Renewed objectives and methods: **To apply PGH to an increasing range of genetic diseases.** 1. A service innovation grant for this purpose was obtained from the Guy's and St Thomas' Charity with a post for a molecular biologist, now appointed, to take the project forward. We are concentrating on diseases that tend to be associated with a specific region of a particular chromosome (e.g. the X chromosome) whereby the development of a suitable matrix of short tandem repeats (STRs) allows application to a range of diseases without further workup. We have already done this for the gene rich Xq27_28 region, which houses the L1CAM, ABCD1, MECP2, IKBKG and Factor VIII genes. We also intend to test whether relevant trisomies can be detected at the same time as the specific genetic diagnosis. Initially, single amniocytes available following age-related prenatal diagnosis testing will be used to assess the power of the selected markers on DNA that has undergone whole genome amplification (WGA). Once the accuracy and efficiency of the WGA process on the detection of known trisomies has been established, DNA will be tested retrospectively from stored embryos once the outcome of a pregnancy is known, or from samples that have not

resulted in a pregnancy to try and establish an incidence of false positive results.

2. To examine and improve the allele dropout rate in WGA and validate new WGA methods to increase efficiency and accuracy. When new WGA kits become commercially available they will be tested on embryos that are not suitable for transfer to determine if they reduce the allele drop out rate and increase the efficiency of WGA to improve the quality of the service.

3. To try and automate some of the PGH technique so new robotic methods can be applied. A small robotic precision liquid handling work station was purchased as part of our recent grant and techniques are being modified to utilise robotic technology to simplify and speed up processes for handling an increase in case load.

To improve methods of assessing embryo quality in order to improve embryo selection procedures at embryo transfer.

4. To continue the investigation into the aneuploidy status in embryos not suitable for replacement in ART cycles by detailing the mosaicism and aneuploidy observed in embryos (3.3.ii), using WGA and PCR analysis. This approach has the potential to examine the ploidy status of each chromosome. We hope that by establishing patterns of chromosome loss or gain within different cells from the same embryo, we will gain information on the cell cycle control and frequency of errors in early cleavage divisions in human embryos.

5. Blastocysts for transfer or cryopreservation following embryo biopsy for PGD or during routine IVF are selected on the basis of morphological criteria. However, other than outcome following transfer, there has been little attempt to assess developmental potential other than by estimates of efficiency for stem cell derivation (Stephenson et al 2006). We propose to examine embryos not selected for transfer or cryopreservation, to relate stereomicroscope morphology to cell number using DAPI staining of whole embryos, and then examine the ratio of ICM to trophectoderm by double staining for markers of the two cell lineages. We hope to relate this information not only to better ways of predicting embryos suitable for cryopreservation and thaw, but also to relate it to likely hESC derivation efficiency.

Examining further embryos at various cleavage stages to complete the work on MtDNA by real time PCR.

6. To complement the studies already underway regarding mitochondrial number and synthesis during development, the same analysis will be made on embryos grown under low oxygen conditions, either from the pronuclear stage, or from day 4 of development when fresh donated PGD embryos enter the research programme. It has been shown that a better blastocyst outcome and significant improvement in pregnancy rates and live birth is achieved following low oxygen culture (Waldenstrom et al. 2008). However the mechanisms behind this are not clear. The detrimental effects of high oxygen culture on mammalian embryo development (altered gene expression, indiscriminate damage to lipids, proteins and DNA, perturbation in cellular function and eventually apoptosis or necrosis) are mediated through the action of reactive oxygen species (ROS). Mitochondrial DNA is particularly vulnerable to ROS

due to the proximity to the site of production of free radicals, the lack of histone protection and minimal repair mechanisms. Therefore the mitochondrial competency of embryos may be playing an important role in determining developmental competency. This study will enable the relationship between gas phase, embryo morphology and mitochondrial number to be assessed, with the aim of improving selection criteria during IVF. This also directly links to our stem cell research licence (R0133) where we have begun to study the metabolic quality of hESC by measuring mitochondrial function, activity and turnover, and assessing the influence of the oxygen environment on derivation by using embryos cultured in low and high oxygen conditions. With the significant man-power and financial investment required to generate clinical-grade hESC lines, it is important that the lines are of the best possible metabolic quality and functional competence, which begins with ensuring we are culturing embryos in the optimum environment.

Lay summary of research undertaken

Preimplantation genetic diagnosis (PGD) is a reproductive option for couples at substantial risk of conceiving a pregnancy affected with a known genetic disease who wish to avoid the emotional burden associated with an affected child, termination of pregnancy or recurrent miscarriages. PGD has been offered as a service at Guy's and St Thomas' for over ten years, and it is now the busiest and most successful unit in the country. PGD has been used for single gene diseases such as cystic fibrosis, for diseases which only affect males by selecting female embryos, and for couples with chromosome rearrangements. For single gene diseases, one cell is removed from a 3- day old embryo and tested for the mutation. A separate PGD test has to be developed for every different mutation, requiring substantial resources not always available in state-run medicine. In addition, these tests are technically difficult and very sensitive to contamination with non-embryo DNA. Over the duration of our previous licence, we developed a new technique at Guy's, Preimplantation Genetic Haplotyping (PGH) which improves the reliability of single cell genetic testing and enables it to be extended to a wide range of diseases. It has also allowed us to move away from sexing embryos as a means of avoiding some genetic disease as we can use PGH to detect distinguish unaffected males in addition to unaffected or carrier females We intend to work over the next three years, further developing this approach for a wider range of genetic disorders, and to see whether we can extend the approach to include tests for some serious or lethal chromosomal trisomies such as Edward, Patau and Down syndrome. Further research will look at effect of mosaicism on diagnosis, and the impact of mitochondrial function during early development.

Peer reviewers comments

The application to renew the research licence for this project was subject to external peer review. The reviewer recommended that the application be accepted without any changes and stated that the applicants have reported good progress in a number of different areas, impacting on PGD and also on aspects of conventional IVF culture techniques and that the research progress has also fed directly into improvements in clinical provision.

Highlighted areas of firm compliance

There is a system in place which records each time material is handled. Evidence of this was seen during review of the laboratory log books.

The procedure for disposal of material has been documented in a protocol. This was provided to the inspection team. Staff were able to demonstrate their procedures to ensure that embryos are not stored beyond the statutory storage period. Two systems are in use; the first is a database system which, the researchers informed the inspectorate, is checked by the assisted conception unit personnel as well as the research team. A file is also maintained which includes records for all embryos awaiting use in research. This was seen to be organised chronologically and a clear log is also kept at the end of the file which listed all embryos awaiting use and their statutory storage date. Review of the log and the file indicated that no embryos are being stored outside the statutory storage period and the next embryos to reach their expiry date will do so on the 23rd March 2009. An audit of all stored material has been conducted in the past year. A record of this audit was provided and this stated that only minor administration discrepancies had been found during the audit.
Issues for consideration
Staff explained that there is a procedure in place to ensure embryos are not cultured beyond 14 days. However, the procedure as documented in the transfer of embryos to a research licence protocol specifically relates to practices to be followed in the other research project conducted at the centre (R0133). Code of Practice Standard 8.8.1.1 (b) requires that "where embryos are to be used for research the research Centre shall record, before commencement of the project: the procedure to be used to ensure that embryos do not develop after 14 days or (if earlier) the appearance of the primitive streak". It is recommended that the procedure to be followed for this research project be documented to ensure that embryos are not cultured beyond 14 days.
Executive recommendations for Licence Committee
Not non compliance with Code of Practice Standard 8.8.1.1 (b).
Areas not covered in this inspection
None

Report compiled by:

Name……Sarah Hopper …….

Designation……HFEA inspector…….

Date…27th February 2009 ……

Appendix A: Centre Staff interviewed

The Person Responsible and four other members of the research team took part in meetings with the inspection team.

Appendix B: Licence history for previous 3 years

R0075 Status	Licence	Type	Active From	Expires
Active	R0075/9/B	Research Project	18/06/2008	31/08/2009
Replaced by New Version	R0075/9/a	Research Project	01/09/2006	31/08/2009
Expired	R0075/8/b	Research Project	13/06/2005	31/08/2006
Replaced by New Version	R0075/8/a	Research Project	01/09/2003	31/08/2006

There are no conditions on the current licence.

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT
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Research Licence: 0075
Centre Number: 0102
Name of PR: Prof Peter Braude
Date of Inspection: 26th February 2009
Date of Response 11th May 2009

I have read the inspection report and agree to meet the requirements of the report.

Name: Peter Braude
Date: 11th May 2009

1. Correction of factual inaccuracies

(a) Page 2 Brief description of project: Para2 Line 5…..It has also allowed us to move away from sexing embryos as a means of avoiding some genetic disease as we can use PGH to **detect and distinguish** unaffected males in addition to unaffected or carrier females….

(b) Page 11. Our research nurse although now employed by the Guy's and St Thomas Trust, has 0.2 WTE devoted to the HFEA licensed projects, for which the Trust receives reimbursement from my relevant MRC grants. Hence the statement should read: The research nurse is employed by the Guys and St Thomas' Hospital NHS Foundation Trust which is reimbursed by the MRC for her time devoted to the individual MRC funded research project.

2. Comments and additional information.

Having read carefully the papers received in response to my request for licence variation, I appreciate that the Committee have handled the unwitting breach of premises licence with understanding and consideration. However it is my submission that the handling of the variation request put us in breach conditionally on its issue:

1. Having sought advice on conditions for our new premises, I applied for a licence variation in good time and in good faith, appreciating that it would be necessary to have the 11th floor research laboratories and storage licensed, in order to continue research activity without hiatus.
2. The fact that the licence was issued on the 18th June, more than 10 weeks before any intended move to the new premises, gave the reassurance that application for licensing of the new premises, had been done in a timely fashion.
3. If revocation of the 4th floor premises licence was conditional on issue of the 11th floor licence, it would have meant that all research work, which was continuing as usual prior to the intended move, and storage of embryos would have been made illegal by default.

4. Since the 11th floor premises were neither ready, nor intended to be ready, by the date of issue of the variation, it would have meant that all stored embryos would have had to be destroyed thenceforth.
5. To the best of my awareness there was no information provided with the notice of the variation to the effect that the 4th floor licence was to be revoked on its issue.
6. If such information had been received, I would immediately have contested the obligatory nature of the breach and dealt with it by requesting both premises to be licensed in the variation.
7. I am sure that, in the same way that the effect of the variation was not fully appreciated by me at the time, its effect might not have been immediately apparent to the Licence Committee issuing the variation.

I ask that these facts be taken into account by the committee in their intention to record this as a breach in the unit's licence history, as immediate breach on issue of the variation was inevitable without due warning.

3. Actions taken:

(a) Breach 1: Use of 4th floor following licence variation. This was attended to with immediate effect and application made so that both floors would be considered as licensed premises. An incident report was submitted on and received by HFEA on 11th March 2009. I now understand that the circumstances of the breach, as outlined in my incident report, were not seen by the Licence Committee and therefore have been presented above.

Having made the final move to the new unit for all clinical and research purposes, work now only takes place in 11th floor premises, and the 4th floor is being dismantled.
A request is hereby made to revoke the 4th floor as licensed premises.

(b) Non-compliance: Area for improvement;
We have appended our revised statement of procedures which ensure that embryos are not grown intact beyond the 14 day statutory limit. For this project embryos would seldom be cultured beyond 7 days as most information relevant to this project would be obtained prior to that.

(c) Page 13. The requirement to be satisfied that appropriate information is given prior to donation.

It may be worth reiterating here, the three sources of embryos for our research and how patients receive information.

1*. 'In house' infertility patients* – fresh embryos. These are never used for 0133 (stem cell project) as it is our belief that if a cleavage stage embryo can develop to the blastocyst stage suitable for stem cell derivation, then it is probably worth cryopreserving for the patient's own use in therapy. These embryos are seldom of a quality useful in research other than to be disaggregated and used as single blastomere research –genetic (PGD) or embryo quality. Thus all fertility patients attending our patient information evenings receive a pack including written information about our research projects and intentions, and this is mentioned and any queries answered at the presentation. These patients are not recruited to the project to derive stem cell lines; thus their consents only relate to 0075.

2. *In house patients, and patients from other centres who have cryopreserved embryos which they no longer wish to use in their therapy.*
Each of these patients is contacted by embryology staff in their 'home' unit, and given the option of disposal, donation to another, or donation to research. If they opt for the latter, then each of them is spoken to by our research nurse, who obtains specific consent as to which of the two general projects they are prepared to donate, and if (0133) stem cells, then the specific hESCCO stem cell consent form is completed.

3. *Guy's PGD patients*: Each patient who has agreed in principle to donate to research embryos unsuitable for their treatment, is seen by our research nurse and details of the two projects discussed as above. Specific consent is obtained and the hESCCO form completed if appropriate.

I suspect that if there were any specific project consent forms outstanding in the notes, then these would have applied to the in-house fertility patients only, who donate solely to one project (0075) for which they would have received information previously.
I am therefore satisfied that appropriate information is being given to patients prior to research in both written and verbal forms.

HFEA Research Committee Meeting
20 May 2009

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 1

Guy's Hospital (0102; R0075) -- Renewal

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: Graham Miles, Morgan Cole

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 (71 pages)
- tabled papers (7 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 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 papers and tabled response from the PR and noted that the Person Responsible had applied for the licence to be

renewed for a period of three years and for the licence to be varied to include the creation of embryos in vitro.

2. The Committee noted that this project is being conducted to further develop Preimplantation Genetic Haplotyping (PGH) to be used for a wider range of genetic disorders to include some serious or lethal chromosomal trisomies and to conduct further research to look at the effect of mosaicism on diagnosis, and the impact of mitochondrial function during early development.

3. The Committee noted the decision of a previous meeting of the Committee on 11 March 2009 concerning a breach of section 12(1)(a) of the HFE Act 1990 (as amended), which states: the following shall be conditions of every licence granted under this Act – that the activities authorised by the Licence shall be carried on only on the premises to which the licence relates and under the supervision of the Person Responsible.

4. The Legal Adviser confirmed that the identified breach had been dealt with by the Committee on 11 March 2009 by that Committee noting the breach but determining that no further action should be taken. On that occasion the Committee also agreed to vary the licence to include both the 4th and 11th floors whilst the transition was taking place. Accordingly, it was unnecessary to deal with that issue further apart from clarifying the scope of the licensed premises in the licence to be renewed.

5. The Committee noted the further explanation made by the Person Responsible about the unwitting nature of the breach. The Committee also noted that the 4th floor is no longer required to be used and that the licensed premises should now be restricted to the 11th floor.

6. The Committee noted that the response of the Person Responsible included documentation which outlined the standard operating procedure for ensuring that embryos are not cultured beyond 14 days. The Committee agreed that it was satisfied that the Centre was now compliant with Code of Practice Standard S.8.1.1.

7. The Committee considered the need for the creation of embryos in vitro in relation to this project. The Committee noted the response of the Person Responsible to the Peer Review and was satisfied with the explanation that embryos in the early stage of development are rarely donated to the project and that the results from experiments on frozen embryos at this stage are open to criticism due to the effects of cryoprotectant agents or the freeze-thaw process.

The Committee's Decision

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

9. The Committee decided that these activities are necessary and desirable for the following purposes:
    - Promoting advances in the treatment of infertility
      HFE Act 1990 (as amended) Schedule 2 3(2)(a)
    - Increasing knowledge about the causes of congenital disease
      HFE Act 1990 (as amended) Schedule 2 3(2)(b)
    - Increasing knowledge about the causes of miscarriages
      HFE Act 1990 (as amended) Schedule 2 3(2)(c)
    - Developing methods for detecting the presence of gene or chromosomal abnormalities
      HFE Act 1990 (as amended) Schedule 2 3(2)(e)
    - Increasing knowledge about the development of embryos
      HFE (Research Purposes) Regulations 2001 2(a)
    - Increasing knowledge about serious disease
      HFE (Research Purposes) Regulations 2001 2(b)
    - Enabling any such knowledge to be applied in developing treatments for serious disease
      HFE (Research Purposes) Regulations 2001 2(c)

10. The Committee decided that it was satisfied that the proposed use of embryos is necessary for the purpose of research. In making this decision, the Committee took into account that the purpose of this project is to develop a technique for human application, so it is important to use human tissues to ensure accurate translation of the technique. Adult cells or animal embryonic stem cells would not be suitable for the research.

11. The Committee agreed that it was satisfied with the patient information and Consent Forms.

12. The Committee considered itself satisfied that it was appropriate to grant a licence, noting that the application had been paid, the suitability of the Nominal Licensee and that it was satisfied with the character, qualifications and experience of the Person Responsible.

13. The Committee decided to grant a licence for a period of three years and, to vary the licence to include the creation of embryos in vitro.

14. Additionally, the Committee agreed that for the purpose of R0075, the licence should be varied, with immediate effect, to state that the Licence covers "ACU premises on the 11th floor, Tower Wing, Guy's Hospital".

Signed..... Date 25.5.07
Emily Jackson (Chair)