Research Renewal Inspection Report

Date of Inspection: 12 April 2011
Purpose of inspection: Renewal of Research Licence
Length of inspection: 6 hours
Inspectors Dr Andrew Leonard
Mr Parvez Qureshi

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 1 January 2010 and 27 May 2011.

Date of Licence Committee: 20 July 2011

Centre details

Project Title	Genetic screening of the preimplantation embryo
Centre Name	The Assisted Conception Unit (ACU), Birmingham Women's Hospital
Centre Number	Centre 0119
Research licence Number	R0186/1/b
Centre Address	Centre for Human Reproductive Science (ChRS), The Assisted Conception Unit, Birmingham Women's Hospital, Edgbaston, Birmingham, B15 2TG
Person Responsible	Dr Jackson Kirkman Brown
Licence Holder	Dr Sue Avery
Treatment centres donating to this research project	Centre 0119 only
Date Licence Issued	01/10/2008
Licence expiry date	30/09/2011
Additional conditions applied to this licence	None

Contents

Purpose of the Inspection Report

The purpose of the inspection is to assess whether research using human embryos is carried out in compliance with the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended) and the HFEA Code of Practice 8th edition (CoP) and that progress is made towards achieving the stated aims of the project. The report summarises the findings of the licence renewal inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the Research Licence Committee (RLC) which makes the decision about the centre's licence renewal application.

Report to Research Licence Committee

Brief description of the centre and its licensing history:

Centre 0119 has held research licences since 2004. The research premises used for project R0186 comprise the clinical embryology laboratory in the Assisted Conception Unit, Birmingham Women's Hospital (*i.e.* HFEA centre 0119). The project uses a dedicated research incubator in the laboratory, as well as air flow cabinets and an embryo biopsy microscope with micromanipulation stage, which are also used for treatment activities.

The project was inspected for its initial licence application on the 18 July 2008 and first licenced from 1 October 2008 for three years. The project was reviewed at an interim inspection on 17 June 2010 and it was observed that five recommendations, made when the project was first licensed, had been implemented. The interim inspection report made two other recommendations, which the Person Responsible (PR) agreed to implement, and the ELP considering the report agreed to continue the licence.

The PR is a Senior Lecturer with the University of Birmingham, 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 has completed the PR entry programme. The Licence Holder (LH) is the PR of the Treatment and Storage licence at centre 0119.

Variation to Licence

The PR and LH have not applied to vary the centre's licence as part of the renewal process.

Title of research project:

Genetic screening of the preimplantation embryo

Summary for licensing decision

In considering overall compliance, the inspection team considers that it has sufficient information drawn from documentation submitted by the centre prior to inspection and from observations and interviews conducted during the inspection visit to conclude that:

- the PR is suitable and has discharged their duty under Section 17 of the HF&E Act 1990 (as amended)
- the premises are suitable
- the practices are suitable
- the centre has submitted appropriately completed documentation in application for renewal of their licence, as required by paragraph 20 of General Direction 0008.
- the centre has submitted fees to the HFEA in accordance with requirements

The inspection team note that the patient information and consent forms meet the statutory requirements.

The inspection team note that the peer reviewer provided an opinion that it was appropriate to carry out the proposed research.

The RLC is asked to note that there is one area of 'other' practice requiring improvement which is. The inspection team recommends that the RLC requires that the PR complies with the following recommendations within the prescribed timeframes set out in the inspection report

Critical areas of concern: None
Major areas of non compliance: None
Other areas of practice that require improvement:

- The PR should ensure that the annual 'Research information and data sheet' for the project is submitted to the HFEA by 31 January of the following year.

The inspection team recommend the renewal of the centre's licence for a period of three years without additional conditions subject to compliance with the recommendation made being implemented within the prescribed timescale.

The activities to be licensed are:

- The use of embryos in research
- The storage of embryos

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

The storage of embryos and their use in research are necessary or desirable for the following purposes, as defined in Schedule 2 3A (2) to the HFE Act 1990 (as amended):

- Promoting advances in the treatment of infertility Schedule 2 3A (2)d

The reason for this, as stated by the PR, is: 'Techniques for genetic examination of the embryo are rapidly evolving and become an essential adjunct for many couples with multiple problems alongside subfertility. Knowing more about the early stages of embryo development and how and where aneuploidy may arise, we can resolve certain issues around miscarriage and genetic complications for IVF babies.'

The peer reviewer states: 'Identifying embryos with chromosome abnormalities and excluding them from transfer is a major way to improve the treatment of infertility in older patients or those with a pre-disposition to aneuploidy (ie patients carrying chromosome translocations) and the team plan to try and improve the technology for identifying chromosomal abnormalities, to advance such treatments and make them more efficient, reliable and robust. In addition, the team is investigating the basis for chromosomal mosaicism in embryos, a common phenomenon which can potentially confound accurate genetic diagnosis and is a common cause of arrest in embryo development. Although many observational studies have been carried out in the area of human embryo mosaicism and a variety of techniques have been utilised, the approach described in this application is novel and should yield interesting new information regarding the origin of chromosomal mosaicism and its consequences for ongoing embryo development.'

- Increasing knowledge about the causes of miscarriage Schedule 2 3A (2)e

The reason for this, as stated by the PR, is: 'Through a better understanding of early genetic screening of the embryo, we can hope to better understand the causes of

miscarriage and the early stages of embryo development, and also gain knowledge for treatment and diagnosis of the same.'

The peer reviewer also stated: 'At least one major cause of early miscarriage is chromosomal aneuploidy of the growing foetus. The Birmingham team are intending to investigate origins of such chromosomal abnormalities in early embryos and also are intending to carry out studies aimed at improving the diagnosis of such aneuploidies, to improve screening programmes for early embryos. By this two pronged approach, selection of embryos with a normal chromosomal complement should be possible, thereby decreasing the possibility of miscarriage in susceptible patients.'

- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation Schedule 2 3A (2)g

The reason for this, as stated by the PR, is: 'As part of our study we will repeatedly sample blastomeres from an embryo and screen for the number of chromosomes and, or other genetic mutations. This should enable us to better clarify the 'mosaicism' observed in the early embryo which currently confounds accurate preimplantation diagnosis of conditions such as aneuploidy.'

The peer reviewer also stated: 'The Lead investigator has assembled an outstanding team of experts to work on this project and it is expected that cutting edge molecular biology tools will be applied in new and different ways in order to identify chromosomal abnormalities and genetic mutations in embryos. The studies described represent an exciting alliance of novel experimental embryology alongside very detailed diagnostic testing methods (FISH and molecular arrays) and it is likely that such studies will lead to improved, more accurate methods of embryos sampling and genetic testing.'

- Increasing knowledge about the development of embryos Schedule 2 3A (2)h

The reason for this, as stated by the PR is: 'As part of our study we will repeatedly sample blastomeres from an embryo and screen for the number of chromosomes and, or other genetic mutations. This should enable us to better clarify the 'mosaicism' observed in the early embryo which currently confounds accurate preimplantation diagnosis of conditions such as aneuploidy.'

The peer reviewer also stated: 'All of the work described in the project outline is aimed at elucidating the genetic basis of embryo development and implantation and the basis for genetic aneuploidy, a major cause of developmental arrest in embryos.'

The use of human embryos is necessary in the opinion of the peer reviewer because: 'The team wishes to study directly the genetics of human embryos in order to identify aneuploidy and the origins and possible causes of chromosomal aneuploidy. All this work would be meaningless in an animal model system, where chromosomal aneuploidy is vanishingly rare.'

Recommendation to the Research Licence Committee:

The inspection team considers that, overall there is sufficient information available to recommend the renewal of this centre's licence for a period of 3 years without additional conditions. In making this recommendation it is noted that the PR has responded satisfactorily to all recommendations made in this inspection report.

Summary of project

The renewal application provides a lay summary which states: ‘When embryos are produced by IVF, during the first few days after fertilisation when they are still just a few cells, one or two of these cells can be taken without affecting the health of a future child. The reason to do this is to use genetic screening to check for severe debilitating illnesses or things which would cause a miscarriage and the associated upset. In an ideal world these can be avoided as IVF creates a number of embryos and so we could only pick those without problems to put back. Currently one suggested problem with these diagnoses is that in the early embryo not all cells are the same and the one cell that you take and sample may not be representative - you could make a misdiagnosis.

‘Through use of embryos that would otherwise be disposed of, we aim to establish clear and safe techniques to make an accurate diagnosis in these early embryo stages. The project aims to develop and validate genetic screening procedures that can be used on the pre-implantation embryo.

‘We will utilise embryos, which would otherwise have gone for disposal, donated by patients attending for infertility treatment at the Birmingham Women's Fertility Centre, Birmingham Women's Hospital. The donated embryos fall into three categories (1) fresh embryos surplus to treatment, (2) fresh embryos unsuitable for treatment (3) frozen embryos no longer required for treatment. All these embryos would otherwise be disposed of. No embryos will be specifically created for this project and the patient always has the choice to donate to another couple.

‘Embryos will be cultured to the four or six cell stage before being biopsied. Depending upon the experiment; a) repeated biopsies will then occur over a number of days maintaining the embryo as a four to eight cell embryo for a week; b) the embryo will be disaggregated and all cells examined; c) the embryo will be subdivided into individual (or paired) blastomeres, in separate empty zona and allowed to divide as for a); d) the embryo will be allowed to develop to blastocyst which will then be studied and a trophectoderm biopsy performed.

‘The blastomeres will be analysed by Arrays / FISH. We have the latest array technology available in the West Midlands Regional Genetics laboratories and are in discussion with 'BlueGnome' about arrays for our initial research. After seven days any embryos still held at cleavage stage will be allowed to develop to blastocyst stage. These blastocysts will be examined again as above via trophectoderm and whole blastocyst spread to confirm results.

‘The patient population attending the Birmingham Women's Fertility Centre is particularly ethnically diverse - in 2005, 37% of the Birmingham population was from an ethnic minority. As it is known that amongst the Birmingham biraderies there are many rare and severe genetic phenotypes due do consanguinity, testing for these will also be developed.’

Objectives of the research:

It is stated by the PR in the licence renewal application form: 'The main aim of this work is to assess the effects of multiple-time embryo biopsy as a method of reducing the chance of misdiagnosis due to embryo genetic mosaicism. Alongside this, these results and testing data will provide the platform for development and validation of the PGS / PDS testing services that Birmingham Women's will offer under the treatment licences. As a part of the final testing regime all embryos will be totally disrupted for analysis leaving no viable cells.'

Lay summary of the research undertaken since the last inspection on 17 June 2010:

It is stated by the PR in the licence renewal application form: 'Initial research focused upon developing the protocols and practicing biopsy technique, blastomere spreading for FISH, and preparation of cells for array. Full arrays have only just become available so validation of this technique and technology in Birmingham will be our next stage of research.

'To date a small number of embryos have been biopsied to practice the FISH techniques and initial data been obtained. We now have a better idea of how embryos unsuitable for freezing perform when we biopsy them (poorly) and can reconsider our research strategy accordingly.'

Peer review comments:

The peer reviewer provided an opinion that it was appropriate to carry out the proposed research. The peer reviewer stated after providing this opinion: 'I think this is an excellent project, which is likely to yield clinically translatable scientific results. However, I do have one concern which should be addressed before a renewal license is granted. In the patient information, the PR is the person indicated as appropriate to give further information, should it be needed, to patients considering donation of embryos. This is not appropriate, as the PR is directly involved in the research project. It is indeed good practice to provide details of someone who can discuss scientific issues and implications with a couple considering donation if they wish it, but this person, although having knowledge of the project and the science behind it, should have no direct involvement, in order that they may maintain an impartial stance. There should also be mention that a counselling service is available to discuss any issues which the patients may wish to discuss concerning the provision of consent. I note that these issues were raised during the last HFEA inspection report but have not been addressed in the patient information provided with the renewal application.'

The peer reviewer's concerns are addressed in the report on page 12 of this report.

Regarding the work so far undertaken, the peer reviewer reported: 'Research carried out to date has involved validation of procedures involved in the biopsy of embryos and preparation of the cellular biopsy for FISH or molecular analysis. No detailed results of the diagnostic analyses carried out were reported, which is understandable given that initial work has focused mainly on validation work. The current renewal application is an extension of the work carried out during the last licence, using more sophisticated molecular techniques and diagnostic methods for analysis of genetic complement in embryos and having now validated most of the methods to be used (apart from the new array technology) progress in the next period is likely to be more rapid.'

Donation and use of embryos:

It was reported in the inspection report from 17 June 2010, that between 1 October 2008 and 17 June 2010, project R0186 received 31 embryos from centre 0119. These were subjected to repeat embryo biopsy according to the project's experimental protocols. No embryos were held in storage at the time of the inspection on 17 June 2010.

The PR reported in the Research Information and Data Sheet for 2010, provided in accordance with General Directions 0002, that five embryos had been used in project R0186 between 1 January and 31 December 2010.

The PR proposes in the renewal application form to use 20 fresh and 20 frozen embryos in each of the three years of the proposed research licence.

The peer reviewer considers the proposed number of embryos to be used to be justified and states further: 'In fact, I consider the number of embryos proposed to be relatively modest for the purposes of the study described. However, the team have managed to optimize their use of embryos by proposing to re-sample the same embryo several times over a period of days in order to observe the dynamic progression of chromosomal errors during development. However, I do have a word of caution, as it may be that in some cases, cellular development will be compromised by the manipulations described and so more embryos may be required in the end to fulfill the purposes of the project. These kinds of manipulations have been routinely carried in mouse embryos, but not often in poor quality surplus human embryos.'

The inspection team note that all embryo usage has complied with Licence Condition R28, i.e. embryos should not be cultured for more than 14 days post-fertilisation.

Details of inspection findings

Inspection findings

Ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos
(Guidance note 29, 30, 31)

What the centre does well.
Evidence provided on inspection indicated that the research project was approved on 4 August 2008 by an appropriately constituted Local Research Ethics Committee (LREC). The PR stated on inspection that this ethical approval is still in place and will remain so until the PR, as project lead, informs the LREC that the project has terminated.

A peer review was obtained for this renewal application. The peer reviewer is supportive of the licence renewal, but had two concerns regarding patient information, as discussed in 'Give prospective and current patients and donors sufficient, accessible and up-to-date information…' on page 12.

The activities to be licensed are: The use of embryos in research; The storage of embryos. These proposed activities are not prohibited by the HF&E Act 1990 (as amended) and are considered by the applicants necessary or desirable for the following purposes, as defined in Schedule 2 3A (2) to the HFE Act 1990 (as amended):

- (d) promoting advances in the treatment of infertility,
- (e) increasing knowledge about the causes of miscarriage,
- (g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- (h) increasing knowledge about the development of embryos.

In the opinion of the inspection team, appropriate justifications that the activities to be licensed are necessary or desirable for these statutory purposes, have been provided by the PR and the peer reviewer, as discussed in detail in the 'Summary for Licensing Decision' on pages 3 – 5. The peer reviewer has also stated that the use of human embryos is necessary, for reasons also provided in the 'Summary for Licensing Decision'

What they could do better: Nothing noted at this inspection

Have respect for the special status of the embryo when conducting licensed activities
(Guidance note 15, 18, 22, 25, 26)

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

1. The centre has documented procedures for the processes by which patients are informed of the research and their consent is taken, and for preventing the use of embryos in activities other than those which are licensed (Licence Condition (LC) R23). These procedures ensure that embryos are used in a respectful manner for only the purposes specified in patients' consents, as required by Schedule 3 to the HF&E Act (1990) as amended.
2. The PR stated that research recruitment practices ensure that no money or other benefit is given to patients donating embryos to the project, as required by LC R24. This is also clearly stated in the information provided to patients.
3. Centre 0119 has documented procedures, read by all embryology staff, one of which discusses the separation of research and clinical embryology roles. This ensures that the clinical embryologist on the research licence is not involved in the processing of embryos for treatment which may later be donated to research, as required by LC R27.
4. The transfer of fresh and cryopreserved embryos to research is witnessed to ensure their correct identification, as required by LC T71, and that research consents are present. This check was seen on inspection of the records from the three patients who donated to the project in 2010. When embryos are placed in the research incubator, the clinical embryologist on the research licence is informed and she transfers the embryos to an anonymised dish marked with a research code and returns them to the same incubator, as required by LC R26. The researchers see no patient identifying information after anonymisation.
5. The embryos and their research processing are documented anonymously in the research embryo usage log book. The clinical embryologist on the research licence performs the embryo culture, repeat biopsy and blastomere storage which occur as part of the research activity.
6. The centre has a procedure which documents that embryos should not be cultured for more than 14 days post-fertilisation. The research embryo usage log book is regularly reviewed when the project is active, to prevent the culture of embryos beyond 14 days post-fertilisation. These measures ensure compliance with LC R28.
7. A procedure has been established for embryo disposal at the end of experimental use or their statutory storage period, as recommended by CoP Guidance 22.3. Disposal is witnessed and recorded in the research embryo usage log book.
8. Electronic card key locks are fitted in centre 0119 to the doors controlling access to non-patient areas as well as to the doors to the embryology laboratory and the cryostore where research donated embryos are kept. These locks are accessible to licensed centre staff only. Experimental notes and records, which do not contain any identifying information, are kept within the embryology laboratory or the Centre for Human Reproductive Sciences within centre 0119. These arrangements ensure that the security of the centre is appropriate for licensed activity.
9. There is appropriate equipment for the project, which is well maintained and serviced. It is noted that the embryo biopsy equipment is used for treatment and research, however never at the same time so that treatment and research activities remain separated.
10. The PR ensures that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA, as is required by General Directions 0002.

What they could do better: Nothing noted at this inspection

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

What the centre does well.

Patient information and consent forms were reviewed against the 8th edition of the CoP and were considered to be compliant, with some minor issues discussed below. Review of three patient records on inspection from those patients who donated to the project in 2010, indicated that all consent forms had been appropriately completed.

Research donors at centre 0119 are recruited and consented by the PR of the research project or a research recruiter/consenter who is independent of the research project. The PR said on inspection that the research recruiter/consenter is less involved with the project than at the interim inspection in July 2010. Written and verbal information regarding the research project is first given when the patients attend an information session to introduce them to treatment at centre 0119. They are advised verbally and in writing that research donation will not have any influence on their clinical treatment. Patients can indicate if they are interested in research donation using a tick box in their clinical consent forms and are told that this is not a commitment. The patients next attend a clinical consultation at which HFEA consent forms are competed, after which, if they have indicated an interest in research, they can discuss it with the PR or the research recruiter/consenter and are provided with further information. Patients next attend the clinic for ultrasound scanning, after which they discuss research consent with the PR or research recruiter/consenter and sign consent forms if they so choose. When research consents have been signed, they are stored in the patient record and a checklist on the front of the record is amended to indicate the research consent has been provided. These information and recruitment processes are documented in standard operating procedures (SOPs).

The PR has recently attended an accredited training course for informing and consenting patients and the training certificate was provided to the inspection team after the inspection. The research recruiter/consenter has been trained in the role by the PR.

Centre 0119 has documented selection criteria for patients to donate embryos to research. Research consented patients who choose not to freeze embryos or whose embryos are of too poor a quality for freezing, are approached about the embryos' use in research. If patients agree, their fresh embryos are transferred to the research incubator with witnessing of the embryo's identification and that research consents are in place.

Patients with cryopreserved embryos are sent research information and a consent form if they request them in response to an annual letter asking what they wish to do with their stored embryos. They are also offered the opportunity to discuss donating with the PR on the telephone or in person. The embryos of patients complete these consent forms are taken into the research project, however they remain stored in their original dewar location until required. When needed, the embryos are taken from the dewar, with documented witnessing of the embryo's identification and that research consents are in place. They are then thawed and cultured in an incubator dedicated to research, before being used in the research project. The PR stated on inspection that there are currently no embryos in storage which have been consented to project R0186.

What they could do better.

1) The availability of independent counselling when patient couples consider the decision to donate to research, is discussed in the section within the patient information titled 'What does this involve for me?', as required by LC R18. The peer reviewer thought that no reference was made to counselling in the patient information. The inspection team suggest that it would enhance the patient information's clarity, if the availability of independent counselling was discussed in a separate, appropriately titled, section regarding counselling within the patient information, and that this section also includes contact details for a member of centre staff through whom an appointment for counselling can be booked. These are suggestions for improvement however and the inspection team accept that the patient information contains the information on this issue required by LCs and the CoP.

2) The peer reviewer notes that the PR is the named contact in patient information if further information is needed and considers: 'This is not appropriate, as the PR is directly involved in the research project. It is indeed good practice to provide details of someone who can discuss scientific issues and implications with a couple considering donation if they wish it, but this person, although having knowledge of the project and the science behind it, should have no direct involvement, in order that they may maintain an impartial stance.' This issue was previously raised in the report of the initial licensing inspection on 18 July 2008. When the situation was reviewed at the interim inspection on 17 June 2010, it was noted that patient information contained the contact details for the PR and the research recruiter/consenter who should be contacted 'for any queries'. It was noted that the recruiter/consenter is well informed about the project but not dependent on it. The inspection team considered no further action was needed and this was agreed by the ELP.

The PR explained at this inspection that the research recruiter/consenter is now more involved with other activities so is less likely to be available for the research project. Thus the PR is, in general, the person providing further information and also the person who assists patients in completing their consent forms. The PR considers it best that he provides further information because he knows the research project's aims, methodologies and intricacies, such as the method of embryo disposal, which is apparently a common subject for further enquiries. The PR stated that a person not associated with the project could understand the research and its aims, but probably not the intricacies, and would not be well placed to answer all enquiries. He also noted the previous and recent training he has undertaken in informing and consenting patients, which makes it highly unlikely that he would be biased when providing information to patients.

The inspection team note the most relevant regulation in this area is LC R22, which states: 'The centre must ensure that a designated individual, who is not directly involved in the patient's treatment is available to discuss with the patient the project of research and the possibility of donating material to the project. CoP Guidance 22.14(a) conveys an almost identical requirement. Thus there is no restriction within LCs or the HFEA CoP which prevents the PR being the person to whom further research enquiries are directed since he is not associated with their treatment. The inspection team also notes CoP Guidance 22.15: 'Consent should not be obtained under duress…..' and that there is no evidence in the form of patient complaints to the HFEA or centre to suggest that duress is occurring. Given these observations, the inspection team considers there to be no regulatory issue with the PR being the person to whom further enquiries are directed. The inspection team suggests however that, where possible and practical, the PR pass such enquiries to the research recruiter/consenter.

Conduct all licensed activities with regard for the regulatory framework governing treatment and research involving gametes or embryos within the UK, including:

- **maintaining up-to-date awareness and understanding of legal obligations**
- **responding promptly to requests for information and documents from the HFEA**
- **co-operating fully with inspections and investigations by the HFEA or other agencies responsible for law enforcement or regulation of healthcare**

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

What the centre does well.

All research activity is carried out under the supervision of the PR, as required by LC R1, who is present within centre 0119 for at least 12 hours per week. When the research project is active, the PR meets with the embryologist who is on the research licence at least once a week to ensure effective supervision.

The PR implemented all the requirements in the reports of the initial licensing inspection on 18 July 2008 and the interim inspection on 17 June 2010.

The centre does not use embryos which have been derived from egg sharing arrangements or import/export embryos for research purposes. Indeed the project uses embryos only from centre 0119.

Cryopreserved embryos donated to research remain stored in their original dewar location until required, and are thus included in the dewar storage audit and 'bring forward' system used in the treatment activities at centre 0119. This prevents research donated embryos being stored over their consented storage period. The PR stated on inspection that there are currently no embryos in storage which have been consented to project R0186.

The centre has an incident reporting protocol compliant with HFEA requirements.

Complaints from patients regarding the research project are dealt with through the established complaints procedures used for treatment and storage activities at centre 0119, which were considered compliant with HFEA requirements when last inspected.

The PR ensures that appropriate records of embryo usage are maintained. Annual embryo usage on the project in 2010 was reported to the HFEA, as required by General Directions 0002, albeit not within specified timeframes, as discussed below.

The PR has in the past been reasonably prompt in responding to requests for information from the HFEA Executive, and was so during and after this inspection.

The centre has documented SOPs for research processes from receipt of embryos through to their use and disposal.

What they could do better.

The PR returned the 'Research information and data sheet for 2010' which reports annual embryo usage, after the required date for submission stated in General Directions 0002.

Changes / improvements since the last inspection on 17 June 2010:

Area for improvement	Action required	Action taken as evidenced during this inspection
The SOP for embryo culture does not incorporate a check that viable embryos are not cultured for more than 14 days post fertilisation, noncompliant with Licence Condition R28. .	The SOP for embryo culture should state that researchers should regularly review culture records to ensure that viable embryos are not cultured for more than 14 days post fertilisation. This change should be made by 1 November 2010	The SOP for embryo culture was seen to be modified to state that viable embryos should not be cultured for more than 14 days post fertilisation. No further actions are necessary
The centre's procedures do not document that once embryos have been donated to research, they cannot then be used in treatment. This is required to prevent the possibility that research donated embryos could be used in treatment, contrary to HFE Act (1990) as amended, Section 15 (4).	The centre's procedures should document that once embryos have been donated to research, they cannot be used in treatment. This change should be made by 1 November 2010	The SOP for embryo culture was seen to be modified to state that embryos transferred to research could not be used in treatment No further actions are necessary

Areas of practice that require the attention of the Person Responsible

The section sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been classified into critical, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Standard Licence Conditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well as the timescales in which these improvements should be carried out.

Critical area of non compliance

A critical area of non compliance is an area of practice which poses a significant direct risk of causing harm to a patient, donor or to an embryo. A critical area of non compliance requires immediate action to be taken by the Person Responsible

Area of practice and reference	Action required	PR Response	Executive Review
NONE			

Major area of non compliance

A major area of non compliance is a non critical area of non compliance:

- which poses an indirect risk to the safety of a patient, donor or to an embryo through the procurement, use, storage or distribution of gametes and embryos, which do not comply with the centre's licence;
- which indicates a major shortcoming from the statutory requirements;
- which indicates a failure of the Person Responsible to carry out his/her legal duties
- a combination of several "other" area of non compliance, none of which on their own may be major but which together may represent a major area of non compliance.

Area of practice and reference	Action required	PR Response	Executive Review
NONE			

Other areas of practice that requires improvement

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

Area of practice and reference	Action required	PR Response	Executive Review
The PR returned the annual 'Research information and data sheet' which reports annual embryo usage on the project, after the required date for submission stated in General Directions 0002.	The PR should ensure that the annual 'Research data and information sheet for the project; is submitted to the HFEA by 31 January of the following year.		

Additional information from the Person Responsible

HFEA Research Licence Committee Meeting

13 July 2011

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 1

Centre 0119 (Birmingham Women's Hospital) - Renewal Inspection Report for Research Project R0186

Members of the Committee:	Committee Secretary:
Emily Jackson (lay) – Chair Andy Greenfield (Professional) Neva Haites (Professional)	Terence Dourado Legal Adviser: Stephen Hocking, Beachcrofts

Declarations of Interest: members of the Committee declared that they had no conflicts of interest in relation to this item.

The following papers were considered by the Committee:

- Renewal Research Inspection report, 12 April 2011
- Renewal Application form
- Publications: NONE
- Anonymised Peer Review
- Licence Committee Minutes 16 September 2008; initial licence application inspection report
- Executive Licence Panel Minutes 10 September 2010; Interim inspection report

The Committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation

- Indicative Sanctions Guidance
- HFEA Directions 0000 – 0012
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Background

1. Research Project R0186 ‘Genetic Screening of the Preimplantation Embryo’ was first licensed at Centre 0119 on 01 October 2008. The objective of the project is to develop and validate genetic screening procedures that can be used on the pre-implantation embryo.

Consideration of Application

2. The Committee had regard to its Decision Tree. The Committee was satisfied that the application was submitted in the form required, and contained the supporting information required by General Direction 0008. Furthermore, it was satisfied that the appropriate fee had been paid. The Committee noted that the application was made by the current designated Person Responsible (“PR”).

3. The Committee was satisfied that the PR possesses the required qualifications and experience and that the character of the PR is such as is required for supervision of the licensed activities. It was further satisfied that the PR will discharge his duties under section 17 of the Act. The Committee noted that the Inspector was satisfied the PR had satisfactorily completed the PR entry programme and is suitably qualified and experienced to undertake the role. The PR has been in post for some time and to date has a history of compliance with the HFEA’s legal and regulatory framework.

4. The Committee was satisfied that the premises to be licensed are suitable for the conduct of licensed activities as the Inspector confirmed that the premises were suitable and secure.

5. The Committee was satisfied that the licence application involved the authorisation of activities for the purpose of research, and that it did not involve the use of embryos for training purposes or the testing of embryos.

6. The Committee was satisfied that the renewed licence would not apply to more than one project and that the activity of the licence, permitted under the Act, is for ‘the use of embryos for research’ and ‘the storage of embryos’

7. The Committee noted the Peer Reviewer's support for the application and was satisfied that the activity to be licensed is necessary or desirable for the following purposes, specified in Schedule 2 paragraph 3A(2) to the Act, for the following reasons:

    - *Promoting advances in the treatment of infertility* (Schedule 2 paragraph 3A(2)(d) to the Act): the research plans to improve the technology for identifying chromosomal abnormalities, to advance such treatments and make them more efficient, reliable and robust. Additionally the Centre is investigating the basis for chromosomal mosaicism in embryos; a common phenomenon which can potentially confound accurate genetic diagnosis and is a common cause of arrest in embryonic development.
    - *Increasing knowledge about the causes of miscarriage* (Schedule 2 paragraph 3A(2)(e) to the Act): the research plan is to investigate origins of chromosomal abnormalities in early embryos and carry out studies aimed at improving the diagnosis of such aneuploidies, to improve screening programmes for early embryos which may help reduce the rate of miscarriage in susceptible patients.
    - *Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation* (Schedule 2 paragraph 3A(2)(g) to the Act): the research involves novel experimental embryology alongside very detailed diagnostic testing methods (FISH and molecular arrays)
    - *Increasing knowledge about the development of embryos* (Schedule 2 paragraph 3A(2)(h) to the Act): the research is aimed at elucidating the genetic basis of embryo development and implantation and the basis for genetic aneuploidy, a major cause of developmental arrest in embryos.

8. The Committee was satisfied that the proposed use of embryos is necessary because the research project involves the direct study of the genetics of human embryos in order to identify aneuploidy and the origins and possible causes of aneuploidy. All this work would be less relevant in an animal model system, where chromosomal aneuploidy is rare.

9. The Committee was satisfied that the research project had received approval from the Black Country Research Ethics Committee. It also noted that it had previously seen the patient information and consent forms, and that these met the statutory requirements.

Decision

10. As it was satisfied regarding all the requirements set out above, the Committee agreed to renew the Centre's licence for a period of three years without additional conditions. The Committee was satisfied that a three year period would be appropriate because the research project had previously been licensed and the Centre is experienced and has a history of regulatory compliance.

Signed: Date: 01/08/2011

Emily Jackson (Chair)