Research Renewal Inspection Report

Date of Inspection: 10 February 2011
Purpose of inspection: Renewal of Research Licence
Length of inspection: 5.5 hours
Inspectors: Wil Lenton (Lead HFEA)
Andy Leonard (HFEA)

Inspection details:
The report covers the pre-inspection analysis, the visit and information received between 18 June 2008 and 18 May 2011.

Date of Research Licence Committee: 18 May 2011

Centre details

Project Title	Pluripotency, reprogramming and mitochondrial biology during early human development
Centre Name	Newcastle Fertility Centre at Life
Centre Number	0017
Research licence Number	R0152-3-D
Centre Address	Bioscience Centre, International Centre for Life, Times Square Newcastle upon Tyne Tyne & Wear, NE1 4EP
Person Responsible	Prof Alison Murdoch
Licence Holder	Dr Mary Herbert
Treatment centres donating to this research project	0017
Date Licence Issued	01/12/2009
Licence expiry date	31/07/2011
Additional conditions applied to this licence	None

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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 Code of Practice 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 Authority's Research Licence Committee which makes the decision about the centre's licence renewal application.

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Report to Research Licence Committee

Brief description of the centre and its licensing history:

The centre is centrally-located within a science park, a five minute walk from Newcastle main train station. The centre is also licensed to carry out treatment services and has been licensed since 1992. During 2010 the centre provided in excess of 900 licensed treatment cycles to NHS and self funded patients in the North East of England.

Up until October 2009 the centre had three research licenses:

• R0145: Understanding and harnessing pluripotency in human embryos

• R0152: Derivation of human embryonic stem cell lines using therapeutic cloning and parthenogenetically activated oocytes.

• R0153: Mitochondrial DNA disorders: Is there a way to prevent transmission.

In October 2009, the research Person Responsible (PR) applied for a variation to licence R0152, asking for this project to be varied, to include the activities and objectives of the other two licences (R0145 and R0153). The variation was agreed in November 2009.

The laboratories at the centre underwent extensive refurbishment in 2007.

The PR has been in post since the inception of the licence in August 2004, has the appropriate qualifications and experience for the role and has successfully completed the PR Entry Programme (PREP).

Variation to Licence

The PR has applied to vary the centre's licence, as part of the licence renewal process, in order to include two new rooms (B2.20 and B2.28) as part of the licensed premises. The rooms were inspected during the present licence renewal process. Documentation has been supplied in support of this variation and will be presented to the Research Licence Committee on 18 May 2011.

Title of research project:

Pluripotency, reprogramming and mitochondrial biology during early human development

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
- the centre has paid fees to the HFEA in accordance with requirements

The Licence Committee is asked to note that there are no areas of practice that require improvement.

The inspection team recommends the renewal of the centre's licence for a period of three years without additional conditions.

The activities to be licensed are:

Storage of embryos
Storage of eggs
Creation of embryos in vitro
Use of embryos for research
Derivation of human stem cell lines

The above activities have been licensed previously.
None of the proposed activities are prohibited by the HF&E Act 1990 (as amended)

The above activities are necessary or desirable for the following purpose(s), which have been licensed previously.

- Increasing knowledge about the development of embryos
  HFE Act 1990 (as amended) Schedule 2 3A(2)(h)

- Increasing knowledge about serious diseases or other serious medical conditions
  HFE Act 1990 (as amended) Schedule 2 3A(2)(b)

- Developing treatments for serious diseases or other serious medical conditions
  HFE Act 1990 (as amended) Schedule 2 3A(2)(a)

- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
  HFE Act 1990 (as amended) Schedule 2 3A(2)(g)

The use of human embryos is necessary because:

Animal studies have been performed to address the questions under investigation in this research but there are known species specific differences between, for example mouse, the most commonly used model species, and human early development and stem cell derivation. Optimisation of techniques for human embryo culture and production of human stem cells will therefore necessitate the use of human embryos.

The patient information and consent forms meet the statutory requirements.

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.

The inspection team also recommend that the research licence is varied, to include new research rooms (2.30 and 2.19A). The PR has submitted the required documentation in compliance with General Direction 0008 paragraphs 8 and 22.

Summary of project

Lay summary of the research project:

In addition to the treatment of infertility, IVF-based techniques can be used to prevent transmission of genetically inherited disease. Abnormalities of the genes in mitochondria (the power sources in cells) are an important cause of genetic disease, which can cause still births or death early in life. Disease associated with mutations in the mitochondria are transmitted from mother to child, and a woman who is herself relatively symptom-free can give birth to severely affected children. A specific aim of our research therefore is to investigate the feasibility of using IVF-based techniques to prevent transmission of mitochondrial disease and to better understand how mitochondrial DNA divides itself between cells during early development. This research will study the processes that occur in the human egg just before fertilisation and over the next few days. This involves laboratory studies on the way that eggs start to divide using different stimulation methods. We will also take a nucleus from a cell donated by adult volunteers, put it into an egg then stimulate the egg to divide so that the genetic material in the donated nucleus is reprogrammed. We will transfer the nucleus from one abnormally fertilised egg to another so that we can study how the mitochondria are passed between cells. We will derive embryonic stem cells from embryos and from reconstructed embryos. The normal activation process occurs as the sperm enters the egg. We will inject sperm directly into the eggs that we have reconstructed so that we can ensure that the rate and processes of development over the following few days is normal. We will investigate the process of stimulation (activation) of the egg after nuclear transfer by injecting a sperm into the egg for a few hours. It will then be removed so that the genetic material of the sperm is not incorporated in the reconstructed egg. In order to interpret and improve the results we need to optimise the processes under which we grow the embryos. We understand little about how in vitro manipulations might influence the early human development. An integral aim of our research therefore, is to ask whether these processes are affected by laboratory procedures such as in vitro culture and freezing. Stem cells can be derived from embryos and reconstructed embryos and it is recognised that these cells may be useful in the treatment of serious disease. For clinical use, they will need to be grown under specific defined conditions. This needs modification of the routine IVF methods. We therefore aim to establish a system for deriving embryonic stem cells which is compatible with their future use in clinical treatment. We believe that our research will lead to a better understanding of early developmental events and to improved treatments for infertility and for a range of debilitating diseases.

Objectives of the research:

Objective 1.
To optimise SCNT techniques using freshly harvested mature human oocytes by adapting methods used in rhesus monkey

Objective 2.
To compare the efficacy of different methods of artificial egg activation in promoting blastocyst development and nuclear reprogramming.

Objective 3.
To test the feasibility of performing SCNT with immature oocytes with a view to testing the hypothesis that SCNT into immature human oocytes promotes efficient transcriptional silencing and nuclear reprogramming.

Objective 4.
To optimise karyoplast fusion techniques

Objective 5.
To optimise techniques of spindle (ST) and pronuclear transfer (PNT) to minimise carryover of mitochondria using Metaphase II oocytes and abnormally fertilised zygotes;

Objective 6.
To investigate mitochondria carryover following ST, PNT and SCNT

Objective 7.
Determine whether the egg reconstruction procedures predispose embryos to chromosomal and epigenetic aberrations.

Objective 8.
To derive human embryonic stem cells (hESCs) from embryos produced by SCNT

Objective 9.
To determine whether the cell proliferation and partitioning of blastocyst cells to different lineages is influenced by (i) embryo culture conditions (ii) cryopreservation (iii) blastomere biopsy

Objective 10.
To derive hESCs from embryos donated by IVF patients including those with genetic disorders such as those carrying mutations in mitochondrial and nuclear DNA.

Objective 11.
To optimise GMP-compatible and xeno-free methods for derivation, expansion and cryopreservation of human embryonic stem cells (hESCs).

Lay summary of the research undertaken since the last inspection on 15 May 2008:

This is a programme of ongoing research and the work outlined below describes progress made since the award of this Licence in December 2009. As this report is not confidential, we are unable to provide a detailed account of experimental procedures and data. 1) To develop IVF-based technologies and disease models for the prevention and treatment of diseases associated with mitochondrial DNA mutations Pronuclear/spindle transfer(i) During the past year we have continued to optimise procedures for pronuclear transfer using abnormally fertilised human zygotes. Following manipulation the zygotes are either cultured to determine their developmental capacity, or lysed and stored as lysates of whole embryos or of individual blastomeres for mitochondrial carryover analysis and nuclear genotyping. (ii) We have also made progress towards optimising vitrification techniques for human oocytes and zygotes. This is an important development as it is not always possible to perform reciprocal transfers from donated material. The development of reliable vitrification procedures will also enhance the feasibility of pronuclear/spindle transfer as a treatment option. Our objective is to develop techniques that are compatible with post-thaw manipulation and subsequent onward development. The work is ongoing. (iii) We have commenced experiments to determine whether the programme of lineage restriction in the human blastocyst is disrupted in pronuclear transfer embryos. This work builds on our previous findings that the hallmark events associated with lineage specification are conserved between mouse and human blastocysts are recapitulated during culture in vitro (manuscript submitted). A total of 368 embryos have been used in these experiments.2) To improve the outcome of infertility treatments through gaining a better understanding of the cellular and molecular events occurring during preimplantation development in vitro, and to determine how these are affected by routine laboratory procedures. (i) Ongoing experiments aim to determine the effect of culturing embryos in reduced O2 and on the effect of growth factor supplementation on blastocyst development, number of ICM cells, and NANOG expression. (ii) We have completed a study, which aimed to characterize lineage restriction events un the ICM of human blastocysts (manuscript submitted) A total of 1127 embryos have been allocated to these experiments during the last year.3) To optimise techniques for deriving (a) isogenic and allogeneic hESC lines (b) and clinical grade hESC lines for use in the development of cell therapies. Embryonic stem cell derivation(i) To optimise techniques for hESC derivation from embryos created by somatic cell nuclear transfer (SCNT), we are assessing methods of deriving hESCs from poor quality and arrested embryos. (ii) We have produced and validated a clincial grade human fibroblast cell line for hESC derivation and culture and have optimised the design of a custom built isolator-based bioprocessing system for derivation of clinical grade hESC lines. To validate our feeder cell line we compared the efficiency of derivation using a number of different feeder cell lines. Using this system have also derived a new hESC line in compliance with the standards of GMP. Ongoing experiments are aimed at developing feeder free conditions for hESC derivation. (iii) We have applied to deposit four research grade hESC lines in the UK Stem Cell Bank and we plan to bank the clinical grade hESC line upon successful completion of bio-safety testing. A total of 276 embryos have been used for hESC derivation. This represents a subset of the total of 1127 embryos used in Aim 2 above somatic cell nuclear transfer (SCNT)During the past year 152 oocytes have been donated by 17 donors for SCNT. We have taken several steps to optimise the techniques of SCNT with a focus on reducing the incidence of chromosomal abnormalities in SCNT embryos. We have also compared developmental competence of SCNT embryos derived from different donor cell lines. SCNT embryos have been either lysed and stored to measure persistence of donor cell mitochondrial DNA or fixed to assess the extent of nuclear reprogramming. We have presented data from this work at a joint CIRM/MRC Workshop on SCNT in San Francisco organised by CIRM/MRC.

Peer review comments:

The peer reviewer agrees that the proposed research project is desirable for the following purposes;

- Increasing knowledge about serious disease or other serious medical conditions
- Developing treatments for serious disease or other serious medical conditions
- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
- Increasing knowledge about the development of embryos

They also agree that the creation and use of human embryos are both necessary for the proposed research project, including the creation of human embryos by somatic cell nuclear transfer (SCNT) and that the proposed number of embryos to be used, although relatively high, at 2000 fresh embryos each year, is justified as the application covers a number of interlinked projects and the predicted usage is consistent with the level of embryo usage reported over the last twelve months and with outlined on-going program of research.

The peer reviewer believes that the derivation of human embryonic stem cell lines is Justified and that the same aims / results could not be obtained if either adult stem cell line(s) or induced pluripotent stem cells (IPs) were used and concludes by stating that it would be appropriate for the prosed research work to be undertaken.

Donation and use of embryos:

The number of embryos used; embryos created and eggs used during the period 1 January to 31 December 2009:

Number of Embryos received / used	**Source of Embryos**	
	Fresh	**Frozen**
Total number donated:	**2419**	**74**
Total number received or thawed for research:	**2144**	**69**
Total number used for research:	**2131**	**69**
Total number disposed of:	**1953**	**69**

Embryos	Created	Used
Total number created	**97**	**97**

Number of eggs received/used	**Source of eggs**		
	Fresh	**Failed to Fertilised**	**Frozen**
Total number donated:	**291**	**1594**	**NA**
Total number submitted or thawed for licensed research	**284**	**113**	**NA**
Total number used for licensed research:	**267**	**108**	**NA**
Total number disposed of:	**209**	**108**	**NA**

Donation and use of embryos:

The number of embryos used; embryos created and eggs used during the period 1 January to 31 December 2010:

Number of Embryos received / used	**Source of Embryos**	
	Fresh	**Frozen**
Total number donated:	**2294**	**101**
Total number received or thawed for research:	**2003**	**10**
Total number used for research:	**1993**	**10**
Total number disposed of:	**1503**	**10**

Embryos	Created	Used
Total number created	**45**	**45**

Number of eggs received/used	**Source of eggs**		
	Fresh	**Failed to Fertilised**	**Frozen**
Total number donated:	**186**	**1123**	**NA**
Total number submitted or thawed for licensed research	**186**	**150**	**NA**
Total number used for licensed research:	**150**	**144**	**NA**
Total number disposed of:	**68**	**102**	**NA**

Estimated projected annual use of licensed material:

Fresh eggs	150
Frozen eggs	50
Failed to fertilise eggs	150
Fresh embryos	2000
Frozen embryos	130

The peer reviewer noted that although the projected annual use of embryos looked high at 2000 fresh embryos, the application covers a number of interlinked projects and that the predicted usage is consistent with the level of embryo usage reported over the last twelve months and with the outlined on-going program of research.

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.

The centres current research licence was displayed within the patient waiting area (Standard research licence condition R4 – SRLC R4). The Person Responsible (PR) has successfully completed the HFEA PR Entry Programme (PREP) (R/1012/7) (SRLC R7)

The PR was able to demonstrate, via a communication dated 24 March 2010, that the present research project, R0152 had received approval from the Newcastle and North Tyneside 1 research ethics committee.

The peer reviewer has stated that the use of human embryos is necessary and justified for the proposed research and that the same results could not be obtained with adult stem cells or induced pluripotent stem cells. The peer reviewer also stated that although the proposed number of embryos to be used is high at 2000 fresh embryos each year, the application covers a number of interlinked projects and therefore the predicted usage is consistent with the level of embryo usage reported over the last twelve months and with the outlined on-going program of research.

What they could do better.

No issues were identified.

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.

All research activities are carried out on licensed premises which are located within the same building (SRLC R1).

A documented procedure (SC015 – Termination of embryos) is in place to ensure that embryos do not develop beyond fourteen days. The PR stated that due to the nature of the research an embryo would not usually continue in culture past days five to seven, as the inner cell mass would be removed (SRLC R28).

The research laboratory is physically separated from the associated clinical IVF laboratory and the clinical IVF laboratory manager stated that in order to make certain that clinical and research roles are clearly separated, there is a SOP in place which ensures that research staff are not present within the clinical laboratory when decisions about the use of embryos for embryo transfer, freezing or research are made (SRLC R27).

The PR and centre staff confirmed that embryos are witnessed by two staff members when transferred to research and evidence of this was seen on laboratory sheets during inspection. Each embryo donated to research is assigned a unique code and the coding information is kept secure within the senior scientists office (SRLC R26).

The PR confirmed that consents are checked and it is documented on the laboratory sheet when embryos are to be passed to research. Any such embryos obtained for research would not be subsequently used for another purpose or transferred back for treatment (SRLC R23).

The isolator/incubator equipment used within the research laboratory is specifically designed for its current use (SRLC R52) and was seen to have been validated for this use (SRLC R53). Parameters such as temperature (ºC) and percentage carbon dioxide (% CO_2) are continually logged as part of the facility monitoring system (FMS). The temperatures of the storage dewars are also continually logged. The FMS sounds an alarm if a logged parameter deviates from a prescribed norm. There is an out-of-hours auto-dial system in place in order to contact staff if an alarm condition occurs outside of normal working hours. Documented procedures are in place to ensure that laboratory equipment and facilities were cleansed regularly (SRLC R53/R55).

Staff access to the research facilities is restricted via a security swipe-card system which is continuously logged electronically.

What they could do better.

No issues were identified.

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.

It was confirmed via discussions with research staff, review of research information and inspection of patient records, that all necessary information is provided to patients who choose to donate embryos to research, prior to them giving consent. The centre's patient research information and consent forms were seen to include details about the withdrawal of consent. Staff stated that there was a documented procedure in place to follow if this situation arose (SRLC R19).

Through examination of staff training logs it was established that information concerning the research at the centre is given to patients by appropriately trained research staff, who are not involved with clinical treatment cycles (SRLC R21/R22).

Research staff stated that patients are made aware of the availability of counselling prior to any consents being signed. This was confirmed via the review of patients' notes [Schedule 3 to the HF&E Act 1990 (as amended)].

What they could do better.

No issues were identified.

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.

An organisational chart, dated December 2010, was provided by the research PR, which gave details of all personnel involved in the research project together with lines of managerial accountability (SRLC R42).

The PR stated that the centre had sufficient numbers of staff presently in post, in order to pursue the current research project objectives. Examination of staff training files showed that induction and basic training had been undertaken and that research staff had access to continual professional development (CPD) (SRLC R43/R45).

The PR stated that four research grade human embryonic stem cell (hESC) lines, derived at the centre had been deposited with the UK Stem Cell Bank. A further four research grade hESC lines, together with one clinical grade hESC were presently awaiting to be deposited (SRLC R30).

The PR stated that an adverse event reporting structure was in place, but that there hadn't been any adverse events to report over the last twelve months (SRLC R40).

What they could do better.

No issues were identified.

Changes / improvements since the last inspection on 15 May 2008:

Area for improvement	Action required	Action taken as evidenced during this inspection
Although there is a process for the periodic review of stored donated material no formal written SOP is in place.	A written SOP for the periodic review of stored donated material to be formalised.	The centre has a procedure in place that reviews all cryo-stored material on a monthly basis. Issue resolved therefore no further action is required.
There was no record of patients having been sent and/or discussed relevant background information concerning research. During discussions it was concluded that a tick-box be established within the notes to denote that such information had been sent/discussed.	A record to be established within the notes indicating that information about research projects had been sent and/or discussed with patients.	This was seen to be in use on inspection. Issue resolved therefore no further action is required.

f practice that require the attention of the Person Responsible

n sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been c
, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Stan
onditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well
in which these improvements should be carried out.

ical area of non compliance

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

actice	Reference	Action required	Timescale for action	PR Response	Executive Re
areas of ance .					No PR respon received.

or area of non compliance

ajor 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, storag 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 toge may represent a major area of non compliance.

actice	Reference	Action required	Timescale for action	PR Response	Executive Re
reas of ance .					No PR respon received.

er areas of practice that requires improvement

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

actice	Reference	Action required	Timescale for action	PR Response	Executive Re
f ere nt.					No PR respon received.

information from the Person Responsible

ponse received.

HFEA Research Licence Committee Meeting
18 May 2011

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 1

Centre 0017 (Newcastle Fertility Centre at Life) - Research Licence Renewal Inspection report and variation to research licence R0152 to add two new rooms (B2.20 and B2.28)

Members of the Committee:	Committee Secretary:
	Terence Dourado
Emily Jackson (lay) - Chair	
Clare Lewis-Jones (lay)	Legal Adviser:
Andy Greenfield (Professional)	Sarah Ellson, Field Fisher
Neva Haites (Professional)	

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:

- Research renewal inspection report (R0152) including the PR response
- Research licence renewal application form
- Latest research publications from centre 0017
- Redacted Peer Review
- Executive summary research licence variation (to include two new rooms, B2.20 and B2.28)
- Floor plan showing new rooms to be added to licence
- Research licence variation application form
- Previous Research Licence Committee minutes for the last 3 years
    - 19 May 2010 – Variation to include creation and use of embryos via donated gametes
    - 18 November 2009 – Variation to R0152 to include activities within research licences R0153 and R0145
    - 15 July 2009 – Variation to include PGD for four mitochondrial mutations
    - 11 March 2009 – Variation to add the storage of eggs

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
- Update on SCAAC recommendations concerning alternative methods for deriving human embryonic stem (hES) cells or hES-like cells

Background

1. The Centre holds a licence for research project R0152: Derivation of human embryonic stem cell lines using therapeutic cloning and parthenogenetically activated oocytes. In November 2009 the project was varied to include the activities and objectives of separate licences previously held for two projects: 'Understanding and harnessing pluripotency in human embryos' and 'Mitochondrial DNA disorders: Is there a way to prevent transmission'. The current research licence expires on 31 July 2011.

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 because the Executive noted that the Centre has submitted the appropriate fees in accordance with the HFEA's requirements. The Committee noted that the application was made by the current designated Person Responsible ("PR") who has held a licence at the Centre for several years.

3. The Committee was satisfied that the PR possesses the required qualifications and experience and that her character is such as is required for supervision of the licensed activities. It was further satisfied that the PR will discharge her duties under section 17 of the Act. The Committee was satisfied that the PR had satisfactorily completed the PR entry programme (7th Code of Practice edition) and is suitably qualified and experienced to undertake the role. The PR has been in post for a considerable time and

she has a history of compliance with the HFEA's legal and regulatory framework.

4. The Committee was satisfied that the premises to be licensed (including the additional research rooms) are suitable for the conduct of licensed activities as the Executive had confirmed that the premises were suitable.

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 consolidated project and that the activities of the licence, permitted under the Act, comprise the 'storage of embryos', 'storage of eggs', 'creation of embryos in vitro', 'use of embryos for research' and the 'derivation of human embryonic stem cell lines'.

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:

    - *Increasing knowledge about serious disease or other serious medical conditions (Schedule 2 paragraph 3A(2)(a) to the Act);* The Committee considered the activity to be licensed is desirable for this purpose because a number of serious neurological and myopathic syndromes have been linked with abnormalities of mitochondrial DNA and as such offspring may inherit them from asymptomatic mothers. This research contributes to a greater understanding of how mitochondrial DNA replicates and is propagated throughout the early preimplantation stages of the developing embryo.

    - *Developing treatments for serious disease or other serious medical conditions* (Schedule 2 paragraph 3A(2)(b) to the Act); There are currently no satisfactory treatments for a range of serious mitochondrial diseases such as, Neuropathy, Ataxia, and Reginitis Pigmentosa, (NARP) and Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) amongst others, and the conditions can generally only be supportively managed. In the absence of treatment for what are frequently multi-system syndromes, techniques to avoid the transmission of affected mitochondrial DNA at conception offer a possible option for alleviating these conditions in the future.

    - *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 random transmission of maternally derived mitochondria to daughter cells during cell division in the preimplantation embryo can result in differing levels of homo/heteroplasmy which in turn

influence the likelihood of mitochondrial DNA disease states being expressed. This research will elucidate the conditions under which mtDNA mutations are likely to be expressed and is developing more sensitive assays to quantify hetroplasmy.

- *Increasing knowledge about the development of embryos* (Schedule 2 paragraph 3A(2)(h) to the Act); the development of human somatic cell nuclear transfer (hSCNT) will potentially provide a model system to understand the mechanisms associated with nuclear reprogramming events and cell lineage regulation at the earliest stages of development. It has been shown that subtle developmental defects at these early stages can have serious later health consequences.

8. The Committee was satisfied that the proposed creation of human embryos by a variety of technologies is integral to this project. Animal studies have been performed to address the question under investigation in this research but there are known species specific differences between for example mouse, the most commonly used model species, and human early development and stem cell derivation. Optimisation of techniques for human embryo culture and production of human embryonic stem cells will therefore necessitate the use of human embryos.

9. Furthermore, the Committee was satisfied that the use of embryos is necessary because it is still unclear to what extent and under what conditions adult stem cell lines would be a sufficient substitute for human embryonic lines. Although there is now a potential to produce induced pluripotent stem cells (iPS) from affected patients, the procedure at present is inefficient, and it is still not clear how well iPS cells lend themselves to directed differentiation into the full range of tissues that is possible from embryo-derived ES cells. Current evidence suggests that iPSCs are functionally and molecularly distinct. At the present moment the use of SCNT must be considered the preferred option for potential clinical applications.

10. The Committee noted that while the number of embryos to be used in the research may seem high, the project consolidates a number of interlinked projects and the predicted usage is consistent with the level of usage outlined in the Centre's ongoing programme of research. The Committee recognised that some of the research is technically very demanding and at the cutting edge of technological development. The Committee therefore considered that the number of embryos used and proposed number of embryos to be used in the research is justified.

11. The Committee was satisfied that the research project had received approval from the Newcastle and North Tyneside 1 Research Ethics Committee. It also noted that the Executive has seen the patient information and consent forms, and that these met the statutory requirements.

Decision

12. As it was satisfied regarding all the requirements set out above, the Committee agreed to renew the Centre's licence and to vary it to include within the premises the two additional rooms to be used for research (2.30 and 2.19A). The licence is renewed for a period of three years without additional conditions. The Committee was satisfied that a three year period, which is the maximum that can be given for a research licence, would be appropriate because the research is clearly making progress and could potentially meet several currently unmet health needs; the project had previously been licensed and the Centre is well established and has a history of good regulatory compliance.

Signed: Date: 31/05/2011

Emily Jackson (Chair)