

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

MINUTES OF THE SCIENTIFIC AND CLINICAL ADVANCES ADVISORY COMMITTEE

Meeting held at Etc. venues Bonhill House, 1-3 Bonhill Street, London EC2A 4BX on Wednesday 10 June 2015

COMMITTEE MEMBERS	Sue Price (Chair) Kate Brian Alan Thornhill Yacoub Khalaf Jane Blower (External advisor)	Daniel Brison (External advisor) Joyce Harper (External advisor) Raj Mathur (External advisor) Gudrun Moore (External advisor) Sheena Lewis (External advisor)
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COMMITTEE APOLOGIES	Andy Greenfield, Robin Lovell-Badge	Melanie Davies
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EXECUTIVE	Sarah Testori Hannah Verdin Vongai Karimazondo	Sally Cheshire Peter Thompson Juliet Tizzard
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INVITED SPEAKERS	Dr Abha Maheshwari
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OBSERVERS	Steve Pugh
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1. Welcome, apologies and declarations of interest

- 1.1 The Chair welcomed Committee members to the meeting and introduced Sheena Lewis, Jane Blower and Gudrun Moore as new committee advisors. Dr Abha Maheshwari was welcomed as guest speaker and Steve Pugh as observer.
- 1.2 The Chair conveyed apologies on behalf of Andy Greenfield, Melanie Davies and Robin Lovell-Badge.
- 1.3 In relation to the meeting agenda, interests were declared by Alan Thornhill, who works for Illumina, a company which produces technologies used for embryo testing; Sheena Lewis, who is CEO of Lewis Ltd which provides a diagnostic service for male fertility health; and Daniel Brison who carries out research utilising embryonic stem cells for therapeutic use and has acted as an advisor to Anecova on the AneVivo project two years ago, with no subsequent contact since.

2. Matters arising

- 2.1 Minutes of the meeting held on 4 February 2015 were agreed remotely prior to the meeting. Matters arising from previous minutes were noted and agreed.

- 2.2 Steve Pugh informed the Committee that the pre-election period had caused a delay in the publication of the Home Office guidance on the use of human material in animals. However, the process of publication has resumed.
- 2.3 Ongoing updates to the patient information web pages on reproductive immunology, fertility preservation and preimplantation genetic screening were discussed. Regarding the fertility preservation page, the Committee highlighted that the website content should reflect live births per embryo thawed and success rates of ovarian tissue freezing, and the Committee recommended that the HFEA updates the website to inform visitors that the content on the website had been reviewed.

Actions:

- 2.4 The Scientific Policy Manager will circulate to the Committee data showing the total number of PGS cycles that have been conducted between 2012 and 2013 in the UK.

3. Alternative methods to derive ES and ES-like cells

- 3.1 The Committee gives an annual consideration into the alternative methods to derive ES and ES-like cells. This is to advise the HFEA Research Licence Committee and inform their decisions on the use of viable embryos as still "necessary or desirable" for the purposes of deriving stem cell lines, as set out in the HFE Act 1990 (as amended). The Committee last reviewed the subject in June 2014. In February 2015, SCAAC advised the HFEA that alternative methods to derive hES cells should remain a high priority for the Committee and the Authority during 2015/16.
- 3.2 The Scientific Policy Manager introduced a paper on updates on alternative methods used to derive embryonic stem cells (ES) and embryonic like stem cells and communicated the comments of one of the external advisor's.
- 3.3 The Committee agreed with comments, which expressed the necessity of the continuing use of human embryos for the derivation of new embryonic stem cell lines. This is due to the fact that a) there will be a requirement to derive them for experimental reasons to test the normality of embryos derived after specific procedures, for example when assessing embryos derived by pronuclear transfer, maternal spindle transfer or polar body transfer for mitochondrial donation, and b) to act as the gold standard to which all other pluripotent cells are compared, be they naive, primed, iPSCs, or derived by SCNT.
- 3.4 The Committee agreed to continually review the creation of stem cells from embryos, and also that further work is needed to characterise the genetic and epigenetic aberrations involved in transformation protocols.

Ground state cells

- 3.5 The Committee was updated on recent developments which have focused on studying culture conditions needed to revert human embryonic stem cells to ground state (the origin of all future embryonic lineages).
- 3.6 Committee members discussed whether or not studying the metabolic stages involved in reverting to ground state could have any clinical use in future.
- 3.7 One member of the Committee volunteered to provide input at the next committee meeting relating to epigenetics surrounding iPS cells retaining memory from the tissue of origin.
- 3.8 A few members highlighted that in this type of research, considerations need to be made when assessing the variation in embryonic stem cell quality which may have resulted from a range of factors including criteria used to select type of oocyte donor and length of stimulation.
- 3.9 The Executive explained that accessing information from the HFEA Register on the type of oocyte donor and linking this information to quality of embryonic stem cells may be difficult to access and therefore make this type of research difficult.

Generation of Clinical Grade Stem Cells

- 3.10 Committee members were informed of the developments in generating a clinical-grading system for pluripotent stem cells for use in patients.
- 3.11 Committee members agreed that it was important to have a defined criterion on what constitutes a clinical grade for stem cells.
- 3.12 The Committee acknowledged the work of the UK Stem Cell Bank in this area, and requested a representative of the UK Stem Cell Bank to provide some information to the Committee on the clinical implications of grading stem cells.

Somatic Cell Nuclear Transfer

- 3.13 The Scientific Policy Manager summarised studies on somatic cell nuclear transfer (SCNT). The Committee was informed of two publications (Yamada et al. 2014 and Chung et al. 2014) which showed that it is possible to use nuclei from adult stem cells to generate embryonic stem cells.
- 3.14 The Committee commented that further explanation is needed in understanding mechanisms involved in the evidence presented in Deuse et al. (2015) paper, which reported mitochondrial DNA generating an immune response against genomic DNA from SCNT.

SCNT versus iPSCs

- 3.15 The Scientific Policy manager informed the committee on papers that have been published showing conflicting evidence regarding which technique, iPSC or SCNT

provides a better tool for creating autologous pluripotent stem cells for specific patient-matched therapies.

Genome editing in human embryos

- 3.16 The Committee was also informed of advances in the use of genome editing techniques such as CRISPR-Cas-9 in modifying embryos in China.

Actions:

- 3.17 The Committee agreed that genome editing in reproductive medicine should be added as a topic for consideration during the annual horizon scanning process.
- 3.18 The Committee requested for the Deputy Chair to provide an overview of the Nuffield Council of Bioethics work on genome editing at the next Committee meeting

4. Novel process application

- 4.1 The Scientific Policy Manager presented an application for authorization of a novel process: the intrauterine culture of gametes/embryos, and in particular use of the Anecova AneVivo intrauterine device which is porous titanium chamber which allows fertilisation and the first day of embryo development to occur in the patient's uterus, exposed to tubal and uterine fluids, rather than in an artificial medium, in an incubator. The device is then removed and the embryos are cultured until day 5 at which point an embryologist can select the blastocyst with the best morphology for transfer.
- 4.2 The Committee was asked to:
- consider whether the use of intrauterine culture devices (such as Anecova AneVivo) constitutes a novel process
 - provide a view on which licensed activities ('keeping gametes', 'processing gametes', 'keeping embryos' and/or 'processing embryos') the process of using an intrauterine device should fall under
 - consider whether there is evidence to suggest that the use of an intrauterine culture device is effective
 - consider whether there is any evidence to indicate that the use of an intrauterine culture device is unsafe (either to patients or embryos) and
 - to provide feedback on the current procedure in place for processing applications for novel processes, such as the application forms used, the information submitted to the Committee, and timeframes involved.
- 4.3 The Committee agreed that intrauterine culture devices such as the Anecova AneVivo constitutes a novel process, both because it exposes the embryo to a

novel environment (the device itself, which contain a number of components, and the uterine fluids where the embryo would usually develop in the fallopian tube) and because the embryos are placed in the woman and then removed again.

- 4.4 The Committee discussed carriage, distribution and biosecurity elements of the Anecova Avevivo intrauterine device and how this may affect HFEA guidance on consent, import and export of gametes and embryos.
- 4.5 The Committee agreed that use of an intrauterine culture of gametes and embryos addresses multiple categories of licensable activities which include, processing gametes, processing embryos, keeping gametes and keeping embryos.
- 4.6 The Committee commented that sample sizes of people included in each study were small, and also the paper may be misleading when describing the experience of the embryo as more 'natural' in comparison to the lab environment when the device is placed in the uterine cavity. Committee stated that naturally the embryo should be in the fallopian tube at this stage in development.
- 4.7 Due to the limitations of the data provided the Committee felt that they could not make an assessment of the efficacy of the process. However, the Committee noted that Anecova AneVivo intrauterine device as it has been used in for treatment in three European countries resulting in a number of live births, suggesting that it is sufficiently effective to give successful IVF outcomes some of the time.
- 4.8 The Committee agreed that insufficient evidence was provided in the application to determine the whether intrauterine culture of gametes and embryos in a device such as the Anecova AneVivo intrauterine device is safe.
- 4.9 The Committee requested additional data, such as that submitted for CE marking of Conformity on the Anecova AneVivo intrauterine device, be made available to the Committee. In particular the Committee felt that information regarding the effect of all the components of the device on embryos, perhaps in an animal system would be useful to aid their decision to determine the impact of the device on embryos.
- 4.10 Some members of the Committee commented on the lack of information provided in the paper regarding patient experience and patient risks though recognised that this information was beyond the remit of their considerations.
- 4.11 The Committee agreed that a defined framework, in addition to the decision tree, would be useful to determine applications for novel processes.

Actions

- 4.12 The Scientific Policy Manager agreed to contact the PR from the applying clinic to inform them of SCAAC request for additional information and to arrange a teleconference for SCAAC to further consider any information provided.

5. Freeze-all cycles

- 5.1 Dr Abha Maheshwari presented on the topic of freeze-all cycles with particular focus on recent developments in freeze-all techniques, recent results from clinical trials, advances in her work and up-and-coming research.
- 5.2 Dr Abha Maheshwari informed the Committee of varying literature findings which seem to suggest that pregnancies arising from the transfer of frozen thawed embryos have better outcomes both for mothers and babies in comparison to those after fresh embryo transfer. The rationale for such a freeze-all strategy is that it would avoid any of the adverse effects which ovarian stimulation might have on endometrial receptivity during the treatment cycle. In addition to this, the risk of ovarian hyperstimulation syndrome (OHSS) is increased when embryo transfer is performed in the stimulated cycle and therefore freeze-all should, to a large extent prevent OHSS from occurring.
- 5.3 The Committee was informed of a study being conducted at the University of Aberdeen which will determine if a policy of freezing all created embryos, followed by thawed frozen embryo transfer is a more clinically effective, safer and cost effective way to provide in-vitro fertilisation when compared with the current practice of transferring fresh embryos.
- 5.4 The Committee discussed whether or not embryo freezing techniques had improved over the years or whether selecting embryos at day 5 which are better to freeze had an effect on the improved health baby rate.
- 5.5 The Committee discussed the implications of clinics taking part in the freeze all study and the consequence of this on success rate data provided on the Choose a Fertility Clinic search function on the HFEA website.
- 5.6 The Committee suggested that Choose a Fertility Clinic should flag up which clinics are taking part in the study, both to aid enrolment of patients in the study and to explain any potential differences in success rates. The Committee also discussed potential challenges in recruiting participants to the study.
- 5.7 The Committee discussed the impact that freeze-all cycles would have on the incidence of OHSS and agreed that it would eliminate most but not all cases of OHSS.
- 5.8 The Committee went on to discuss improvements in embryo freezing techniques, noting that the technology had not advanced much over the past few years but that our understanding of the stages of embryo development that are most amenable to freezing has, and this has resulting in improvements in frozen embryo transfer success rates.

Actions

- 5.9 The Committee agreed that the HFEA website should include information on current and recruiting clinical trials taking place in the UK.
- 5.10 The Scientific Policy Manager agreed to contact SCAAC members outside of the meeting context to collate a list of clinical trials and Yacoub Khalaf agreed to inform SCAAC of relevant trials in the field of ART, in his role as a committee member to the Royal College of Obstetricians and Gynaecologists.

6. Preimplantation genetic screening (PGS)

- 6.1 The Scientific Policy Manager presented a paper detailing the ethical, legal and practical implications of the current preimplantation genetic screening (PGS) technologies as well noted issues from previous meetings regarding current PGS technologies.
- 6.2 The presentation informed the Committee on:
- the most appropriate patient group for treatment with PGS
 - the generation of additional genetic data from some PGS techniques
 - patient information and counselling and
 - embryo biopsy practitioner competency

The efficacy of PGS

- 6.3 Some members of the committee highlighted that the levels of mosaicism (the phenomenon whereby a single cell, or small group of cells, may not represent the chromosomal complement of the entire embryo) in IVF cleavage stage embryos has a bigger range than 10-30% stated in a study referred to in the paper (Munne et al. 1994; Delhanty et al 1997).
- 6.4 Some members of the committee disagreed with the statement in item 7 section 3.7 stating that 'These two techniques effectively enable PGD to be carried out by a methodology that has been designed primarily for PGS'
- 6.5 Members were asked to consider whether any points in the Code of Practice PGS guidance note should be amended and, if so, provide comments to the Executive regarding possible amendments; and in particular consider:
- whether the Committee agrees with the Executive's recommendation to remove the requirement for clinics to validate the use of PGS for each category of patient to which they offer it from the Code of Practice, and to replace this by highlighting licence condition T49;
 - whether the current Code is comprehensive enough in detailing the information patients should be given prior to treatment, in particular whether information should be provided on uninterpretable results and on the stage and risk of embryo biopsy;

- whether the Code should specifically require clinics to provide genetic counselling prior to and after treatment, or whether providing patient information is sufficient;
- whether we should ask to centres to go beyond providing information on the lack of efficacy FISH, and ask them to specifically justify their use of this technique over one of the newer ones;
- whether clinics should be encouraged to assess key performances, including misdiagnosis rate and inconclusive results rate, in collaboration with their embryo testing laboratory (either through an update to the PGS or Third party agreement guidance notes, or through means of a clinic focus article).
- Consider whether the HFEA has any role to play in facilitating or encouraging PGS RCTs to take place and trials in other relevant areas.

- 6.6 One Committee member informed the committee that based on the current level of evidence it is not appropriate to recommend PGS use in any patient group.
- 6.7 The Committee discussed the patient groups which should be offered PGS. In current practice one member highlighted that PGS is offered to both good prognosis patients as well as patients who have had miscarriages.
- 6.8 The Committee recommended that the HFEA website content on PGS should be reviewed to highlight that PGS should not be offered only to poor prognosis patients.
- 6.9 The Committee commented that with increasing level of technology and more complicated genetic screening, the information coming out from PGS reports will be more difficult for fertility clinics to understand. As a result reports from PGS should be interpreted by experts in genetics and embryo testing.
- 6.10 The Committee discussed the need for providing genetic counselling for patients receiving PGS reports from a fertility clinic.
- 6.11 Some members highlighted that it might be useful for patients to be provided with guidance on the types of questions they should ask when attending genetic counselling in order for them to feel empowered and informed.
- 6.12 Safety of embryo biopsies and staff competency was also discussed by the committee. The Committee emphasised the importance of the HFEA in having a role in the regulation of embryo biopsy competency assessments made by the Person Responsible at each centre.
- 6.13 The Committee agreed that there is a need to standardise the way key performances are assessed and agreed that the HFEA should indicate factors which the Person Responsible should observe.

- 6.14 Committee members recommended consulting professional societies when setting benchmarks for assessing practitioners' competencies for PGS.
- 6.15 In terms of guidance the HFEA provides clinics on PGS (outlined in the HFEA's Code of Practice) , the Committee recommended removing item 9.1.b.ii which states that people seeking treatment should be given information explaining 'the method of fluorescent in situ hybridisation (FISH) on embryos, using a limited number of chromosomes, is not effective at increasing live birth rates'. This is due to the fact that FISH is no longer used in UK centres.
- 6.16 The Committee recommended removing item 9.1.c which states that people seeking treatment should be given information explaining 'that embryos biopsied may not be available for cryopreservation and for use in subsequent treatment cycles'. This is due to the current routine practice of freezing embryos and the trend in improved success rates of both biopsied and non-biopsied embryos.
- 6.17 The Committee agreed to change item 9.1.d which currently states that people seeking treatment should be given information explaining ' the misdiagnosis rates associated with PGS for aneuploidy, including the fact that false results can be positive or negative' to include information that samples received by an embryo testing lab from a clinic can also generate no results.
- 6.18 The Committee agreed to remove item 9.1.e which states that people seeking treatment should be given information explaining 'that the more chromosome tests are carried out, the higher the possibility of the test not working and the lower the chance of finding suitable embryos for transfer'. This is due to the fact that FISH is no longer used in UK centres.
- 6.19 The Committee agreed that clinics need to explain the concepts of mosaicism and segmented aneuploidy and their implications to patients before treatment.
- 6.20 The Committee agreed that more PGS randomised controlled trials are needed
- Actions
- 6.21 The Executive agreed to amend the current PGS guidance note in the Code of Practice to take in to account the recommendations of the Committee.
- 6.22 The Scientific Policy Manager agreed to redraft the PGS patient information for the HFEA website to incorporate information on current PGS practice, success rates, and to highlight that data supports only the use of PGS for good prognosis patients.
- 6.23 The Executive agreed to consider SCAAC's advise regarding the criteria PRs should used when assuring themselves of the competence of embryologists.

7. Meeting summary

7.1 The Chair thanked the Committee, Dr Abha Maheshwari and its observer for their time and for a productive meeting.

8. Any other business

8.1 The Committee discussed a recently published editorial regarding the use of calcium ionophore in culture medium to enhance fertilisation which demonstrated that the editors misunderstand the role of the HFEA and the SCAAC Committee in regulating novel processes.

Actions

8.2 The Executive agreed to write a response letter to the article which would be circulated for comment.

Next meeting: Wednesday 21 October 2015

I confirm this to be a true and accurate record of the Meeting.

Signature:

Name:

Position: Committee Chair

Date: