Scientific and Clinical Advances Advisory Committee (SCAAC) - minutes

16th October 2017

Conwy Room 10 Spring Gardens, London SW1A 2BU

Authority members	Present	Yacoub Khalaf Sally Cheshire Kate Brian Anne Lampe	
	Apologies	Tony Rutherford Andy Greenfield	
Members of the Executive		Anna Quinn (lead) Rasheda Begum (secretary) Hannah Verdin Peter Thompson Lisa Whiting	Anna Coundley Caylin Joski-Jethi Jessica Watkin
External advisors	Present	Gudrun Moore Joyce Harper Melanie Davies Daniel Brison Sheena Lewis	
	Apologies	Robin Lovell-Badge Raj Mathur Jane Blower	
Invited speakers		Kathy Niakan Jackson-Kirkman Brown	
Observers		Kim Hayes (DH)	

1. Welcome, apologies and declarations of interest

1.1. The Chair welcomed Committee members to the meeting.

1.2. In relation to the meeting agenda, interests were declared by Yacoub Khalaf who works in an assisted conception unit where sperm tests are requested by patients. Kate Brian declared she is a lay member on the HABSELECT (a large randomised study assessing the effectiveness of hyaluronic acid binding for sperm selection) committee. Daniel Brison carries out university based work that involves sperm DNA fragmentation and is also a co-applicant for HABSELECT. Sheena Lewis declared commercial interests in relation to the discussion that would be held on DNA fragmentation as she is the CEO of a company that markets a sperm DNA fragmentation test.

2. Matters arising

2.1. Minutes of the meeting held on 16 June were agreed remotely prior to the meeting.

2.2. The Scientific Policy Manager updated the Committee on matters arising. The horizon scanning spreadsheet is being modified. The horizon scanning process will begin later in the year. The ICSI paper from the previous meeting is in the process of being reformatted into a paper which can be submitted to a journal for publication. A letter is currently being drafted to be sent to the MHRA regarding concerns on embryo culture media.

3. Chair's business

3.1. The chair raised that the committee annual review will take place in the coming months to confirm that the Committee meets its purpose. There will also be a review of the membership to see if there is enough representation in the all areas that SCAAC covers.

3.2. The HFEA has recently released a new version of its website with an emphasis on giving good patient information. There will be updated information on embryo research to increase awareness and to help to increase research.

4. Genome editing: literature review

4.1. The Scientific Policy Officer gave an introduction to the topic of genome editing, highlighting the increasing public interest with advances in research appearing in the media. Genome editing has also been subject to ethical reviews by the Nuffield Council on Bioethics and the US National Academies of Sciences. Key CRISPR studies were described that have been carried out for genome editing on human embryos in China and the US. Members were asked to discuss any other relevant areas and also discuss the potential clinical applications of genome editing.

4.2. There was discussion on research in countries outside the UK. The Committee generally agreed that any international collaborative work with connection to the UK would need to meet UK regulatory and ethical standards.

4.3. A Committee member expressed concern that if genome editing were to be permitted in treatment, it will might be used on embryos for conditions where PGD could have sufficed. Whilst PGD has

an established risk profile supported by clinical data, genome editing still has risks that have not been fully characterised yet. The International Summit on Human Gene Editing issued a statement supporting the use of genome editing only where there is no other safe alternative.

4.4. There was a concern that in clinical applications there would be no way to know which embryos created during a treatment cycle have a genetic defect and therefore genome editing would need to be done on all embryos, leading to editing of embryos which do not have a genetic defect.

4.5. The Chief Executive clarified that genome editing in a reproductive context is illegal in the UK, whilst genome editing of human embryos for research is permitted; a change in primary legislation would be required to permit reproductive uses.

5. Genome editing: practical experiences

5.1. The Chair welcomed Dr Kathy Niakan who had been invited to the SCAAC meeting to provide an update on her research using genome editing (CRISPR). Her presentation began with a reference to a SCAAC paper from January 2009 on genetic modification of embryos for research, intended to inform the HFEA's Research Licence Committee. Dr Niakan commented that the regulation had preceded development of the technology.

5.2. Dr Niakan's research focuses on the first seven days of embryo development. In her presentation, she gave an overview of the differences in development of human embryos compared to mouse embryos. She described the use of CRISPR to remove a gene called *OCT4*. This gene was selected for study as it is the first detectable factor in the 8-cell embryo right after embryo gene activation. They were able to avoid using embryos with aneuploidies in their research as these would have arrested before the 8-cell stage. The OCT4 protein eventually becomes restricted to epiblast progenitor cells at 6 days, which is the optimal time to derive embryonic stem cells. OCT4 may have an important role in pluripotency because by inhibiting it, embryonic stem cells become differentiated. Inactivation of *OCT4* also has a clear effect before implantation as seen in the mouse.

5.3. Dr Niakan gave an explanation of the CRISPR technique and described how her research targeted the *OCT4* gene for editing. This included testing several guide RNAs with human ES cells and use of mouse embryos to establish optimal conditions for microinjection of CRISPR. By removing the *OCT4* gene, time-lapse images showed development had been affected compared to a control embryo, showing that OCT4 has important functions not only in the ICM, but also in the trophectoderm, which is not the case in mice.

5.4. In her summary, Dr Niakan highlighted that studies in genome editing will enhance our understanding of human biology and will hopefully improve stem cell biology, IVF treatments and help us understand causes of pregnancy failures. The next steps of her research will be to further study the role of OCT4, as well as other factors such as TGF-B and Nodal signalling.

5.5. After the presentation, Dr Niakan welcomed questions from the Committee. One member asked whether genetic information from the parents was obtained, for the purpose of grading the embryos. Dr Niakan elaborated that the embryos had been in storage for several years and as such there is no consent for genotyping of the parental DNA. A member reiterated that any additional genetic information that may be obtained from embryos cannot be passed back to the patient without their consent.

5.6. Another question was whether the researchers knew the basis of any infertility in donors. Dr Niakan responded that the donors of embryos had at least one successful pregnancy. Members suggested that embryos from fertile patients should be used where possible as a control. The issue of using mouse models to inform human study was raised, and that genome editing studies aimed at increasing our understanding of early human development should be done on human embryos where possible.

6. New patient information on treatment add ons

6.1. The Scientific Policy Manager gave a brief introduction, mentioning that the HFEA had published patient information on treatment add ons on the website and this page at that time had been the 22nd most visited page across the whole website.

6.2. Dr Jackson Kirkman-Brown gave a presentation on the practice and evidence base of three proposed additions to the treatment add ons patient information: Intracytoplasmic morphological sperm injection (IMSI), physiological intracytoplasmic sperm injection (PICSI) and DNA fragmentation. He referred to IMSI and PICSI as techniques for advanced preparation of sperm. IMSI consists of selecting sperm based on their features under high magnification. PICSI involves selecting sperm based on how well they bind to hyaluronate. IMSI is based on physical appearance of sperm and PICSI is a functional test. A recent systematic review in Human Fertility concluded there wasn't enough evidence to offer either of these tests clinically. There are studies in Brazil that find positive outcomes for IMSI however Dr Kirkman-Brown commented the data from these labs is poor. A question was asked on whether the sperm incur damage when removed from hyaluronate surface during PICSI, Dr Kirkman-Brown said the sperm do not undergo extensive damage from this. He also noted that sperm that bind have better acrosome and DNA quality. The data from the HABSELECT trial of PICSI will be released at Fertility 2018 in January so for that reason Dr Kirkman-Brown suggested to wait for the results before publishing patient information.

6.3. There was a question was on whether IMSI and PICSI studies look at relevant outcomes such as pregnancy rate. Pregnancy outcomes are being looked at in HABSELECT and also have been looked at in some IMSI studies.

6.4. The final part of Dr Kirkman-Brown's presentation focused on DNA fragmentation tests. The literature for DNA fragmentation is not reliable because of inconsistent data. There are four main tests, each of which have their own evidence base.

SCSA

6.5. The sperm chromatin structure assay (SCSA) involves use of Acridine orange to indirectly identify sperm DNA fragmentation, usually by flow cytometry. Acridine orange does not have predictivity for ICSI outcomes. Not many centres are carrying out this test. The test is not a direct measure of DNA damage. The test shows change in fluorescence depending on the packing of DNA however there is no evidence that difference in fluorescence is due to strand breaks or direct DNA damage. The assay can be influenced by factors other than DNA damage.

Halo test

6.6. Halo test is a decondensation assay. In this test, a decondensation (a process of unwinding DNA) stimulus is applied to sperm which releases DNA to spread around sperm to form a "halo" in good sperm. In bad sperm a halo does not form. This assay out of all four assays covered has the least

clinical supporting evidence. However, some large studies on the halo assay have not been published. Use of the halo assay has risen in the UK because it is a simple test to carry out.

Comet

6.7. The Comet assay is the opposite of the halo assay, whereby cells are permeabilised and then placed in agarose where an electric charge is applied so that DNA moves out of the sperm head towards the negative charge (to form a "tail") and the more breaks there are in the DNA, the more material the tail will contain. The literature for this assay contains alkaline and neutral forms however systematic reviews have treated these two forms as the same.

TUNEL

6.8. The final test presented was TUNEL. This assay has been used in other disciplines as well as reproductive medicine, so the methodology is more widely accepted. This assay involves adding a fluorescent marker to DNA where there are breaks. There are widely different protocols between different labs and some studies carry out the assays incorrectly.

6.9. In summary, all of the tests described require experienced staff and quality controls, although halo test is easier to perform in a clinic. Dr Kirkman-Brown referenced a systematic review from 2012 which found DNA damage correlated with miscarriage, in ART and also in spontaneous conception. The data from this review is being updated, trends show that Comet and TUNEL are more likely to be predictive for miscarriage prognosis. There have been two systematic reviews (Cissen et al. 2016 and Simon et al. 2017) in the last year, both of which are flawed in their interpretation of data which had opposing conclusions. The Cissen et al. paper extracted data from 30 studies and did not find evidence to support use of sperm DNA fragmentation tests. The Simon et al. paper which had mostly the same dataset as Cissen et al. concluded that DNA damage has a negative effect on pregnancy and testing for damage should be offered to patients. Both systematic reviews were considered invalid because they grouped different tests together in their analysis. Findings from testing of DNA damage could affect patient choice, as they could opt for surgical sperm extraction over ejaculation. It is thought that sperm DNA damage occurs after sperm leaves the testes.

6.10. Committee members expressed concerns about poor quality of IVF research, particularly research on DNA damage testing. Dr Kirkman-Brown informed the Committee that the data adequately supports that elevated DNA damage is more likely to lead to miscarriage. Sperm DNA damage should not be a reason to use donor sperm. The Chair highlighted that it is strange DNA damage is correlated with both miscarriage and also no implantation. It was also raised that patients are not aware of the different types of tests. Dr Kirkman-Brown further reiterated the complicated evidence base for sperm DNA damage testing, because the findings of the test can be skewed by the operator and the particular methodology used for performing the test.

6.11. The HFEA Chair requested the Committee to make a decision on what they recommend are the next steps for the HFEA on ensuring patient information is accurate. The Committee discussed that the effectiveness of an add on does not relate to its safety and this needs to be made clear in the traffic light rating. The Committee were asked to give their individual rating (green, amber or red) for each of the three add ons. Most of the members chose a red rating for IMSI and PICSI, however for PICSI this is subject to change because the HABSELECT results need to be published. For DNA damage testing, members gave an amber or red rating, and there was discussion on whether the four tests should be given their own rating instead of being grouped together.

Action

6.12. HFEA will modify the patient information with the Committee's suggestions and seek further advice from an expert in evidence assessment to peer review the committee's traffic light ratings.

7. Register research: ideas to increase research impact and engagement

7.1. The Head of Intelligence at the HFEA informed the Committee that the newly formed Intelligence team is trying to maximise the impact of the work that the Register Research Panel oversees. Since 2010, the Panel has authorised seven research requests for data, all of which have resulted in multiple publications. The Head of Intelligence will be presenting a report to the HFEA Board in November containing information on what the HFEA does with publications from register research. One issue to be addressed was whether research groups know about the data that the HFEA holds and there will be work to promote research.

7.2. The Head of Intelligence welcomed questions from the Committee on her intelligence work. One comment was there has been a loss of ease of accessibility for professionals who are not directly linked to clinics. The Head of Intelligence will be approaching an internal Digital Communications Board to propose the addition of a page on the website dedicated to register research. A suggestion was made if HFEA could partake in getting funding for data linkage studies. There was a question on ways to make research institutions without a connection to clinics aware of the register data and the importance behind the data.

7.3. The Head of Intelligence asked how to measure the quality of research output from register data to decide what publications are shown on the HFEA website. The Chair suggested circulating publications to members of SCAAC for review, to which the HFEA Chair agreed would be the right process.

7.4. A member raised the issue of the IfQ project that the HFEA carried out to reduce information required for the register as a means to reduce the burden on clinics. However, some members would like to see more information on the register such as NHS numbers and types of embryo culture media used.

8. Data research consent

8.1. The HFEA Information Access and Policy Manager informed the Committee of her work on a project aiming to increase rate of consent from patients to use their data in research. In 2016, there was an average of 72% of patients agreeing to use of their data for research, however there is considerable variation between clinics. Significant factors contributing to this variation included the attitudes of staff giving information about consent, and how patients are given information. Planned work in this project includes a patient leaflet about consent to data research, a digital tool so that clinics can see the rate of their consent and a Code of Practice guidance note recommendation.

8.2. The Information Access and Policy Manager welcomed thoughts from the Committee. The Committee responded positively to the project, although a concern was raised that patients are already overwhelmed by the number and complexity of consent forms, and often reluctant to consent to disclosure or research as well. One member suggested to focus on non-contact research as it is more straightforward than contact research. Another suggestion was to add information on the website.

9. Any other business

9.1. An HFEA Policy Manager briefly gave an overview of her embryo research project, which is an initiative to promote and increase embryo research. This has involved making changes to application forms and peer review forms. A brief for Research Ethics Committees is also being produced to establish HFEA's role so that there is no overlap between the HFEA and RECs. In Spring 2019 the Authority will assess the impact that this project has had on the number of embryos being donated to research.

9.2. The issue of Kitazato media was raised by the Scientific Policy Manager as the MHRA have given a derogation order for Kitazato to be used without CE marking. The DH observer said this is not a safety issue and the MHRA will be making a decision on what will happen in November when the derogation order expires.

9.3. In the last meeting, plans were made to reformat the ICSI paper into a paper for journal publication. This has been sent to the Chair who will circulate his comments.

10. Next meeting:

10.1. Monday 5 February 10 Spring Gardens, London SW1A 2BU.

Signature 

Name Yacoub Khalaf

Committee chair

Date 14/12/2017