# Scientific and Clinical Advances Advisory Committee (SCAAC) - minutes

## 13th June 2016

## Conwy Room, Spring Gardens, London SW1A 2BU

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| Committee members | | Yacoub Khalaf (Chair)<br>Kate Brian<br>Andy Greenfield<br>Anne Lampe | Tony Rutherford |
| Members of executive | | Anna Rajakumar (lead)<br>Anna Quinn (secretary)<br>Peter Thompson<br>Joanne Anton | Nadia Huq<br>Jessica Watkin |
| External advisors | Present | Daniel Brison<br>Raj Mathur<br>Gudrun Moore<br>Jane Blower | Joyce Harper<br>Sheena Lewis |
| | Apologies | Robin Lovell-Badge<br>Melanie Davies | |
| Invited Speakers | | Stuart Lavery<br>Dagan Wells<br>Elpidia Fragouli<br>Dina Abdul | |
| Observers | | Louise Winstone (HFEA Inspector) | |

## 1. Welcome, apologies and declarations of interest

**1.1.** The Chair welcomed committee members to the meeting and welcomed Tony Rutherford to his first SCAAC meeting as an Authority member.

**1.2.** The Chair conveyed apologies on behalf of Robin Lovell-Badge, Melanie Davies and Kim Hayes.

**1.3.** In relation to the meeting agenda, interests were declared by Daniel Brison who is an IVF Director and has research interests culture media and embryo glue; Kate Brian who is a member of the

NICE guidelines committee; Tony Rutherford who is an IVF Director and is also a member of the NICE guidelines committee; and by Yacoub Khalaf who has previously provided advice to NICE.

## 2. Matters Arising

**2.1.** Minutes of the meeting held on 3 February 2016 were agreed remotely prior to the meeting

## 3. Chair's Business

**3.1.** The Chair noted that future meetings will always take place on a Monday and the location will always be at Spring Gardens. The next committee meeting will be held on 17 October 2016.

## 4. Committee work plan

**4.1.** The committee discussed the format of the embryo testing meeting that will take place in October 2016 and highlighted the importance of having a balance of viewpoints when considering potential speakers.

**4.2.** The committee considered whether it would be necessary to have an item on In vitro maturation given that this technique is rarely used in the UK and the Committee highlighted that if the use of such a method is reduced, it would be useful to understand why. One member pointed out the potential for using In vitro maturation more in the future for oncology patients. All members agreed that new technologies in genetic testing, genome editing and in vitro derived gametes were suitable topics for the meeting.

**4.3.** It was agreed that a discussion about intracytoplasmic sperm injection (ICSI) would be held when the BFS publish their best practice guidelines.

**Action**

**4.4.** The Scientific Policy Manager will approach potential speakers for the embryo testing meeting in October 2016.

## 5. Novel process application

**5.1.** The Scientific Policy Manager introduced an application for authorisation of a novel process: Mitochondrial DNA quantification. The aim of this process is to quantify mitochondrial DNA (mtDNA) levels in embryos that have been shown to be chromosomally normal (euploid) following preimplantation genetic screening (PGS). The quantification method is carried out using real-time polymerase chain reaction (PCR) to analyse amplified DNA samples from PGS embryo trophectoderm biopsies. The process is aimed at identifying euploid embryos that are most likely to implant with the intention to improve success rates for patients already undergoing PGS, and who have more than one euploid blastocyst available for transfer.

**5.2.** The Chair welcomed the applicants to the meeting to answer questions about the novel process application and provide further clarification if needed.

**5.3.** The committee asked the applicants if the results observed in their study could be explained by the technique capturing cells in different stages of cell division, thus making mtDNA levels a

marker of cell cycle stage. Applicants explained that a study of 1000 embryos has been conducted in New York, and other centres in the USA. The cut-off point observed in the smaller, 15 embryo study is maintained in this larger study. The difference in implantation observed above and below this mtDNA cut off point is too dramatic to be caused by cell cycle stage. The applicants also confirmed that the data from the 1000 embryo study will be published in due course.

**5.4.** One applicant commented on the results of the New York study, confirming that embryos are not discarded on the basis of their mtDNA levels. The mtDNA quantification process is used as a marker of embryo quality. Embryos are first assessed according to their PGS results, then on the mtDNA levels and finally they are assessed according to morphology. They also explained that no embryos with mtDNA levels above the cut-off point have implanted and implantation rates are 5 to 10% higher when mtDNA level is considered compared with PGS alone.

**5.5.** The committee asked the applicants which patient groups they expect mtDNA quantification will be most useful for. The response was that there is no indication that any one patient group will benefit more than others and that the technique is most helpful in patients who have four euploid blastocysts to select from. The applicants told the committee that the mtDNA quantification technique provides another method for grading embryos, providing descriptive information to help chose the best quality embryo for transfer. The method will not be used to identify embryos that will be discarded.

**5.6.** One committee member asked the applicants about the expected psychological effect on patients from the additional information mtDNA quantification will provide. The committee were informed that clinic staff will be clear with patients, manage their expectations and provide the offer of counselling.

**5.7.** The committee asked whether any patients appear to be predisposed to having embryos with high levels of mtDNA. One applicant explained that they have not seen any patient groups who are predisposed and all patients have had at least one embryo with mtDNA levels below the threshold. Another added that the test is not predictive of future cycles and can only provide a better indication of which embryo to transfer in the current cycle.

**5.8.** The applicants were then asked if they have considered why elevated mtDNA levels seem to be detrimental to the embryo and whether the test detects elevated mtDNA within the organelles themselves or an increased number of mitochondria per cell. The applicants posed two theories in response: that an embryo with high levels of metabolic activity is poorer quality according to the ‘Quiet Embryo’ hypothesis (Leese 2002), and that increased number of mitochondria per cell may indicate a compensatory mechanism to counter a larger proportion of failing mitochondria. The group also discussed mitochondrial mutation rates.

**5.9.** One committee member questioned whether mtDNA cut-off point, above which embryos do not implant is strict or whether embryos with mtDNA levels slightly below this point have a lower chance of implanting. The applicants explained that in their research to date, no embryos with mtDNA levels above the cut-off point have implanted and there is no indication that embryos just below this point are less likely to implant. The applicants also pointed out that mtDNA levels appear to be normally distributed with a longer tail at the high end.

**5.10.** The committee expressed concerns about the lack of live birth data after the use of this technique and whether any babies born will be followed up to study any long term health impacts. The

applicants confirmed that all embryos below the cut-off point progressed to clinical pregnancy but were unsure if there had been any live births to date. Applicants reminded the committee that mtDNA quantification is not currently being used to deselect embryos for transfer or to favour embryos with lower mtDNA levels.

**5.11.** One committee member asked the applicants whether they have observed a difference in average mtDNA levels between euploid and aneuploid embryos. The applicants said that aneuploid embryos tend to have slightly elevated mtDNA levels, however their data refers to euploid embryos only as any aneuploid embryos are not transferred.

**5.12.** The Chair thanked the applicants for attending the meeting and for providing clarification on several points, including discussing no initial charge to patients receiving the treatment and refining patient information. The applicants then left the room for the committee to have a private discussion about the novel process application.

**5.13.** The committee discussed that this technique is proposed as an add-on to PGS, which is already permitted in the UK.

**5.14.** Members of the committee expressed concerns about the lack of information regarding miscarriage, live births and follow up data after mtDNA quantification is used. Some members were also concerned that the availability of this technique would alter patient behaviour by encouraging more people to use PGS, which involves embryo biopsy.

**5.15.** The committee agreed that there is currently not enough information about mtDNA quantification to assess its safety and efficacy. The committee agreed that they would need to see more peer reviewed, published data before being able to assess safety and efficacy, as well as information on live births and miscarriages.

## 6. CE marking guidance

**6.1.** The Scientific Policy Manager presented a draft copy of a CE marking guidance document produced by both the HFEA and the MHRA. The aim of the document is to provide clarity for clinics on CE marking issues. The committee were asked to review the guidance, discuss their views on whether it addresses relevant issues relating to CE marking and identify any areas where further clarity is needed.

**6.2.** One committee member confirmed that an ESHRE culture media group will shortly be publishing a paper on culture media which includes reference to CE marking.

**6.3.** The committee agreed that the draft guidance read well, however there should be more information on the implications of off-label use and the implications.

Actions:

**6.4.** The Scientific Policy Manager will ask HFEA inspectors if they ever receive enquiries about whether fertility clinics can make culture media ‘in house’.

**6.5.** The Scientific Policy Manager will update the draft to incorporate the committee’s comments and recirculate the updated draft to the group.

## 7. IfQ website content update

**7.1.** The HFEA Communications Manager outlined proposals for a 'traffic light' system to categorise treatment add-ons and presented the suggested categories for particular treatment add-ons. The committee were asked to discuss this further and agree where each treatment add-on should sit in a traffic light system.

**7.2.** Committee members were asked to volunteer to be a topic expert on each of the treatment add-ons, with each topic expert being available to review website content in their given area outside the meeting.

**7.3.** The committee agreed that a three category system was most appropriate and that a five point system or sliding scale may be confusing for prospective patients. One member pointed out that whilst a traffic light system is most accessible for patients, a single rating for each treatment add-on may not apply to all patient groups as any one treatment add-on may be of greater benefit to different patient groups.

**7.4.** The committee discussed that the BFS are also rewriting a lot of patient information and agreed that information should be shared between organisations to ensure a consistent message from professional bodies and the regulator. One member requested that information be shared with Infertility Network UK, who are also rewriting their website content. The committee also agreed that where one organisation is only providing a small amount of information on any one topic, they can provide a link to more detailed information if it is provided by another organisation.

**7.5.** The committee considered the suggested categories for each treatment add-on presented by the Communications Manager.

**7.6.** The committee agreed that some treatment add ons may need to be re-categorised as experimental. They also discussed that embryo glue could be considered to be 'backed up by clinical trials'. The Committee agreed to conduct further review of the text and classifications over the coming months to ensure that each treatment was accurately categorised.

**7.7.** Members considered whether measures of effectiveness would change if the cost of treatment add-ons were also factored into the discussion. The Communications Manager informed the committee that there will be some cost information presented on the new HFEA website and agreed to consider the financial cost to patients of these treatment add-ons.

Actions:

**7.8.** The Communications Manager will consider the cost of treatment add-ons and include some information about this on the website if enough information can be gathered from clinics.

**7.9.** The Executive will being an update on treatment add-ons to the committee once a year to ensure that the information on the HFEA website remains accurate and up to date.

## 8. Alternatives to derive embryonic and embryonic-like stem cells

**8.1.** The Scientific Policy Officer introduced a paper on alternatives to derive embryonic and embryonic-like stem cells and relayed comments from one committee member who was unable to attend the meeting.

**8.2.** The committee were in agreement that their view had not changed since the 2015 update to this paper. The committee agreed that scientists are still in the early stages of understanding human development and it remains necessary to produce human embryonic stem cells as they provide

the gold standard to which other stem cell technologies can be compared, and to aid the understanding of normal development of cells.

## 9. Any other business

### Embryo 'Squishing'

**9.1.** The committee discussed a paper published in Nature Communications regarding 'embryo squishing'. The paper showed that by measuring the rigidity or 'squishiness' of fertilised human and animal eggs, it is possible to predict the likelihood that they will develop to healthy blastocysts. One committee member suggested that this technique has been shown to be as predictive as time-lapse imaging up to the four cell stage.

### 14 day limit

**9.2.** The committee discussed recent advances in embryo culture that suggest it may be possible to culture embryos up to the 14 day limit currently enshrined in law. Committee members held a range of views regarding the potential increase in understanding that could be gained if the 14 day limit were to be extended, without commenting on any potential ethical issues that could be implicated in the event of a change in the law. Some members agreed that culturing embryos beyond 14 days could lead to a great increase in knowledge of human development whilst others believed that any increase in knowledge would be limited by the ability to obtain high quality human embryos. The Executive confirmed that the HFEA would not carry out work on this topic unless it was commissioned by the Department of Health and there are no plans to amend the legislation.

### IUI NICE guidance update

**9.3.** One committee member presented the British Andrology Society response to the NICE guidelines discussions on IUI verses expectant management. The committee discussed the guidance and the decision to compare IUI with expectant management rather than with IVF. One committee member will be attending the next NICE meeting about this guidance as an observer and will report back to the group.

### Embryo research project

**9.4.** The Policy Manager informed the committee about an upcoming project relating to embryo research and access to embryos for use in research. The committee noted issues regarding obtaining consent for donation of embryos to research and, on request by the Committee for a representative, one member volunteered to act as an advisor during the project.

### Mitochondrial donation

**9.5.** The Scientific Policy Manager informed the committee that the HFEA will shortly be reconvening the independent scientific expert panel to consider the safety and efficacy of mitochondrial donation techniques. The committee were informed that call for evidence would be published in due course.

### Horizon Scanning Panel meeting at ESHRE

**9.6.** The Scientific Policy Manager informed the committee that the Executive will be holding their annual horizon scanning panel meeting during the ESHRE conference in Helsinki in July. All committee members were invited to attend the meeting being held on 4 July 2016.

## 10. Next meeting

**10.1.** The next committee meeting will be held on 17 October 2016, the venue will be the HFEA offices at Spring Gardens.

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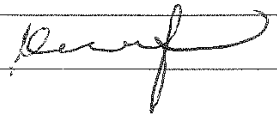
| Signature |  |
| Name | Yacoub Khalaf |
| Committee chair | |
| Date | 18/10/16 |