

Scientific and Clinical Advances Advisory Committee (SCAAC) - minutes

18 June 2018, 11 am-4.00pm

Conwy Room, 10 Spring Gardens, London SW1A 2BU

Authority members	Present	Yacoub Khalaf (Chair) Kate Brian Anne Lampe Andy Greenfield Sally Cheshire	
	Apologies	Tony Rutherford	
External advisors	Present	Gudrun Moore Sheena Lewis Daniel Brison Joyce Harper Robin Lovell- Badge	Melanie Davies Raj Mathur
	Apologies	Jane Blower	
Members of the executive		Anna Quinn (lead) Rasheda Begum (secretary) Laura Riley Peter Thompson Clare Ettinghausen	Stevan Cirkovic
Invited speaker		David Miller	
Observers		Kim Hayes (DH)	

1. Welcome, apologies and declarations of interest

- 1.1.** The Chair welcomed the Committee members to the meeting.
- 1.2.** In relation to the meeting agenda, interests were declared. Daniel Brison is a Scientific Director at an IVF unit with research in areas covered in the agenda. Sheena Lewis is involved in a spin out company for DNA fragmentation testing. Yacoub Khalaf is the Head of an IVF unit and one of the authors on the HABSelect paper.

2. Matters arising

- 2.1.** Minutes of the February 2018 meeting were agreed remotely prior to the meeting.
- 2.2.** The Scientific Policy manager gave an update on an action relating to updating patient information on ICSI which is with the Communications team.
- 2.3.** In the June 2017 meeting, a literature review on ICSI was considered by SCAAC. There was discussion on submitting the paper to a journal. The Chair is working on the draft of the paper, this will be sent to the Scientific Policy Manager.
- 2.4.** The Scientific Policy Manager is in contact with Andy Vail regarding assessing the evidence for three new treatment add-ons: DNA fragmentation, PICSI and IMSI. Discussion on these add-ons will be moved to the October 2018 meeting.
- 2.5.** The Scientific Policy Manager is currently establishing whether any centres are using intrauterine culture and will update the Committee at its October meeting.
- 2.6.** Members had raised that there were potential errors in the authorised process list. The list will be reviewed with the HFEA Compliance team, members will be contacted for their comments on what changes should be made to the list.

3. Chair's business

- 3.1.** The Chair reminded members that the annual Horizon Scanning Panel meeting will take place on Tuesday 3 July at the ESHRE conference. Members are welcome to join the meeting and should inform the Scientific Policy Manager if they would like to attend.
- 3.2.** The Committee noted that the Nuffield Council on Bioethics report on genome editing and human reproduction will be published soon.

4. HABSelect results

- 4.1.** The Chair welcomed Dr David Miller who was the Chief Investigator for the HABSelect trial. Dr Miller began his presentation by notifying the Committee that the monograph for trial has been approved for publication. The trial was a randomised controlled trial aiming to find out whether selecting sperm for ICSI using hyaluronic acid can improve the chances of having a live birth or reduce miscarriage rates.
- 4.2.** The trial was carried out to determine the efficacy of a HA selected system (physiological ICSI, or PICSI dish) in comparison to standard ICSI on live birth. Chromatin integrity was also evaluated

mechanistically. There were 14 NHS and two private clinics involved. The mechanistic work was conducted in three labs. Effort was made to interfere as little as possible with standard clinical practice. Patients were recruited in clinics and then allocated to either have PICSi or standard PVP ICSI. Leftover sperm was frozen for further analysis. The inclusion criteria were broad in terms of age and BMI. Exclusion criteria included non-ejaculated sperm, use of donor gametes, vasectomy, cancer treatment and previous participation.

- 4.3.** The primary outcome was full term live birth. Secondary outcomes included clinical pregnancy rate at 6-9 weeks, miscarriage and pre-term live birth.
- 4.4.** Dr Miller reported that PICSi did not significantly impact upon live birth rate. He also reported that there was a significant reduction in miscarriage rate in the PICSi group compared to standard ICSI.
- 4.5.** The mechanistic analysis was done to see the relationship between clinical outcomes and sperm DNA fragmentation. Several different tests were used to test sperm DNA fragmentation. It was thought that heavily fragmented DNA could not bind to HA, and the egg could not repair DNA damage. Sperm were analysed based on HA binding score. Sperm motility increased with HA binding score. Sperm concentration reduction correlated with higher DNA fragmentation. Well compacted DNA correlated with good motility.
- 4.6.** Conclusions from the study were that PICSi offered no advantage over standard ICSI for term live birth but did significantly lower miscarriage. The mechanistic analysis also showed that female age had significant effect on outcomes. Miscarriage reduction effect was confined to older women. There was no single indicator for sperm DNA integrity.
- 4.7.** Dr Miller welcomed questions from the Committee. One member asked whether aneuploidy levels were looked at as this is related to maternal age. Dr Miller responded that aneuploidy could be looked at samples that have not been processed. Another question was on the time when miscarriage occurred in patients, this was not looked at in study.
- 4.8.** Another member asked about evidence on differential capacity for the eggs of older and younger women to repair damaged sperm DNA. Dr Miller responded that it is not clear what the DNA repair mechanisms are. The HABSelect study did not show that increased DNA fragmentation had an effect on miscarriage.

5. Reviewing current treatment add-ons traffic lights

- 5.1.** The Scientific Policy Manager provided an overview on the work that had been done on treatment add-ons to date. In February 2017, the patient information and traffic light ratings system were finalised for nine commonly offered treatment add-ons. At their meeting in February 2017 the Committee made a commitment to regularly review the evidence supporting the use of add-ons. The Scientific Policy Manager presented a paper to the Committee which provided details of research carried out on the nine treatment add-ons since February 2017. The Committee were asked to consider the literature presented and whether they wished to revise any of the traffic light ratings currently provided on the HFEA website.
- 5.2.** The Committee discussed the traffic light system as a whole. Only a green rating indicates that there is evidence from at least one good quality study that the add on is effective and safe.

Members were in agreement that an amber rating indicates conflicting evidence and this should be made clearer in the patient information. There was a suggestion to include examples of green add-ons or highlight that there are no green add-ons.

Action

5.3. The Scientific Policy Manager and Officer will look at the introductory text on the add-ons page.

Assisted hatching

5.4. Assisted hatching currently has a red traffic light rating. The Chair commented that the most recent evidence was a meta-analysis which showed that assisted hatching still does not appear to have an effect on live birth rate.

5.5. Members discussed that hardening of the zona pellucida by vitrification could be a possible subgroup analysis as it could influence hatching. A recent cohort study has suggested that assisted hatching has an adverse effect. The Chair highlighted that the findings of cohort studies are not as robust as RCTs.

5.6. Members agreed to keep the traffic light rating as red.

Elective Freeze All

5.7. Elective freeze all is currently rated amber on the HFEA website. Members discussed evidence which shows that this add on could be effective mainly in polycystic ovary syndrome (PCOS) patients and the evidence does not suggest that freezing all embryos is unsafe. A potential adverse effect of freezing all embryos that has been identified in the literature is higher birthweight.

5.8. Members agreed to keep the traffic light rating as amber.

Action

5.9. The patient information for this add on will be reviewed to ensure it is made clear that it refers to treatment where patients choose to freeze their embryos.

Embryo glue

5.10. The Scientific Policy Manager informed the Committee that there have been requests that this add on should not be referred to as “embryo glue” as this is a product brand name and its use might imply the HFEA supports the product. One member suggested that if the term embryo glue is not used patients may be confused as this is how the add on is commonly known. There was discussion that this add on could be referred to as hyaluronate enriched medium, with embryo glue included as an example.

5.11. The available evidence was found to support routine use of embryo glue.

5.12. Members agreed to keep the traffic light rating as amber.

Action

5.13. The Scientific Policy Officer will work with Communications to modify the naming of embryo glue in the patient information.

Endometrial scratching

5.14. Along with the studies included in the paper, there are still ongoing trials on endometrial scratch, including the SCRaTCH trial which has finished recruiting and a New Zealand study which is about

to be published. One member raised that there is difficulty having only one traffic light rating considering that endometrial scratch may show different outcomes in certain scenarios such as first cycles, recurrent implantation failure and IUI cycles which may warrant split traffic light ratings.

5.15. One member highlighted that a section in patient information that says endometrial scratch is intended to correct problems in the womb lining is inaccurate.

5.16. Members agreed to keep the traffic light rating as amber.

Action

5.17. The Scientific Policy Officer will work with the Communications team to correct the patient information.

PGS

5.18. Members discussed the possibility that using PGS could lead to discarding of viable embryos. However, some patients may be reassured that PGS could help them identify the best embryo to transfer first time, leading to a possible reduction in miscarriages. It was also raised that PGS can be expensive for patients. PGS may be helpful only to patients who have many embryos which may not be the case for older women.

5.19. The HFEA Chair suggested that the patient information could be amended to reflect the differing viewpoints on PGS. The HFEA Chair also informed the committee that HFEA has been offered the keynote speech at the November Fertility Show and suggested that a collective statement on PGS could be part of the speech.

5.20. Members agreed to keep the traffic light rating as amber for day five PGS and red for day three PGS.

Action

5.21. The Scientific Policy Manager will redraft the patient information on PGS to indicate conflicting evidence.

Reproductive immunology

5.22. Members did not find that the new evidence relating to reproductive immunology indicated any benefit of using this add on.

5.23. Members agreed to keep the traffic light rating as red.

Time lapse-imaging

5.24. Members agreed to keep the traffic light rating as amber.

6. New project: Supporting research

6.1. The Scientific Policy Manager introduced the background of a new project on supporting research. One of the key visions of the HFEA 2017-2020 strategy is safe, ethical and effective treatment and an aim relating to this is to improve the quality of treatment by encouraging more world class research and clinical trials. A desired outcome from this is for clinics to be more research focused with proper testing of new techniques, larger and higher quality evidence base leading to improved outcomes in fertility treatment, and for patients to be more aware of the research they could take

part in and understand the benefit of research. Relevant work has already been carried out for facilitating human embryo research, this has included improving patient information on the website and resources on the clinic portal to support coordinating of research partnerships. Future work to be carried out includes re-evaluating the number of embryos donated to research to measure the impact of the embryo research project. This will inform whether specific consent needs to be revised. In addition, the HRA are looking at the IRAS system and HFEA as an IRAS partner is considering whether and how the application process for embryo research from HFEA might be integrated into the new IRAS front-end so that only one application needs to be submitted.

- 6.2.** Statistics on consent to disclosure across all clinics were presented to the Committee. Patients need to provide informed consent in order for their identifying information to be used in research. The consent rate for non-contact research has been consistently higher than contact research. Consent rates vary considerably between clinics. Another project is being carried out on consent to non-contact research and patient information is being developed on the benefits of data research and the ways in which their identifying data might be used in research so that patients are better informed. An online facility is being produced which will allow clinics to view their own consent rates in comparison to the national average. The project will hopefully help to understand the reasons for variation of consent between clinics and also help clinics to identify barriers to participation and share good consent to research practices.
- 6.3.** The new project on supporting research is in scoping phase. All types of research are being considered including human embryo research which the HFEA directly regulates as well as data research and clinical trials. Suggested avenues for the upcoming project were presented. One of these was engaging with patients to explore reasons why they may be reluctant to take part in research. There was also the possibility for SCAAC to develop recommendations for research high priority areas to disseminate to funding bodies. The HFEA could also strengthen relationships with funding bodies or explore a function to provide letters of support for researchers to include in their applications. Another way to support research could be to bring together members of the research community to explore innovative ways to carry out research. The project could also look at ways to promote data sharing between clinics to enhance the evidence base for treatments.
- 6.4.** The Committee was asked to provide feedback on the ideas proposed for the project. It was clarified that the consent to disclosure is separate to consent to embryo research. Members also indicated that research on oocytes could be an area to facilitate and questions if patients are aware they can donate oocytes for use in research. The HFEA does not regulate research on oocytes unless they are being used to create embryos. The Scientific Policy Manager highlighted that patients do make enquiries about donating oocytes to research and raising awareness may be something to include in the project. Members agreed integration into the IRAS system will make applications easier.
- 6.5.** One member asked if the rates of consent to disclosure will be inspected against. It was explained that the comparison could allow clinics that are outliers to address how their consent rates could be improved. The Committee agreed that the rise in uptake to consent to research is promising, they are interested to see the breakdown of rates for contact and non-contact research.
- 6.6.** Members discussed the suggestion that SCAAC could develop research high priority areas. Members commented that research which does not meet these criteria may be at a disadvantage and that there may not be enough expertise to identify all priority areas. It was suggested high

priority areas should be areas that are under researched. The Royal College of Obstetricians and Gynaecologists is already involved in prioritisation of research areas from clinical study groups.

- 6.7.** One member highlighted that generic consent would allow development of an embryo biobank so that research groups could apply to use these embryos and also allow importing of embryos for research. Others discussed that current interpretation of informed consent in Department of Health regulations requires that patients consent to donating embryos only to a specific named study each time, which would not permit consenting to an embryo banking arrangement that would require the donor's consent for the bank to distribute banked embryos to research projects or purposes which meet certain criteria.

7. Embryo-like entities

- 7.1.** The Scientific Policy Officer introduced the commentary that had been written by the HFEA Policy team with help from SCAAC members. The paper set out different types of embryo-like structures that could be termed embryo-like entities or ELEs. Members were asked to consider the scientific and clinical implications of the ELEs described in the paper and whether a spectrum could be devised with a standard embryo created by fertilisation of an egg derived from an ovary at one end and all the different types of ELEs placed on the spectrum in relation to how closely they resemble the standard embryo.
- 7.2.** One member highlighted that an embryo created from in vitro derived gametes may be considered a non-permitted embryo rather than an ELE. Non-permitted embryos fall under the remit of the HFEA, which cannot be used for embryo transfer, though can be used for research. It was raised that ELEs may not come under HFEA regulation. Members discussed the distinction between a standard embryo and an ELE, and the threshold could be developmental potential. The Chief Executive outlined that the HFEA is often asked about ELEs, and the purpose for bringing this to SCAAC was to help the HFEA to consider the subject. Members discussed whether ELEs have the potential to develop into a human being.
- 7.3.** Members suggested that the subject of ELEs should be part of an annual update at SCAAC meetings.

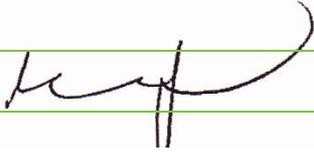
8. Any other business

- 8.1.** One member asked about the consensus statement for new technologies. There is a draft of the statement that will be circulated to the working group.
- 8.2.** Treatment add-ons were further discussed, with suggestions to engage clinics to see how many are offering treatment add-ons. The Executive is currently repeating an audit of clinic websites to determine which treatment add-ons are commonly advertised to patients, and how much patients are charged for using them. The Chief Executive explained that the Code of Practice is being updated with more stringent guidance for clinics who are offering treatment add-ons.

9. Date of next meeting

- 9.1.** Monday 15 October 2018, HFEA Offices

Signature

A handwritten signature in black ink, appearing to be 'Yakoub Khalaf', written on a light blue background. The signature is stylized with a large, sweeping flourish at the end.

Name Yakoub Khalaf

Committee chair

Date 04/10/2018