

Scientific and Clinical Advances Advisory Committee (SCAAC)-minutes

15 October 2018 11:00am- 4:00pm

Derwent Room, HFEA Offices, 10 Spring Gardens, London SW1A 2BU

Authority Members	Present	Yacoub Khalaf (Chair) Kate Brian Andy Greenfield Anne Lampe	
	Apologies	Tony Rutherford Gudrun Moore	
Members of the Executive		Anna Quinn (lead) Rasheda Begum (secretary) Laura Riley Clare Ettinghausen	Nick Jones Mhairi West Julia Katsaros Victoria Askew
External advisors	Present	Jane Blower Daniel Brison Melanie Davies Joyce Harper Sheena Lewis	Robin Lovell-Badge Raj Mathur
Observers		Steve Pugh (DH)	
Invited speaker		Nick Macklon Andy Vail	

1. Welcome, apologies, declarations of interest

- 1.1. The Chair welcomed the Committee members to the meeting.
- 1.2. Apologies had been received from Gudrun Moore and Tony Rutherford.
- 1.3. In relation to the meeting agenda, interests were declared by Sheena Lewis who had interests relating to sperm DNA damage. In relation to intrauterine culture, interests were declared by Daniel Brison who was an adviser for Anecova in 2013.

2. Matters arising

- 2.1. Minutes of the meeting held on June were agreed remotely prior to the meeting
- 2.2. The Scientific Policy Manager updated the Committee on matters arising, several of which related to treatment add-ons which was to be discussed later in the agenda at the meeting. One outstanding action from the June 2017 meeting was for the Chair to review the ICSI literature review which is to be submitted for publication to a journal as discussed at the June 2017 meeting.

3. Chair's business

- 3.1. The Chair reminded the Committee that Andy Greenfield will be reaching the end of his role as an Authority Member and Deputy Chair, though will still be a part of SCAAC as an external adviser. The Chair also announced that Anna Quinn will be leaving her post as Scientific Policy Manager, and leaving the HFEA at the end of October, and the Committee commended her work to support SCAAC to date, with thanks.
- 3.2. The Committee will be contacted for the annual self-evaluation of committee effectiveness which is undertaken by all HFEA committees.

4. Recent publications

- 4.1. The Scientific Policy manager circulated two recent papers^{1,2} to the Committee to hear their views and suggestions for any useful actions for HFEA.
- 4.2. The first paper discussed was Williams et al., 2018. This was a linkage study that used HFEA register data to investigate cancer risks in women who had undergone assisted reproductive treatment. The study found an increased relative risk of in situ breast cancer, and of invasive and borderline ovarian cancer but in the context of a low absolute risk. The results could be due to characteristics specific to these patient groups and the authors have recommended ongoing monitoring of this population. The Committee were asked for their thoughts on the paper and implications for the HFEA.
- 4.3. One member who was also one of the authors of the paper explained that subgroup analysis found that the increased risk of ovarian cancer was not present in couples with male factor

¹ Verpoest W, et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. Human Reproduction. 2018 Aug 6;33(9):1767-76.

² Williams CL, et al.. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation. BMJ. 2018 Jul 11;362:k2644.

infertility. The increased risk was found in couples with female factor infertility, particularly in endometriosis cases. The findings from the study suggested possible concerns for women with endometriosis and infertility who undergo assisted reproduction treatment, however further research is required to establish any increased risk.

- 4.4.** Members discussed whether the follow-up period was sufficient for the symptoms to be caught, given that the average follow-up in the study was 8.8 years.
- 4.5.** The Committee discussed consent to disclosure which was introduced in 2010, where clinics were required to obtain explicit consent from patients to the disclosure of their personal identifying information from the HFEA Register (for women who underwent treatment after October 2009) for use in research. The HFEA is working to facilitate improved provision of information about available options around research, including by developing new HFEA website content which can be converted into a patient leaflet and providing an online tool allowing clinics to check their own consent to disclosure rates compared to an average across all licensed clinics. A member commented that a leaflet may not be the most suitable approach as patients are already overwhelmed with information. A suggestion was made that someone other than a clinician in the clinic can speak to a patient about non-contact research. A member asked what clinics with high consent rates do to achieve these high rates. The Committee agreed that this is usually a reflection of a research-positive culture in clinics with many patients being involved in a discussion of their options around research.
- 4.6.** Members felt that the findings from the Williams et al., 2018 paper examining cancer risks in women who had undergone assisted reproductive treatment. do not have an impact on advice currently given to patients, as the increased risks could be related to factors that were not included in the paper such as BMI. There was agreement that factors such as BMI should be collected in the HFEA register. The Director of Compliance commented that is something that can be discussed after the HFEA's new system for data collection has been introduced.
- 4.7.** The Committee moved on to the second paper which was by Verpoesto et al., 2018. This study was the first RCT funded by ESHRE which investigated whether preimplantation genetic testing for aneuploidy (PGT-A) could increase the likelihood of live birth in ICSI. There was no difference in live birth rate in the PGT-A group, however there was a reduction in miscarriage, fewer embryo transfers and fewer embryos frozen.

5. Intrauterine culture

- 5.1.** Intrauterine culture is a procedure that was reviewed by SCAAC and approved by the Statutory Approvals Committee as a novel process in 2015. When a centre wishes to carry out a process which does not appear on the list of authorised processes, it must apply to the Authority for permission. It involves placing fertilised eggs into an intrauterine culture device, which is inserted into the woman's womb. The device stays in place for several hours during the initial stages of embryo development within the womb instead of an incubator as would be done in conventional IVF. When the device is removed, the embryos are removed from it and put in an incubator until they are ready to be transferred back to the womb (without the device) or to be frozen for use in future treatment. After a novel process is approved, the applying clinic is required to submit an outcomes report to the HFEA two years after the initial approval for review by SCAAC. The outcomes report for intrauterine culture from the applying clinic was considered by SCAAC in February 2017. The Committee agreed that more information and data was required from the

centre and suggested that a representative from any clinics planning to implement the technique should be invited to SCAAC.

- 5.2.** The Committee was joined by Professor Nick Macklon, Medical Director at London Women's Clinic who had been invited to provide insight into clinical experiences and outcomes using the AneVivo device which is used for intrauterine culture. A report on clinical outcomes of the AneVivo device from clinics in Spain and Poland had been circulated to the Committee in confidence for commercial reasons in advance of the meeting.
- 5.3.** Prof Macklon explained that a device that could allow human embryos to be placed in the uterus and then removed offered a unique opportunity to research the impact of the embryo on the endometrium and vice versa. Prof Macklon became involved in advising the company and saw it through development to being offered for use in patients. Prof Macklon stressed that the treatment is not currently offered to improve pregnancy rates or to benefit the embryo, rather the claimed benefits to the woman are psychological as she can be more physically involved in the process. Prof Macklon said that he is interested in this technique as an alternative to *in vitro* culture as it may reduce the impact of exposure of the embryo to synthetic *in vitro* culture media.
- 5.4.** Prof Macklon updated the Committee on activity since the novel process application was made on behalf of Complete Fertility Centre to the HFEA for use of the device and approved in 2015, from which point the Complete Fertility Centre was required to collect data on outcomes for reporting back to the HFEA. Training took place before the procedure was ready to be offered to patients. Prof Macklon at that point left the centre and the Trust then began the process of selling the clinic to a private investor. These two factors led to the introduction of the intrauterine culture technique being deprioritised. The technique has been used in a clinical context in Spain and Poland via the AneVivo device. Prof Macklon felt that the technique is ready to be offered to patients at London Women's Clinic.
- 5.5.** The company's aim for the AneVivo device is that it could potentially replace *in vitro* culture up until blastocyst stage by using the uterus as an alternative to a laboratory incubator and synthetic culture media. Data from use of the device in Spain will be presented at Fertility 2019. Prof Macklon asked the Committee to consider whether there is sufficient data to allow continued use of the device in the UK subject to further review in 2 years' time from now once there is more data. During this time period, Prof Macklon anticipates the device will become available for longer term intrauterine culture up to blastocyst stage.
- 5.6.** The Committee were asked for questions and comments. One member commented that the device does not mimic 'natural' development as the embryo would usually be in the fallopian tubes in the early stages of development. Prof Macklon agreed, however as pregnancies still occur when early embryos are placed in the uterus, this indicates that the uterus is not a hostile environment.
- 5.7.** A member asked how much patients would be charged for using the device as an add-on and whether the device could harm the patient. Prof Macklon commented that some people may consider the procedure to be quite invasive as patient will undergo egg collection as well as having the device placed in the uterus and removed some hours later therefore the market will be small. However there has been interest from patients who view the procedure as providing less embryonic exposure to *in vitro* culture. In terms of pricing, Prof Macklon was not able to confirm the price in UK clinics, however, he did note that patients in clinics overseas may be charged approximately 700 Euros.

- 5.8.** One member asked whether there has been research into the psychological benefits described for the device. Prof Macklon commented that there have been focus groups, which highlighted that some patients found using the device empowering, whereas others felt concerned about taking responsibility for the embryos instead of a laboratory. In Spain and Poland, there has been particular interest and enthusiasm in the psychological impact on donor egg recipients. Some donor egg recipients have reported that they decided to use the donor eggs with the device because the device made them feel like they have contributed to the process.
- 5.9.** Prof Macklon was asked what evidence he wants to see before the device can be introduced into routine use in the UK as a method of incubation. Prof Macklon responded that the device should be evidenced as being as safe as standard *in vitro* culture procedures, as well as presenting ongoing pregnancy rates comparative to standard procedures. Longer term follow-up needs to show that babies born from using the device are as healthy as those born from standard *in vitro* fertilisation and vice versa. It will take a long time to collect this data, however there are other approaches which could give some information in the shorter term such as carrying out epigenetic analysis on embryos.
- 5.10.** A member asked about pre-clinical experience with the device using human embryos donated to research. Prof Macklon addressed that this has not progressed due to the lack of embryos donated for research for this purpose. Another question was on whether ICSI needs to be used with this method. Prof Macklon explained ICSI was not in principle required, however ICSI has been used to ensure the sperm got into the device.
- 5.11.** Prof Macklon raised that there is some evidence to suggest that the constituents of embryo culture media may have an impact on children born from ART- associations have been made on birth weight and that IVF children show some cardiovascular differences to naturally-conceived children. Due to the possible negative impacts of *in vitro* culture, Prof Macklon felt it was justified to explore methods which would reduce the time spent in these conditions.
- 5.12.** One member commented on the cost of the device of ~700 Euros, noting that as the technique is still in experimental phase it seemed unreasonable to charge patients.
- 5.13.** The Chair commented that the biological plausibility of the technique is lacking. Prof Macklon highlighted that the technique is being investigated to see whether the uterine environment is better than *in vitro* culture.

Action

- 5.14.** The Executive will follow up with Prof Macklon to review the patient information relating to intrauterine culture.

6. Audit of clinics websites: Treatment add-ons

- 6.1.** The Scientific Policy Officer gave a presentation on findings of an audit carried out of UK licensed clinics' websites to see which add-ons are being offered and how much patients are charged for using them. The Committee were asked to consider the data presented and provide their thoughts on the findings.
- 6.2.** One member was keen for the HFEA to publish the range of costs that the audit found for treatment add-ons as part of publishing the audit in future. Some members commented that

putting information about the range of costs may encourage clinics to charge more if their fees are on the lower end of the scale.

- 6.3.** A member highlighted that a figure for how many clinics do not advertise the price of add-ons was not included in the data. The Director of Strategy and Corporate Affairs notified the Committee that the audit findings were a snapshot of what could be found on clinic websites only.
- 6.4.** The Chair noted that the HFEA do not regulate add-ons however can still help patients by providing information that will enable them to make a choice when being offered add-ons.
- 6.5.** The Data and Insights Analyst gave a presentation on initial findings from the first ever HFEA national patient survey that was carried out in September. Data was presented on responses to the survey that were relevant to patients' experiences of using treatment add-ons. Qualitative and quantitative data was presented.

7. Treatment add-ons: assessment of traffic light ratings

- 7.1.** Currently the HFEA website provides information and a traffic light rating for nine commonly offered treatment add-ons, these ratings are agreed by SCAAC with guidance from an external assessor. Professor Andy Vail joined the meeting via teleconference. As with previous treatment add-ons, the HFEA recruited Prof Vail to carry out evidence assessment for the purpose of developing a traffic light rating for three new add-ons. Prof Vail had carried out an independent assessment of the evidence for three sperm selection methods (PICSI, IMSI and MACS) and was invited to discuss the proposed traffic light ratings for each add-on.
- 7.2.** The Scientific Policy Manager gave an overview of the discussions from previous meetings leading up to the report provided by Prof Vail. It was highlighted that DNA fragmentation was under consideration to be added to the HFEA 'traffic lights' webpage with patient information webpage along with the sperm selection methods. After discussions with Prof Vail and an andrologist, it was concluded that DNA fragmentation is a diagnostic test and does not directly influence live birth rate, making this type of diagnostic test distinct from the claims made for other treatment add-ons in relation to improving the chance of a live birth. The suggested approach to displaying information on DNA fragmentation was a 'pull out box' adjacent to the information on sperm selection methods, explaining that DNA fragmentation is a diagnostic test that may influence a patient's treatment pathway, but that it will not impact on the chances of a live birth.

Intracytoplasmic morphological sperm injection (IMSI)

- 7.3.** The first add-on discussed was IMSI. Prof Vail provided an overview of his findings and recommended a red rating (indicating that there is no evidence to show the procedure is safe and effective). The literature contained findings from RCTs and all studies carried out on infertile men found no impact of IMSI on live birth rate. There was one study that reported a statistically significant difference whose sample was older women, and a theory for this observation was that older eggs were less able to 'fix' DNA damage in sperm. One member asked Prof Vail about the quality of this study. Prof Vail explained that although the study was small it was of reasonable quality.
- 7.4.** A member highlighted that there is a lack of a relationship between IMSI and DNA damage, as IMSI involves looking at vacuole size and DNA damage cannot be picked up this way.
- 7.5.** The Committee agreed with Prof Vail's recommended rating of red for IMSI.

- 7.6.** The Committee were asked for their views on the HFEA patient information for IMSI, particularly on including the possible benefit of IMSI on the eggs of older women, as the reduced capability of older eggs in repair of DNA damage in sperm could be overcome by selecting better sperm. A member highlighted that only one study reported the benefit on older women and asked if that was enough evidence. Prof Vail said the evidence is fairly weak though is still encouraging.
- 7.7.** A member said that the use of IMSI could be acceptable if patients are not charged and claims are not made on the benefits of IMSI. It may be useful for clinics to view sperm at high magnification.
- 7.8.** The safety of IMSI was addressed, as one member outlined that sperm are viewed under a microscope with high magnification which can lead to a heating problem. There is also a very small number of sperm than can be viewed which can deselect viable sperm.
- 7.9.** Draft patient information for IMSI was reviewed by the Committee. Comments were noted, and the patient information for IMSI to go on the treatment add-ons section of the HFEA website will be amended accordingly.

Action

- 7.10.** The Scientific Policy Manager will work with the Scientific Policy Officer to finalise the patient information on IMSI to go on the treatment add-ons section of the HFEA website and circulate to the Committee for agreement.

Physiological intracytoplasmic sperm injection (PICSI)

- 7.11.** The Scientific Policy Manager reminded the Committee that David Miller who was the Chief Investigator of the HABSelect trial³ attended the last SCAAC meeting to present the results of the trial. The trial has not been published yet therefore Prof Vail assessed the available published evidence on PICSI. The HABSelect trial was important due to its large sample size however without the full paper it could not be included in the assessment. Prof Vail indicated that the overall conclusion for PICSI is unlikely to change after including the HABSelect data. The studies included consistently show that findings do not support use of PICSI.
- 7.12.** A member highlighted that the HABSelect trial found a decrease in miscarriage. The Chair emphasised that the primary outcome of live birth rate was not affected by PICSI. A member referred to the patient information for PGS on the treatment add-ons page of the HFEA website which states that PGS can decrease miscarriage rate therefore it needs to be insured that the information is consistent across all the add-ons. There was a suggestion that a traffic light rating per indication for a treatment add-on may be informative, for example freeze-all would have a green rating for OHSS prevention but not for increasing live birth rate.
- 7.13.** The draft patient information for PICSI to go on the treatment add-ons section of the HFEA website was reviewed, one member commented that the wording should not say that PICSI can select better sperm, rather it attempts to.
- 7.14.** PICSI was not found to increase live birth rate and the recommended red rating was accepted.

³ https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/habselect-hyaluronic-acid-binding-sperm-selection_v10/

Action

- 7.15.** The Scientific Policy Manager will work with the Scientific Policy Officer to finalise the patient information on PICS1 to be published on the treatment add-ons page of the HFEA website and circulate to the Committee for agreement.

Magnetic activated cell sorting (MACS)

- 7.16.** The Scientific Policy Manager highlighted that there were only a few studies in the literature for MACS. Prof Vail further added that the literature was contradictory, as one large study did not find any increase in live birth rate whereas two other smaller studies found a large increase in live birth rate for MACS. The two smaller studies were considered as weak in quality.
- 7.17.** The Scientific Policy Manager asked members if there have any experience in using MACS. The Chair answered that MACS is not well practised; therefore, there may be no need for patient information on the treatment add-ons page of the HFEA website at the current time. Due to the lack of activity of the MACS technique in the UK, members agreed that discussion can be placed on hold until a later date.

DNA Fragmentation

- 7.18.** An overview of previous discussions around DNA fragmentation was provided by the Scientific Policy Manager. Jackson Kirkman Brown was invited to SCAAC last year and explained the different tests used for assessing DNA damage. The Committee was advised that an overarching rating could not be applied to the different tests. The Committee were asked whether a rating should be developed or if providing information about the diagnostic properties of the test alongside the sperm selection methods would be sufficient without a rating.
- 7.19.** The Chair highlighted that the literature for DNA fragmentation is mixed in terms of quality and many studies are retrospective rather than RCTs. A member asked whether findings from DNA fragmentation testing can inform whether patients should use donor sperm. The Chair explained that it is unlikely that the advice for patients will go as far as opting for donor sperm, rather DNA fragmentation findings can lead to patients being advised to use testicular sperm extraction which can be expensive.
- 7.20.** A member asked about whether the evidence of DNA fragmentation is being assessed. The Scientific Policy Manager commented that the literature has been collated however was not sent for assessment as it is not planned for a traffic light rating to be developed.
- 7.21.** Members discussed adding investigations such as DNA fragmentation testing to the HFEA website, with their own traffic light ratings. There would need to be a new traffic light rating system for diagnostic tests developed in order to display this information on the HFEA website.
- 7.22.** The Scientific Policy Manager addressed that while there is value in providing information on investigations and diagnostic tests, there needs to be a thorough discussion with the Committee and the Executive about whether it would be feasible for the HFEA to provide this information without confusing patients.

Action

- 7.23.** The Scientific Policy Manager will arrange for a discussion to be had on fertility investigations.

Endometrial scratch

7.24. A large trial that investigated endometrial scratch was carried out in New Zealand which showed no benefit. The findings have not been published yet, therefore only a conference abstract could be assessed. Prof Vail explained that the current rating of amber was based on a Cochrane review which found overall positive effect in patients with multiple implantation failures. The unpublished New Zealand RCT known as the PIP study⁴ included subgroup analysis of this population and found no difference in live birth rate. There are two ongoing studies in the UK and Netherlands. The UK based trial has finished recruitment. Prof Vail advised that a final evidence assessment should be done after the trials have completed.

8. Review of treatment add-ons website information

- 8.1.** Patient information for existing add-ons on the HFEA website had been re-drafted by the Scientific Policy Manager. Comments from the Committee at the previous meeting regarding the tone of the information had been taken account. The Committee were asked to provide feedback on the draft.
- 8.2.** A significant edit made was regarding the language used for amber add-ons, this now read as a rating that indicated a conflicting body of evidence that required further evidence. A suggestion was that contradictory is a more suitable word than conflicting.
- 8.3.** The Committee were asked whether patients will understand the term “routine use”. A member suggested that this can be put forward to patient groups.
- 8.4.** The patient information for embryo glue was reviewed, as embryo glue is a product name the text had been amended to include the name of the substance which is hyaluronan-enriched embryo transfer media. The reference to ‘embryo glue’ will be kept in quotation marks as a subtitle, as patients will be most familiar with the add-on being called embryo glue.
- 8.5.** The members discussed that there has been a lack of research since intrauterine culture was approved as a novel process in 2015 therefore the evidence base has not increased to allow for proper review. The Scientific Policy Manager highlighted the upcoming consensus statement being developed by HFEA and professional organisations on best practice on using treatment add-ons does address that patients should not be charged to take part in a clinical trial, so clinicians can be made aware of the ethical concerns about charging UK patients for using intrauterine culture.
- 8.6.** Members agreed that the patient information on the treatment add-ons section of the HFEA for intrauterine culture needs to be strengthened to emphasise that the technique is not a natural alternative to *in vitro* culture, that it has undefined risks and can be expensive. The Director of Compliance and Information also added that the Inspection team can review patient information to ensure clinics are providing appropriate information before offering treatment.
- 8.7.** Amendments for the patient information for PGS were reviewed, specifically on the evidence for PGS. The traffic lights rating information has been amended to make it clear that PGS will not

⁴ <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/the-pip-studies/>

increase a patient's chances of a live birth, the benefit is a reduction in the possibility of miscarriage.

8.8. A suggestion was made that the possibility of PGS leading to discarding of viable embryos should be included as a risk of the technique. Members also highlighted that the text that says PGS has the same risks as PGD should be removed.

8.9. Another suggested addition was to include that PGS can be referred to as PGT-A.

Action

8.10. The draft patient information will be revised with the suggested changes.

9. Alternative methods to derive embryonic and embryonic-like stem cells

9.1. The Scientific Policy Officer introduced the paper which contained a literature review covering recent studies that investigated alternatives to embryonic stem (ES) cells. Key studies included the first clinical trial which used induced pluripotent stem (iPS) cells to treat patients with neovascular age-related macular degeneration. The Committee were asked for their views on the paper. It was noted that the subject of alternatives to deriving ES cells would be presented together with embryonic-like entities (ELES) at future meetings.

9.2. A member highlighted that ES cells will always need to be derived from embryos. It was also noted that viable embryos are not the only source for ES cells, parthenogenetic embryos and androgenetic embryos can also be used. There are also more types of pluripotency than primed and naïve suggesting a spectrum of differentiation potentials.

10. Any other Business

10.1. The Scientific Policy Manager raised that artificial intelligence is gaining profile in the media and there is increasing interest in using AI in the provision of fertility treatment and asked the Committee whether an information paper on this should be brought to SCAAC. The Chair suggested an expert in the area should be invited to SCAAC, members agreed.

10.2. A member suggested genome editing should be revisited.

11. Date of Next Meeting

11.1. Monday 4 February 2019, The Francis Crick Institute, 1 Midland Rd, London NW1 1ST

Signature *Yacoub Khalaf*

Name Mr Yacoub Khalaf

Committee chair

Date 24/01/2019
