Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

7th June 2021

Teleconference (Zoom meeting)

Authority members of the SCAAC	Present	Yacoub Khalaf (Chair) Gudrun Moore (Deputy Chair) Anne Lampe Tim Child Jason Kasraie	
External advisors of the SCAAC	Present	Jane Blower Andy Greenfield Robin Lovell-Badge Raj Mathur Kevin McEleny	Joyce Harper Sheena Lewis Shankar Srinivas Kate Brian
	Apologies	Daniel Brison Richard Anderson	
Members of the Executive	Present	Dina Halai (Scientific Policy Manager and meeting lead) Matthew Mudford (Scientific Policy Officer and meeting secretary) Victoria Askew (Policy Manager) Nora Cooke-O'Dowd (Head of Intelligence) Jane Darragh (Research Manager) Laura Riley (Head of Regulatory Policy) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Peter Thompson (Chief Executive) Julia Chain (Chair of the HFEA) Rachel Cutting (Director of Compliance and Information)	
Observers	Present	None	

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. Declarations of interest were received by Raj Mathur, Joyce Harper, Kevin McEleny and the Chair.

1.3. Julia Chain, the new Chair of the HFEA, was congratulated on her appointment and welcomed to the meeting on the Chair's behalf.

2. Matters Arising

2.1. Minutes of the meeting held in February were agreed remotely prior to the meeting.

2.2. The Scientific Policy Officer updated the Committee on the matters arising:

2.3. There have been several notable changes to the HFEA website following SCAAC recommendations, particularly the treatment add-on webpage. The red, Amber, Green (RAG) ratings no longer reflect the safety considerations of each treatment. Safety is commented on for each treatment outside of the traffic light ratings. These changes have been live on the HFEA website since February 2021.

2.4. On COVID-19, the HFEA has updated the frequently asked questions (FAQ) vaccination advice in line with British Fertility Society (BFS) and Association of Reproductive and Clinical Scientists (ARCS) guidelines and has published a list of papers discussed at SCAAC meetings on the Clinic Portal.

2.5. At the last meeting, a request was made to amend PRISM data being recorded, in particular, what is being recorded for testicular biopsies for sperm retrieval. It was asked if the reason for the sperm retrieval could be listed as it would be helpful to distinguish between obstructive and non-obstructive causes. That request has now been submitted for consideration by the PRISM Data Review Panel when it convenes.

2.6. The SCAAC workplan has been updated in line with the discussion at the February SCAAC meeting and is shown in Annex A of the matters arising paper for this meeting.

3. Chair's business

3.1. The Chair welcomed two new Authority members, Tim Child and Jason Kasraie, as well as Kate Brian who returns to SCAAC as an external adviser.

3.2. The Chair reminded the Committee that the HFEA's Annual Horizon Scanning Meeting will be held on 2nd July and will include guest speakers on the following subjects:

- HFEA Fertility trends report & Ethnic diversity report
- Artificial Intelligence and data driven technology
- Stem cells and gametogenesis
  - In vitro gametogenesis
  - Synthetic embryo-like entities
  - 14-day rule

- Genetics
  - Polygenic traits
  - Expanded carrier screening
  - Genome editing

4. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy

4.1. No papers were submitted to the HFEA for circulation prior to the meeting.

4.2. One member informed the Committee that their team at University College London (UCL) had written four papers that are being submitted to journals and highlight the challenges of communication from clinics during the pandemic and the impact it had on patients.

4.3. One member brought the V-Safe registry to the attention of the Committee. V-Safe is an app that has been used to register pregnant women in the USA who have received COVID-19 vaccines. The report of their results up until February 2021 has shown no increase in miscarriage rates.

4.4. One member informed the group that BFS had received enquiries about the timing of donating gametes following vaccination. Current guidance is not to donate for seven days after COVID-19 vaccination, in line with guidance on other tissues/cells.

4.5. Guidance on haematopoietic stem cells has now changed (from seven days) as a precautionary measure. This is due to the theoretical risk of the granulocyte-colony stimulating factor (GCSF) injections received by stem cell donors exacerbating the immune response related to vaccine-induced immune thrombotic thrombocytopenia syndrome (VITTS). This was discussed at the BFS and ARCS COVID-19 working group and as GCSF is not given to gamete donors that was not seen as a risk but the group wished to clarify their guidance on the issue. They have stated that ovarian stimulation should not start until seven days after vaccination which will ensure that on average egg collection will happen around 14 days after vaccination.

4.6. A member pointed out that this is inconsistent with guidance for women using their own eggs, who can have their eggs collected the day after vaccination, and the guidance for sperm donors. In response, it was stated that clarification of guidance includes a more cautionary approach for altruistic donors than for those using their own eggs. The inconsistency with sperm donors is due to egg donors undertaking a surgical procedure which increases the risk if done in the context of VITTS.

5. Add-ons application – Endometrial Receptivity Analysis

5.1. The Scientific Policy Officer presented a summary of the application for Endometrial Receptivity Analysis (ERA) to be considered by SCAAC as an add-on for inclusion in the HFEA'S traffic light rated list.

5.2. The ERA application in the accompanying papers was on an updated form and was the first time the form had been used to submit a treatment for consideration as an add-on by SCAAC. The form has been developed so the HFEA can keep an audit trail of how add-ons are considered. It has been developed to provide enough evidence for SCAAC to make a decision about the

treatment's suitability as an add-on. The form is not intended to be used to provide evidence for what RAG rating it should be given. The application form is live on the Clinic Portal.

5.3. ERA is a diagnostic method that classifies the endometrium as receptive, pre-receptive, or post-receptive. It enables women to undergo a personalised embryo transfer (PET) where the exact timing of the transfer is tailored to each woman's personal window of implantation.

5.4. ERA is offered on the websites of 19 UK clinics for the investigation of implantation failure in IVF, for improving the chances of pregnancy and to "improve success rates" and is most often advertised as being for women who have had recurrent implantation failure or multiple failed cycles.

5.5. There are several studies that show embryo transfer guided by ERA does improve chances of pregnancy but very few that look at live birth rate as a primary or secondary outcome. The only RCT that looks at live birth rates, despite a large drop-out, found a significant improvement in pregnancy, implantation and cumulative live birth rates in PET compared with frozen embryo transfer (FET) and fresh embryo transfer groups.

5.6. The additional paper shared before the meeting, a retrospective cohort study published in Fertility and Sterility, also had live birth rate as a primary outcome but found that live birth rates for the ERA group, and the matched non-ERA group were not significantly different, nor was a difference seen in sub analyses based on the prior number of FETs or receptivity status.

5.7. Other published studies do not have live birth as a primary or secondary outcome and have mixed findings as to the effectiveness of the ERA on implantation rates and pregnancy rates.

5.8. The ERA necessitates a freeze-all cycle and repeated medicated cycles to enable the endometrial biopsy, all of which carry a slight risk to the patient or the embryo. There are no new skills or equipment that are not already available in an experienced clinic.

5.9. No professional bodies currently provide any recommendations or guidelines related to ERA.

5.10. The Chair stated that he had found the clear, reproducible framework for add-on applications helpful.

5.11. It was clarified by the Scientific Policy Manager that treatments with robust evidence behind them may be considered a green rated add-on and information could therefore be provided elsewhere on the HFEA website. This application has been developed specifically for add-ons that could be amber or red rated therefore included as part of the traffic light rated list.

5.12. One member was concerned that discussions of add-ons with good evidence (considered green) were not being prioritised over less frequently used red or amber add-ons which may delay the publication of information on green add-ons that have a greater impact on patients.

Action

The Executive will amend the decision tree so that SCAAC have the option to recommend the addition of information for a green rated add-on to the HFEA website, rather than just red/amber.

5.13. One group of clinics has looked at their protocols for medicated/frozen cycles and there was a range of 36 hours that they were using for the number of days of progesterone with no difference in live birth rates which implies variation has little effect.

5.14. It was noted that there is a significant gap between what is available from a clinic (shown on their website) and what is offered to patients in their consultations.

5.15. The Committee followed the directions in the decision tree and concluded that the ERA should be considered an add-on.

Action

A full review of the evidence, including biostatistical analysis from Andy Vail, will be conducted before ERA is considered again at the October meeting and a RAG rating is decided.

6. Artificial intelligence and machine learning – literature review

6.1. The Policy Manager presented the literature review of Artificial Intelligence (AI) and machine learning, detailed in the accompanying paper.

6.2. The use of AI in reproductive medicine could encompass most aspects of a patient's treatment cycle, from patient management and clinical decision-making to gamete and embryo grading.

6.3. There is a lack of high-quality research into the effectiveness of many of these algorithms, with few RCTs having taken place.

6.4. There are potential conflicts of interest with commercial companies funding research into their own products or are the named authors.

6.5. There are concerns about a lack of transparency over decision making, a need for vast amounts of data for training models, a risk of unintended bias in training data and a lack of accountability over each element of a model's output.

6.6. There is a need for regulators to identify gaps in regulation and to learn about AI and apply it to their sectors. The use of AI in the fertility treatment would raise questions about how the Authority would inspect their suitability and appropriate use in centres as well as that of quality assurance systems in place.

6.7. It is likely that regulators as currently resourced will need significant external support and guidance from government and professional expert bodies to be able to regulate AI and data-driven technologies effectively.

6.8. The HFEA and other regulators are already taking steps to share innovation and good practice so far as is possible within the resources and legal powers that we currently have. Despite concerns and regulatory questions, the use of AI in reproductive medicine is developing rapidly with new technologies frequently being introduced to the sector for commercial use, raising questions of prioritisation and resources for HFEA.

6.9. Members are asked to:

- advise the Executive if they are aware of any other recent developments in AI relevant to fertility treatment or research;
- discuss their views on the impact AI will have on fertility treatment as technology advances, including practical and ethical challenges to their application;
- discuss their views on the Authority's regulatory interest around AI systems – scope and limits; and;

- review whether any outputs from the HFEA are currently required that would address the use of AI.

6.10. One member stated that we need to be very clear about what is AI and what is machine learning. They also questioned how SCAAC could effectively comment on how results are generated when commercially sensitive algorithms are owned by companies, are not widely available and they reluctant to release their methodology.

6.11. The Policy Manager clarified that some algorithms which are considered AI are already available and being used in the UK such as embryo grading algorithms. Non-invasive PGT-A for genetic screening is not yet an authorised process so would need to go through a novel process application before it could be used in UK licensed clinics.

6.12. One member stated that in the field of microfluidics, scientists are developing a lab-on chip which, when an egg and a sperm after ICSI are inputted, would perform several functions together- proteomics, genomics, timelapse, etc, and the data is analysed by AI.

6.13. A member drew attention to several publications, in Nature, Medicine and the Lancet, that were a series of guidelines for how to implement AI in medicine. They discussed how algorithms are trained and appropriate diversity was included in that.

Action

The Executive to circulate guidelines for how to implement AI in medicine among SCAAC members.

6.14. Members contested as to whether timelapse incubators such as Embryoscope are currently considered to be using AI. Some decision-making algorithms are programmed by manufacturers, not AI and so currently most timelapse incubators are not learning. Some members considered that static AI and that AI is used increasingly in timelapse imagers.

6.15. Members agreed that SCAAC needs to be careful to have clear definitions and some limits about what is included in discussions.

6.16. One member wanted SCAAC to focus less on defining whether something is AI and more on what it is being used for, particularly what claims clinics are making to patients, how it is being sold and charged for.

6.17. The Chair summarised that AI is here to stay, is a growing industry and has been shown to perform certain clinical functions favourably when compared to clinicians such as diagnostics. The remit of SCAAC should be to filter what is being offered to fertility patients and examine claims on effectiveness and safety so patients are given accurate information to inform their choices.

6.18. One member stated that it would be unproductive for the group to spend too much time focussing on what AI is and what the algorithms are but instead focus on the technique that is being charged to patients e.g., sperm/egg/embryo selection.

6.19. The rapid development of AI is a challenge for all health regulators. At the HFEA, the inspectors in particular are finding it difficult to look at algorithms and the results of algorithms. AI is already being sold to patients as an advanced tool, greater than relying on a clinician's experience, but not all data behind algorithms are being published. Commercial and academic organisations are approaching the HFEA for access to register data with the intention not to publish how an algorithm is developed but to make money from the algorithm which uses HFEA data.

6.20. How effective Embryoscope models are for each clinic is dependent on what data they have been worked up on e.g., is the type of culture medium consistent. There may be also flaws in models that use historical data when there is variation in policies and practices over that time.

7. Fertility Trends Report

7.1. Nora Cooke-O'Dowd presented the findings of the annual Fertility Trends Report. The report looked at changed over the last 30 years.

7.2. Birth rates per embryo transfer have increased for all age groups under 43 and have tripled overall.

7.3. Multiple births have decreased following the triple embryo transfer restrictions then the 'One at a Time' campaign. The target of 10% was reached in 2017 and the rate is now 6%. In another report on ethnic diversity in fertility treatment, it was found that Black patients have higher multiple birth rates.

7.4. In 1991 most cycles were fresh cycles and since then the proportion of frozen cycles has been increasing. There was exponential growth in the number of cycles but that looks like it may be slowing in 2019.

7.5. The use of donor sperm initially increased then decreased with the use of ICSI. More recently donor sperm use has increased again for women in same-sex relationships or those without a partner. Donor egg use has continued to grow.

7.6. Older age groups have a much higher chance of success if they use donor eggs but only 17% of patients over 40 do so.

7.7. The age of women having children has increased. The percentage of cycles on patients over 40 has gone from 10% in 1991 to 22% in 2019.

7.8. There are huge differences in the funding available for patients in the UK. In Scotland, 62% of cycles are NHS funded compared to 23% in London. Under 35s have seen a significant decline in funding available.

7.9. One member noted that there are very few patients over 45 that are successful with their own eggs and the age brackets and figures displayed may be misleading patients who are 46 or over into thinking they have a higher chance than they do. The cases in the 45+ age group will likely comprise mostly patients who are 45, 46 at most, plus data entry errors.

Action

Intelligence team to consider the age brackets used.

7.10. One member suggested that it would be helpful for those looking to compare their chances of success when using their own eggs versus donor eggs if they were shown sample size for each as the number of treatments using donor eggs is much smaller.

7.11. The disparity in NHS funding nationally is a concern. Journalists have contacted Fertility Network concerned that among the problems that the NHS is currently facing, fertility funding may be the first thing to be cut following reviews.

7.12. Preimplantation genetic testing for monogenic disease (PGT-M) numbers are included in absolute numbers each year but reporting success rates separately is a challenge as the patients are so

different. NHS England are wanting to know whether PGT-M is worth the investment as there is a lack of helpful statistics available to back up the provider's observations. There are hopes that the new register will be able to gather more helpful statistics such as cumulative success rates.

7.13. Having a way of presenting the cumulative chance of success from one stimulation cycle would promote good practice

8. Any Other Business

8.1. Robin Lovell- Badge presented a summary of the recently published guidelines from the Field of Stem Cell Research and Regenerative Medicine from the International Society for Stem Cell Research (ISSCR).

8.2. The guidelines are to provide guidance to scientists and reassure the public. They are more valuable in areas where there is less regulation, such as in the USA where there are no federal laws on stem cell research

8.3. They are based around common principles and cover everything from human embryo research to the derivation of human embryonic stem cells to use of stem cells in treatments.

8.4. A lot has changed over 5 years which has required extensive revisions including progress on in vitro derived gametes and the ability to derive structures that look like embryos from stem cells, in particular:

- Integrated stem cell models – include extraembryonic tissue so could develop more like an embryo and theoretically could implant.
- Non-integrated stem cell models - no extraembryonic tissues present so good for modelling aspects of development such as posterior development of the embryo.

8.5. The guidelines also discuss heritable human genome editing, mitochondrial replacement techniques and chimeras.

8.6. Considering all these developments the guidelines determine that there must be a specialised review and oversight process in place to look at experiments that may be of concern. There will now be the following categorisation:

8.6.1. **Category 1A – Exempt from review** e.g., most in vitro stem cell research

8.6.2. **Category 1B – Reportable to oversight Committee but does not necessarily need to be reviewed** e.g., non-integrated stem cell models

8.6.3. **Category 2 – Must be reviewed** e.g., in vitro culture of embryos for research.

- Human-animal chimeras can proceed but care must be taken, and the Committee may have strict rules over what animal can be used, how long it is to be gestated for and whether it can be born.
- Integrated stem cell embryo models are also in this category as they may mimic a human embryo. They are not the equivalent of a human embryo and so there is no time limit on how long they can be cultured. They are unlikely to develop normally if you were to transfer back into a human uterus (which is banned) but the potential of integrated stem cell embryo models means they must be reviewed and that could have an effect on the HFEA.
- Transferring human embryos after mitochondrial replacement techniques (MRT) into the human uterus is also included in Category 2, so far only done in the UK.

8.6.4. **Category 3A - Not allowed** because they are currently unsafe, have unresolved ethical issues or issues relating to public approval e.g., heritable genome editing and modifying mitochondrial DNA.

8.6.5. **Category 3B- Not allowed** because there is no scientific rationale and it is ethically very concerning and is unsafe e.g., gestating human embryo models or transferring chimeras to a human uterus.

8.7. Previously, guidelines stated that the culture of normal human embryos should stop at 14 days but now it is possible to culture embryos past that. Chimeric embryos have been cultured to 20 days which implies that it will be feasible to go beyond the current 14-day limit.

8.8. Going beyond the 14-day limit would give the opportunity of gathering much more information about human embryos but also allow validation of the stem cell embryo models. If they correspond well to human embryos, then regulators could recommend that the models were used instead of culturing human embryos after 14 days. Culturing embryos for longer than 14 days would allow information to be gathered on individual cell types e.g., what happens in germ cells, and has implications for heritable genome editing and MRT.

8.9. The ISSCR decided not to specify a limit on the culture of human embryos though this is conditional on:

8.9.1. Public engagement to establish public support for the experiments in that jurisdiction and;

8.9.2. The oversight of the specialised review process. There must be no alternatives such as validated models.

8.10. Genome editing techniques that do not give double-strand breaks in DNA, such as base-editing and prime-editing, look to be safer than those that make a double-strand break, but introducing genome editing components into an early embryo with any method is not safe enough yet and determining which embryos have only the correct edit is not yet accurate enough. If genome editing could be done in a precursor cell and then derive gametes, this could be a safer process.

8.11. Spermatogonial stem cells are a possibility, are close and human ones are possible. They could be manipulated in culture and transplanted to testes from which resident spermatogonial stem cells have been removed. That is something the HFEA needs to look at and consider how it should regulate it. If sperm are derived *in vitro* from genetically altered spermatogonial stem cells, then their use to fertilise eggs would fall under existing HFEA regulation (currently they would not be ‘permitted sperm’ and could only be used for *in vitro* research).

8.12. One member noted that public discussion of the culture of human embryos past 14 days may generate serious concern when the development of the heart and nervous system are considered. The presence of a beating heart, which can be used to confirm a viable pregnancy, may be troubling. It may be challenging to convince the public of the scientific rationale.

8.13. One member said that the importance of such research must be stressed e.g., implications for congenital heart disease or neural tube defects. It provides an opportunity to understand more about how congenital abnormalities develop which it could be seen to be unethical to ignore.

8.14. One member informed the Committee that the Wellcome Trust has put £10 million into promoting human embryology research and on the back of that they have begun work on public engagement.

8.15. If in vitro derived gametogenesis is ever successful, then has profound implications.

8.16. From the experience of the HFEA, support from the public has been greater where such research may offer potential treatments for serious conditions. Efforts at public engagement is often criticised but necessary. Public support is needed to generate political consensus for any change.

8.17. The HFEA is a trusted regulator, but the ISSCR noted that many countries do not have such a regulator. The guidelines were worded to discourage bad practice anywhere.

8.18. One member congratulated Robin Lovell- Badge on his award from the ISSCR relating to his work on public engagement. There is an obligation to engage in dialogue with the public and listen to the way people express their concerns.

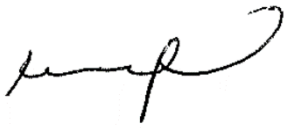
8.19. If stem cell embryo models get to the point where they can develop like a normal human embryo the HFEA will have to consider whether they regulate those experiments.

8.20. One member informed the Committee that ESHRE has set up a working group on add-ons which is considering a long list of add-ons. They asked that SCAAC reconsider whether complementary therapies should be considered as add-ons. The Chair said that the application form was now available for any additional add-ons to be considered by SCAAC.

8.21. The Chair summarised the meeting and thanked the Committee.

9. Chair's signature

I confirm that this is a true and accurate record of the meeting:

Signature: 

Date: 05/08/2021