Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

Monday 3rd October 2022, 11:00am – 3:30pm

Wandle room, 2nd Floor, 2 Redman Place, London, E20 1JQ

Authority members	Present	Tim Child (Chair) Frances Flinter Alex Kafetz
External advisors	Present	Richard Anderson Kate Brian Alison Campbell Yacoub Khalaf Robin Lovell-Badge Raj Mathur Scott Nelson Anthony Perry
	Apologies	Frances Ashcroft Zeynep Gurtin Jason Kasraie (Deputy Chair) Kevin McEleny
Members of the executive	Present	Sonia Macleod (Scientific Policy Manager) Victoria Askew (Meeting lead and Policy Manager) Ashley-Anne Brown (Meeting secretary and Scientific Policy Officer) Peter Thompson (Chief Executive) Julia Chain (Chair) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Ana Hallgarten (Public Policy Manager) Rachel Cooper (Legal Adviser) Zoe Constable (Policy Manager)
Invited speaker	Present	
Observers	Present	

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. Declarations of interest were received from Tim Child, Alison Campbell, and Scott Nelson.

1.3. Apologies were received from Zeynep Gurtin, Kevin McEleny, Frances Ashcroft, and Jason Kasraie.

2. Matters arising

2.1. Minutes of the meeting held on 6th June 2022 were agreed prior to the meeting.

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

2.3. Assessment of further outputs for the impact of the microbiome and if it needs to be considered as a treatment add-on have been moved due to internal resourcing restrictions to June 2023.

2.4. The Committee was asked to highlight and circulate relevant papers about public health impacts on fertility, assisted conception, and early pregnancy. The Committee discussed this in the 'relevant public health developments' agenda item of this meeting.

2.5. The impacts of stress on fertility treatment outcomes, and more specifically, potential stress management tools, should remain a medium-priority topic of the SCAAC. This will be considered by the Executive when creating the SCAAC 2023/24 work plan, to be presented at the February 2023 meeting.

2.6. Following discussions and decisions regarding the application of the addition of androgen supplementation as a treatment add-on Committee members expressed concern over the language used within treatment add-ons eligibility criteria. Amendments made by the Executive will be presented to SCAAC members at the February 2023 SCAAC meeting.

2.7. Following recommendations from the Committee to the Authority that in the absence of good and robust randomised controlled trials (RCTs) or meta-analyses, expanding the evidence base may be necessary and helpful when assigning treatment add-on ratings. This recommendation was taken to the July 2022 Authority meeting. A decision tree on the evidence base was presented to the Committee in the present meeting under the add-ons agenda item.

3. Chair's business

3.1. The Chair thanked Yacoub Khalaf for his seven years of service on the SCAAC committee as a previous Chair of SCAAC, HFEA Authority member, and recent SCAAC External Advisor.

3.2. The Chair highlighted the SCAAC 2023 meeting dates: Monday 6th February, Monday 5th June and Monday 2nd October.

4. Relevant public health developments

4.1. The Chair summarised that following the June 2022 committee meeting this standing item was expanded from monitoring the impact of COVID-19 on fertility, assisted conception and early pregnancy, to public health developments relevant to fertility treatment and embryo research.

4.2. The Chair noted that Committee members had submitted one paper for this agenda item titled the 'Epigenetic Risks of Medically Assisted Reproduction'. However, given that the paper was highlighted just prior to the meeting, many members may not have had the opportunity to read it.

4.3. The Executive highlighted two papers that the HFEA would like the SCAAC Committee's views on:

4.4. *The risk of hypertensive disorders in pregnancy after fresh and frozen embryo transfer in assisted reproduction*

- A member commented that the increased risk of hypertensive disorders in pregnancy following frozen embryo transfer has been a consistent finding within scientific literature. They noted a 3 in 100 baby risk and stated that absolute risk is key. They discussed a rise of 'natural' unmedicated cycles.
- The Chair highlighted a major limitation within the paper; despite demonstrating a link between frozen embryo transfer and hypertension, there is no record of whether frozen cycles were 'natural' or medicated. However, the Committee suggested that it is well known that medicated frozen cycles carry more risk than fresh IVF cycles. A member responded that despite this, the association of an increased hypertensive disorder risk in pregnancy resulting from frozen embryo transfers is still an important finding clinically.
- A member added that the findings on the association of an increased hypertensive disorder risk in pregnancy after frozen embryo transfer compared to fresh embryo transfer or spontaneous conception, highlight the importance of reducing the risk of hypertensive disorders that may be contributing to pre-eclampsia incidence.
- Another member noted that a unified consent form could be developed with the European Society of Human Reproduction and Embryology (ESHRE) or American Society for Reproductive Medicine (ASRM), ensuring patients are told about the risks associated with medicated frozen cycles compared to non-medicated frozen cycles.

Action: Consider including information for patients on the HFEA website about additional risks of treatment related to hypertension in pregnancy following frozen embryo transfer in medicated cycles of fertility treatment.

4.5. *Cancer in children born after frozen-thawed embryo transfer*

- The Committee discussed the key clinical findings of the paper in addition to its strengths and limitations. Members highlighted that despite the study using an extensive dataset, it spanned several decades; this has implications when considering changes in laboratory practices, such as differences in the cryoprotectants used.
- The Committee discussed how these findings related to a previous cohort study that found increased liver cancer risks in babies born from IVF. A member stated that from a laboratory

perspective, patients had not yet contacted them regarding concerns from the findings in this study.

- A member cautioned that a quarter of the babies in this study resulted from multifetal pregnancies, which is significantly higher than expected currently.

4.6. The Committee did not recommend that the HFEA to provide any additional patient or clinic information on these findings at this point.

5. Update on treatment add-ons

5.1. The Scientific Policy Manager provided an update to the Committee on the evidence base to be included when reviewing the HFEA's traffic light-rated list of treatment add-ons.

5.2. The Scientific Policy Manager highlighted that at the July 2022 Authority meeting, it was agreed that the HFEA would:

- Change the presentational aspect of treatment add-ons using a five-category system.
- Include additional outcomes other than live births.
- Expand the evidence base used to rate add-ons in line with SCAAC's recommendation from the June 2022 meeting.
- Implement new criteria for the HFEA to use to aid SCAAC when rating add-ons. The following two criteria items are under development and will be used at the February 2023 SCAAC meeting when add-ons are rated with the new system for the first time.
    - Where evidence of effectiveness for the use of the treatment in a clinical setting is lacking or absent.
    - Where patients need unbiased information about the effectiveness and risks of this treatment.

5.3. The Scientific Policy Manager summarised the next steps for treatment add-ons as follows:

- Develop treatment add-ons webpages, including information about criteria used by HFEA when rating treatment add-ons and carry out user acceptance testing.
- Amend the Consensus Statement in conjunction with the treatment add-ons working group (TAG).
- Externally review relevant papers ready for SCAAC to consider.
- Develop decision tree to aid SCAAC when rating add-ons with input from SCAAC, to be reviewed in the current meeting.
- Rate the add-on using the new system at the February 2023 SCAAC meeting.

5.4. The Scientific Policy Manager introduced the draft evidence decision tree to help SCAAC when considering the available evidence for rating an add-on, developed to reflect the ranking systems of other organisations, such as the National Institute for Health and Care Excellence (NICE).

5.5. SCAAC members raised concerns about using only one external reviewer and queried if there could be two or three reviewers. Members discussed the importance of consistency between

external reviewers, they noted that for less experienced reviewers it would be valuable to have at least two individuals reviewing, but in the case of a very experienced external reviewer one person would be sufficient.

5.6. The Committee discussed the role of cost and effectiveness of a treatment when rating add-ons and if these factors should be considered when ranking. Members then discussed costs associated with add-ons and the sector as a whole. It was highlighted that the HFEA is not a costs regulator.

5.7. The Director of Strategy and Corporate Affairs reminded members that the initial decision for which add-ons would be rated by SCAAC were those that the Committee had felt patients most needed information rather than those most prevalent in practice. The Policy Manager reminded members that the add-ons list is not exhaustive and will continue to develop.

5.8. A member commented that the decision tree was good but ultimately skewed towards the grey category and stressed the importance of a feedback mechanism for add-ons rated grey to be reassessed at set time intervals. Another member echoed worries about too many add-ons becoming grey.

5.9. A member questioned if three RCTs was a number decided based on evidence or followed the process of other organisations such as NICE. The Scientific Policy Manager stated that the decision tree reflected the current processes followed by other relevant organisations. The Scientific Policy Manager concluded that three RCTs are not enough in isolation, hence the quality control step within the decision tree and said that information presented to patients could be tailored to clearly explain the quality of the evidence by which the add-on is being assessed.

5.10. Another member stressed the importance of maintaining the live birth rate at the top of the outcomes list and that live birth rate (LBR) was not the same as the ongoing pregnancy rate (OGPR). The Committee then discussed the appropriateness of OGPR. The Committee spoke on how OGPR is understood by patients and how it differs from LBR. They concluded that if the pregnancy rate was based on those 10-11 weeks post-transfer – this was an acceptable outcome only in the absence of LBR. The Committee also concluded that an add-on should not be rated green without at least one RCT using LBR as an outcome.

5.11. The Committee discussed the importance of robust biological mechanisms and biological plausibility underlying the studies supporting add-ons. A member stated that although biological plausibility is desirable, it was not, in their opinion, essential. The Scientific Policy Manager highlighted that biological plausibility would not be appropriate for all add-ons given the diverse list of treatments.

Action: The Committee agreed on the decision tree. The Committee discussed that live birth is the desired outcome to assess add-ons; however, in the absence of an RCT with LBR as an outcome, OGPR should be considered only when at least 10-11 weeks post-transfer, and in these instances, this should clearly be stated on the HFEA website.

6. Scientific considerations relevant to the '14 day rule'

6.1. The Chair welcomed guest speaker and SCAAC member Professor Robin Lovell-Badge.

6.2. Professor Lovell-Badge presented an overview of the scientific considerations relating to the 14-day rule.

7. Artificial Intelligence (AI)

7.1. The Policy Manager presented a literature review on the use of AI in the fertility sector.

7.2. The HFEA has been considering issues over the use and regulation of AI in the fertility sector for some time. The Committee last discussed the topic at the June 2021 meeting. The Committee raised concerns about how the technology is being used and charged for and that it may be necessary to consider the scope and definition of AI.

7.3. A literature review identified twenty-three studies published in 2022. These papers summarise the recent research developments, including using AI to inform patient pathways, increased clinic efficiency, improve embryo grading, and predict ploidy status. The paper also covers recent policy developments, including the publication of the MHRAs future regulation of medical devices consultation, which included software as a medical device, and the publication of the Office for AI's regulation of AI policy position paper.

7.4. A member asked about the HFEA's regulatory remit regarding AI regulation and how this translates to laboratory and clinical practices. The Policy Manager responded that the HFEA regulates clinics undertaking licensable activities. Processes are then approved to undertake these licensable activities, so called authorised processes. However, the way in which clinics should undertake these authorised process is not specified.

7.5. The Policy Manager used the example of the morphological grading of embryos. This authorised process could include the manual grading of embryos using visualisation of the embryo under a microscope, or using an image or video captured by a camera assessed in an AI model. The Policy Manager then highlighted that it is likely that the Executive will need to identify when authorised processes are sufficiently different using AI and pose sufficiently different risks so that it can be thought of as a new process entirely.

7.6. The Policy Manager highlighted that the HFEA is discussing AI with other regulators experiencing the same challenges in terms of regulation and scope, such as the Care Quality Commission (CQC). The Policy Manager addressed the need for guidance from central government via the white paper to be released by the Office for Artificial Intelligence (OAI) on the national position on AI regulation.

7.7. A member voiced their thoughts on AI becoming a form of treatment add-on over time. Another member agreed with others and stated that SCAAC should take caution, but AI should also be embraced. They continued to voice that if the data used to train these AI models is high-quality, the patient impact should be positive.

7.8. A member shared a summary of their recent attendance at the AI Fertility Society conference. The main themes shared at this conference were:

- Embryo selection, predicting viability, ploidy, LBR, Clinical pregnancy rate; via morphokinetics, genetics.
- Sperm selection.
- Robotics such as for egg collection.
- How to develop the perfect model.

7.9. A member asked what the Authority's view was on clinics using AI technology as part of a trial for a set amount of time in their clinical processes and if this needed to be communicated to the HFEA. The HFEA Chief Executive said that if these methods are currently authorised by the HFEA for use at the clinic these processes are, for the most part, fine.

7.10. A member stated that AI could be separated into new ways of doing old things and new ways of doing new things, and it is the latter that we should be focusing on. The member then gave industry examples of AI use where the HFEA should or should not be concerned based on our regulatory remit. They highlighted the importance of assessing new techniques and understanding the evidence. A member suggested that the HFEA should form a set of principles around AI.

7.11. Two members stated they would be open to assisting with this work and could recommend others in this field that could be of service.

7.12. The Policy Manager highlighted an upcoming meeting between the HFEA and the Medicines and Healthcare products Regulatory Agency (MHRA) about AI technologies that do not fall within our remit but impact patients and who may oversee the regulations of these technologies.

7.13. A member suggested a Clinic Focus article for AI aimed at clinics in the future.

Actions:

- Consider a framework for assessing AI technologies which fall within the regulatory remit of the HFEA.
- Publish a Clinic Focus article for the sector on developments in the regulation of AI

8. Any other business

8.1. The Chair noted that given the lack of time given to members to read the paper titled Epigenetic Risks of Medically Assisted Reproduction, it would be best if an email discussion about the paper were to occur once members have had time to read it. A member concluded that this paper would serve as good background information for Committee members less familiar with the subject matter.

8.2. The subject of preimplantation genetic testing for polygenic disorders (PGT-P) was raised by a member, and discussions were had around the rising frequency of PGT-P. A member highlighted the European Society of Human Genetics position statement on PGT-P.

9. Chair's signature

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

Signature

Chair: Tim Child

Date: 9.12.2022