Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

11th October 2021

Teleconference (Zoom meeting)

Authority members	Present	Tim Child (Chair) Gudrun Moore (Deputy Chair) Jason Kasraie Yacoub Khalaf	Anne Lampe
External advisors	Present	Richard Anderson Jane Blower Kate Brian Daniel Brison Andy Greenfield Joyce Harper Sheena Lewis Robin Lovell-Badge Kevin McEleny	Shankar Srinivas
	Apologies	Raj Mathur	
Members of the executive	Present	Peter Thompson (Chief Executive) Julia Chain (Chair) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information) Sonia Macleod (Scientific Policy Manager) Victoria Askew (Meeting lead and Policy Manager) Ana Hallgarten (Meeting secretary and Scientific Policy Officer)	
Invited speaker	Present	Andy Vail (University of Manchester) Sebastiaan Mastenbroek (University of Amsterdam)	
Observers	Present	Amber Haywood (Policy Intern - HFEA) Csenge Gal (Department of Health and Social Care)	

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. The previous Chair, Yacoub Khalaf, handed over to Tim Child as the incoming Chair of the committee.

1.3. Apologies were received from Raj Mathur.

1.4. Declarations of interest were received by Sheena Lewis, Jane Blower, Daniel Brison, and Yacoub Khalaf.

2. Matters arising

2.1. Minutes of the meeting held on 7th June 2021 were agreed remotely prior to the meeting.

2.2. The Policy Manager updated the Committee on the matters arising from the meeting:

2.2.1. The Committee was asked to highlight and circulate relevant papers about the effects of COVID-19 on reproduction and early pregnancy. This continues to be a standing agenda item.

2.2.2. Suggestions made regarding a decision tree in the application form for new HFEA traffic light rated treatment add-ons will be considered as part of work being undertaken to review the current traffic light rating system.

2.2.3. Following the approval of Endometrial Receptivity Array (ERA) to be included in the HFEA's traffic light rated list of treatment add-ons, an evidence review was completed by an independent reviewer. All relevant published papers were circulated prior to the meeting and form part of the agenda items 6 and 7 of this meeting.

2.2.4. The Executive requested that relevant work and papers in the field of AI in medicine should be emailed for circulation to all SCAAC members

2.2.5. The Intelligence team has been informed about SCAAC's comments regarding the age brackets that are used in the fertility trends reports and will consider this in future reports.

3. Chair's business

3.1. The Chair thanked Joyce Harper and Sheena Lewis for their tenure on the SCAAC, and for their expert advice and influence.

3.2. The Chair welcomed Sonia Macleod (Scientific Policy Manager- Maternity Cover) and Ana Hallgarten (Scientific Policy Officer) as new members of the HFEA Executive.

4. SCAAC governance

4.1. The HFEA Chief Executive and Chair presented the proposed updates to the governance of the committee. SCAAC is a unique committee within the HFEA as it is made up of Authority members as well as external advisors. Currently, the HFEA Standing Orders allow up to five Authority members and up to 11 expert advisors form the committee. Given the range of topics examined by SCAAC it was considered that although it is a large committee it is the correct size, as it allows for a range of people with necessary specialist expertise.

4.2. At present SCAAC members have terms of up to three-years which can be renewed. It is proposed to be limited to a maximum of two terms. Former members can be invited back as expert speakers to participate when there are items of particular interest and expertise. Once the terms of current members who have been part of SCAAC for six years or more come to an end, new members will be appointed to allow SCAAC membership to change gradually.

4.3. The Chief Executive noted the importance of balancing expertise on the Committee as memberships are renewed. Expertise of particular interest included AI and statistical methodologies. A proportion of members should be experts who are active both clinically and in research and within the NHS and private clinics.

4.4. The application process for new SCAAC members will include an open recruitment process to allow for interested parties to apply.

4.5. It was proposed that SCAAC meetings should continue as private meetings. Nonetheless, more efforts need to be made to publicise and draw attention to the work that is done by SCAAC. Suggestions included sharing minutes and the progress of SCAAC to the fertility sector generally, and to include summaries as part of regular HFEA newsletters, Clinic Focus.

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

5.1. The Chair acknowledged the 14 reports, papers and guidelines that had been submitted, shared, and discussed with the Committee in previous meetings. There were no new reports circulated to discuss at this meeting.

5.2. A dedicated webpage has been created with all the relevant literature for professionals to access. The importance of spreading information regarding the effects of COVID and the vaccine on fertility and health is considered of key importance by SCAAC. Work from other groups including Fertility Network UK, the British Fertility Society (BFS), and the Association of Reproductive and Clinical Scientists (ARCS) was highlighted.

Action: The Committee will continue to monitor and share relevant literature. They will review early pregnancy data and live birth rates at the next SCAAC to see the effect of treatment cessation and delay caused by COVID-19.

Additional promotion of the HFEA webpage regarding the effects of COVID-19 on fertility, assisted conception, and early pregnancy should take place.

6. Review of traffic light rating for treatment add-ons

6.1. The Policy Manager gave the background of the HFEA's traffic light rated list of treatment add-ons and defined the Committee's task.

6.2. The Committee were reminded that traffic light ratings are reviewed regularly to determine any effect of newly published randomised controlled trials (RCTs). Traffic light ratings reflect the evidence that a treatment add-on increases live birth rate. Advice for patients about outcomes other than live birth rate or any safety considerations should be considered in line with significant outcomes highlighted by the independent reviewer in their assessment of published RCTs.

6.3. If at any point the Committee recommend that a treatment add-on should be given a green rating, then a new page will be created on the treatment options webpage of the HFEA website. The committee should use their expert opinion and the evidence base to recommend information for inclusion on this new webpage. A link will then be available from the treatment add-ons page to the new webpage for a period of time to raise awareness of the new web-page.

6.4. For this meeting, new RCTs were identified for six treatment add-ons and these were assessed by the independent reviewer.

6.5. Members were asked to:

6.4.1. consider the quality of evidence for each treatment add-on based on the findings from the independent assessor in Annex A; and

6.4.2. agree and recommend traffic light categories for each treatment add-on based on the outcome of live birth rate; and

6.4.3. recommend information about outcomes other than live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome) to be included on the HFEA website for each of the treatment add-ons

Artificial egg activation calcium ionophore - Current rating: Amber

6.6. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.7. SCAAC Recommendation: **Remain Amber**

Assisted hatching - Current rating: Red

6.8. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.9. SCAAC Recommendation: **Remain Red**

Elective freeze-all cycles - Current rating: Amber

6.10. Three new RCTs were reviewed by the external reviewer, who explained his recommendation of an amber rating. Committee members noted that the possible benefits of the technology for reducing ovarian hyperstimulation syndrome (OHSS).

6.11. The Policy Manager reminded the members that at present the traffic light rating system is based on live birth rates, rather than other considerations such as safety.

6.12. The Committee recommended that further clarification was needed on the 'Elective freeze-all cycles' web page, so that patients would be aware of its use as a treatment to reduce the risk of ovarian hyperstimulation syndrome.

6.13. SCAAC Recommendation: **Remain Amber**

Action: Increase messaging about elective freeze-all cycles reducing the risk of OHSS and not reducing patient chances of success.

Endometrial receptivity array (ERA) – Current rating: N/A

6.14. ERA's inclusion in the treatment add-on list was agreed at the June 2021 SCAAC meeting.

6.15. A 10-year literature review was performed to identify any RCTs published, with one being identified. The independent reviewer recommended an amber rating for this treatment add-on. The independent reviewer discussed that the rating for ERA should only be amber or red, as a

green rating requires more than one study that shows positive results. The independent reviewer discussed that the RCT identified was not a high-quality study, due to the early randomisation, and the low number of initial participants that reached the embryo transfer stage. Additionally, the results were non-significant with wide confidence intervals. Nonetheless, the results of cumulative birth were on the promising side, leading to the amber recommendation.

6.16. As there was only one RCT, that was not high-quality, the Committee instead agreed on a red rating, stating that further research in the form of a good quality RCT showing a positive effect would be necessary for an amber rating.

6.17. SCAAC Recommendation: **Red**

Endometrial scratching - Current rating: Amber

6.18. Six new RCTs were identified since the last review in 2020. The reviewer recommended that endometrial scratching should remain amber, or change to a green rating, depending on the Committee's view on the biological plausibility of the timing affecting the impact of this treatment.

6.19. The independent reviewer noted work that was not included in the HFEA analyses, and that there had been an updated Cochrane review. Of the RCTs that he had analysed and were circulated to SCAAC, the results were almost statistically significant, with a 93-94 confidence interval. The gain in live births was found to be between 2 to 3 percentage points, however it was noted that the treatment was shown in some RCTs to show side effects including pain and bleeding.

6.20. The independent reviewer split the trials with one group examining IUI and natural cycles (excluding embryo transfer cycles) and one group examining IVF and ICSI. Endometrial scratching is performed at different times in the cycle between these two groups, therefore the trials were proposing different hypotheses. The independent reviewer stated that there had been several high-quality RCTs looking at IVF and ICSI cycles which consistently estimated odd ratios of between 1 and 1.4. When additional studies from this year were added, the results reduce the confidence intervals and showed a statistically significant benefit. He noted that the Cochrane review excluded the Rodriguez study due to its use of unconcealed allocation.

6.21. The Committee spoke about the need for further work given that none of the studies individually showed effectiveness, the need for more statistical significance, and because of the uncertainty around the biological plausibility of the timing. It was noted that the Cochrane review concluded that evidence does not support the routine use of endometrial injury for women undergoing IVF. It was noted that it was unlikely that such research would take place soon, although a significant piece of meta-data analysis was expected to be published imminently. Due to these concerns, the Committee agreed that endometrial scratching should remain amber in all cases.

6.22. The Policy Manager asked whether any comments on the information related to the safety or risks of endometrial scratching should be distributed online, given the independent reviewer's comments on associated bleeding and pain. The Chair highlighted the information available from the Cochrane review online. The Committee agreed that increasing patient knowledge is important and it was recommended that biological plausibility be assessed.

6.23. SCAAC Recommendation: **Remain Amber**

Action: Increase information about Endometrial Scratching on HFEA web page to increase patient knowledge.

Hyaluronate enriched medium - Current rating: Amber

6.24. One additional high-quality RCT was identified since the last review in 2020 and the independent reviewer recommended that the rating remains amber.

6.25. The Committee noted that although it may have promising benefits, further significant RCTs would be required to confirm beneficial effects to rate the treatment add-on as green. The Cochrane review was discussed given that it suggests that use may be linked to a higher birth rate. It was noted that an amber recommendation would be at odds with the conclusion of the Cochrane review. However, the authors conclusion in the Cochrane review states that the evidence was of moderate quality and that further studies with single embryo transfer need to be undertaken.

6.26. The Chair indicated that an RCT for hyaluronate enriched medium would soon be published. SCAAC will consider any published data as part of future reviews intro treatment add-ons.

6.27. SCAAC Recommendation: **Remain Amber**

Intracytoplasmic morphologic sperm injection (IMSI) - Current rating: Red

6.28. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.29. SCAAC Recommendation: **Remain Red**

Intrauterine culture - Current rating: Red

6.30. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.31. SCAAC Recommendation: **Remain Red**

Physiological intracytoplasmic sperm injection (PICSI) - Current rating: Red

6.32. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.33. SCAAC Recommendation: **Remain Red**

Pre-implantation genetic testing for aneuploidy (PGT-A) Day 5 - Current rating: Red

6.34. No new RCTs identified since the last review in 2020 so no new recommendation was given.

6.35. Members of the Committee commented that PGT-A Day 3 is currently being used in other countries, and that a few years ago complaints had been raised to the HFEA in regard to the red rating of PGT-A Day 5. The Policy Manager confirmed that the treatment add-on is presented as PGT-A on the HFEA website, rather than specifying Day 3 or 5.

6.36. SCAAC Recommendation: **Remain Red**

Immunological tests and treatments - Current rating: Red

6.37. Following the 2020 review it was recommended that immunological tests and treatments should be split into three different traffic light ratings. At the time the Committee felt the information available for each group was not thorough enough to make that recommendation.

6.38. The Policy Manager presented how the wording and information for each category of immunological tests and treatments had been updated on the HFEA website and asked whether the Committee wanted to make recommendations regarding the specific ratings at this point.

Steroids - Current red rating under the umbrella term of immunological tests and treatments

6.39. The independent reviewer reviewed nine RCTs, recommending a change in the rating to amber.

6.40. Members of the Committee were concerned that some of the studies were not immunological treatments, and that the results were small and contradictory. Additionally, there were discussions regarding having androgens and glucocorticoids in the same group, and that potentially an additional category should be considered. They noted that there was a separate question arising regarding the use of steroids prior to fertility treatment rather than as a treatment add-on.

6.41. SCAAC Recommendation: **Remain Red**

Action: Consider androgen supplementation as a separate treatment add-on from immunological tests and treatments.

Intravenous immunoglobulins - Current red rating under the umbrella term of immunological tests and treatments

6.42. The independent reviewer commented on the two RTCs published since the last review. Both studies were very small, and although they both gave small estimates in favour of the treatment, they both had a wide confidence interval; therefore, a red rating was recommended.

6.43. SCAAC Recommendation: **Remain Red**

Intralipids - Current red rating under the umbrella term of immunological tests and treatments

6.44. Three new RCTs were identified. The independent reviewer explained that although the studies were all small, and not of the highest quality, they did show small benefits. As the treatment had not been rated before, these studies indicated a possible amber rating.

6.45. Although the Committee noted the benefits presented by the studies, the RCTs were not considered to be reliable enough for an amber rating. The independent reviewer agreed.

6.46. SCAAC Recommendation: **Remain Red**

Time-lapse imaging and incubation - Current rating: Amber

6.47. One new RCT was identified since the last review in 2020. However, the study was a published protocol that did not present new evidence or data. The independent reviewer noted that a high-quality study is currently in recruitment.

6.48. SCAAC Recommendation: **Remain amber**

Additional comments regarding treatment add-ons:

6.49. Concerns were raised considering the low number of RCTs taking place for treatment add-ons due to lack of funding. Therefore, patients may pay for a treatment that is being done as part of research into the treatment's effectiveness. The ethics of some of these technologies were questioned, as were the possible financial and psychological harms.

7. Update on evolving the treatment add-ons information

7.1. The Scientific Policy Manager (SPM) discussed the development of the treatment add-ons information, and discussions that had taken place at the September 2021 Authority meeting.

7.2. First, it was considered important to determine whether to evolve the presentation of the traffic light rating system for treatment add-ons.

7.3. Second, the Authority were asked to consider broadening the range outcomes that the HFEA uses when assigning ratings to treatment add-ons. At present the patient outcomes are restricted to live birth rate only but could be extended to include reduction in miscarriage rates, reduction in time to pregnancy, or decreased risk of OHSS. The SPM also raised whether only RCT data should be using when assigning ratings to treatment add-ons.

7.4. The SPM noted the difficulty in condensing the large amounts of treatment information into a system that is easy for patients to understand. The system must be simultaneously simple but also show nuance. It is essential to establish what information patients should be receiving in order to make informed decisions.

7.5. Members of the SCAAC supported considering the use of more varied data when assigning ratings to treatment add-ons. Many of the RCTs that are analysed do not use live births results in their research, therefore it would be beneficial to establish what additional data is useful in treatment add-on decisions. Despite positive responses to the use of more 'real world evidence' and big data, concerns were also raised that non-RCT data would lower the current HFEA standards of good evidence and good practice in thorough scientific research.

7.6. It was emphasised that the process of evolving treatment add-ons is in its early stages and that this information is only an overview of what the Authority wants to consider. Consultations with clinics and the public will be undertaken to better establish how the current traffic light system could be improved, and further discussion with SCAAC will take place.

8. New technologies in embryo testing including PGT-M and PGT-A – literature review

8.1. The Policy Manager welcomed the guest speaker Dr. Sebastiaan Mastenbroek from the University of Amsterdam to speak on new technologies in embryo testing.

8.2. The guest speaker introduced his work in IVF and presented his research on the use of morphology analysis of embryos in IVF. Morphological analysis is done to rank embryos for transfer, so that the embryo that is most likely to implant successfully is transferred first. Examples of embryos that would rank poorly on a scale and therefore be discarded included those where growth had arrested, or embryos that had not fertilised correctly. Although using morphological observations does not guarantee a successful pregnancy, it has been shown to work as an accurate tool for ranking embryos.

8.3. The speaker then discussed additional tests that are sometimes applied to perform 'additional discarding'. For example, Pre-implantation Genetic Testing for Monogenic disease (PGT-M) results in fewer embryos that will be available for transfer, as only those with a good morphology and without the monogenic condition will be possible candidates for transfer. He emphasised the need for any additional tests to be accurate, as inaccurate tests can lead to healthy embryos being incorrectly removed from the cohort that could have led to a live healthy birth.

8.4. When considering embryo selection, the speaker presented the different goals that exist: increasing IVF effectiveness, preventing disease, or selecting for traits.

8.4.1. IVF effectiveness can be improved by a range of technologies including morphology screening, timelapse algorithms, non-invasive cell free DNA tests, and Pre-implantation Genetic Testing for Aneuploidy (PGT-A). These technologies all have the goal of increasing IVF effectiveness, and it is hoped that Artificial Intelligence and big data will allow for a further improvement of these technologies. However, none of these tests are 100% accurate and can only be used for ranking embryos. As these methods are labour intensive and expensive, it is important that they provide tangible benefits.

8.4.2. Two possible technologies can be applied to select against genetic conditions in future children: Pre-implantation Genetic Testing for Monogenic disease (PGT-M) and Pre-implantation Genetic Testing for Structural Rearrangements (PGT-SR). As embryos with a poor morphology and presence of the genetic condition will need to be discarded, in most cases there will be the need for additional IVF cycles.

8.4.3. Additional questions are raised by the use of technologies to select for traits in future children such as the use of Pre-implantation Genetic Testing for Polygenic Conditions (PGT-P). The speaker questioned whether it would be the morphology analysis or the PGT-P scores that would be considered more important. The technology has a lower treatment efficiency level as high numbers of embryos may be discarded, therefore leading to a need for additional cycles. Difficult choices will arise, as prospective parents have to decide between implanting an embryo with poor morphology but lower risk of inheriting undesired traits, or implanting an embryo with a better morphology (and therefore a higher chance of a successful pregnancy) but with a 'poorer' PGT-P score. The speaker noted that the use of PGT-P is not permitted in the UK, but earlier this year it was announced that a baby had been born following a polygenic risk score analysis in the USA. The parent of the child compared the use of the technology to preventing disease. This reflects the marketing of companies that are promoting this technology. It is likely that there will be many prospective parents who may want to access this technology.

8.5. Members of SCAAC were particularly concerned with the use of PGT-P to select for or against specific traits. They commented on problems that may emerge with misdiagnosis, the marketing that is taking place surrounding the technology, and the lack of discussion that is presented to prospective parents about the role of both nature and nurture. In addition to these ethical concerns, there were additional apprehensions towards who would be able to access the technology.

8.6. The members also acknowledged that such technologies are likely to be self-limiting both due to the high cost of the technology, and the low number of embryos that would be available for transfer when being highly selective.

9. Any other business

9.1. The annual review of Committee effectiveness is to be carried out after the meeting. Members will receive an email to gather their responses.

9.2. The Chair gave a final thanks to Joyce Harper and Sheena Lewis for their roles in SCAAC.

9.3. The Chair summarised the meeting and thanked the Committee and the guest speakers.

10. Chair's signature

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

Signature Chair: Tim Child

Date: 02/12/2021