Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

19th October 2020

Teleconference (Zoom meeting)

Authority members	Present	Yakoub Khalaf (Chair) Gudrun Moore (Deputy Chair) Sally Cheshire Kate Brian Ermal Kirby Anne Lampe Ruth Wilde	
External advisors	Present	Richard Anderson Jane Blower Andy Greenfield Robin Lovell-Badge Raj Mathur Kevin McEleny	Daniel Brison Joyce Harper Sheena Lewis Shankar Srinivas
Members of the executive	Present	Dina Halai (Meeting lead and Scientific Policy Manager) Matthew Mudford (Meeting secretary and Scientific Policy Officer) Victoria Askew Laura Riley Clare Ettinghausen Peter Thompson Rachel Cutting Cora Sweet Karan Dyal Jane Darragh Bernadette O'Leary	
Invited speaker	Present	Andy Vail (University of Manchester)	
Observers	Present	Sarah Lensen (in collaboration with the Victorian Assisted Reproductive Treatment Authority (VARTA)) Steve Pugh (DHSC)	

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed the Committee members to the meeting. The only apology was from Richard Scott who will be stepping down from the Committee, having accepted a more senior position at Genomics England. The Chair welcomed the new Scientific Policy Officer to the role and congratulated the Policy Manager on her promotion.

2. Matters arising

2.1. Minutes of the meeting held on 8th June were agreed remotely prior to the meeting.

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

2.2.1. Updates on the COVID-19 research that utilise the HFEA register, including the application that has been approved, are in Appendix A of the Matters Arising paper.

2.2.2. SCAAC has agreed to monitor the effects of COVID-19 on reproduction and early pregnancy and to circulate relevant research publications to members. Monitoring the literature and discussing the findings is to be a standing agenda item.

2.2.3. The HFEA treatment add-ons pages had been updated since the last meeting and the Committee was informed of these updates via email.

2.2.4. In line with the recommendation from SCAAC, the Statutory Approvals Committee (SAC) made the decision not to approve the novel process application for the intrauterine AneVivo device in inter-partner and standard egg donation. The minutes of the SAC meeting are included in Appendix B of the matters arising paper.

2.2.5. The Committee has been informed via email of the recent extensions to statutory storage limits for treatment and/or research purposes under new Coronavirus regulations.

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

3.1. The Chair acknowledged the five reports, papers and guidelines that had been submitted and shared with the Committee prior to the meeting.

3.2. The Chair viewed the data as work in progress. The Committee agreed that the evidence presented was not currently robust enough to change HFEA practice, how we advise patients or the recommendations we make.

Action:

3.3. 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.

4. Genome Editing

4.1. Andy Greenfield presented details of the consensus study report, Heritable Human Genome Editing, by the International Commission on the Clinical Use of Human Germline Genome Editing. First, the Committee was asked to note that it is a report following a long and complex process, involving individuals from around the world, and not one that he has written individually. He went on to highlight the themes of the report.

4.2. The Commission concluded that a safe and effective methodology for HHGE does not yet exist, and so no clinical uses would be appropriate at this stage. They recommended further research, including research using human embryos, and noted that such methodologies may be available in future. The Commission also concluded that a safe and efficacious protocol is not enough to warrant use. It aimed to outline a responsible clinical pathway but was aware that there were circumstances in which that was not possible e.g. if irresponsibly modifying the genome for a minor trait. The Commission could not outline a responsible clinical pathway that captured all potential outcomes, so defined categories of use.

4.3. The Commission focussed on *initial* uses, *if* a safe methodology is available and *if* society deemed it politically and ethically acceptable to proceed with HHGE. Those initial uses would have to have the most favourable harm/benefit balance. It divided uses into Categories, A-F. It concluded that initial uses could be justified in addressing severe monogenic diseases, where couples would need HHGE to have a healthy genetically related child: Category A. Some Category B uses may also be justified, but it was agreed that it was unacceptable to use genome editing with the intention of transferring embryos that were unaffected prior to any editing. Unaffected embryos would need to be identified and omitted from any transfer; this will be technically challenging and, in the opinion of some commentators, effectively restricts applications to Category A. Future methodologies may allow allele-specific editing, such that unaffected embryos would not be edited even if containing editing reagents, but further research would be required to identify these.

4.4. Category F includes monogenic conditions that cause infertility where genome editing may be a justifiable solution. This is an area that could be of particular interest to the HFEA.

4.5. The Commission thought it important to involve the best experts worldwide in developing a successful scientific protocol but noted the absence of adequate regulation in many parts of the world. There is an international paucity of regulatory bodies, oversight and expertise, such as offered by the HFEA.

4.6. Robin Lovell-Badge made some comments on the report suggesting that it occasionally lacks rationale. Its remit was to focus on the science and related issues for developing translational pathways but it occasionally strayed outside this into aspects of governance. The report has received criticism from several sources for not going further into these areas of governance such as details of whistleblowing and public engagement, but this was unfair criticism because it was never meant to do so.

4.7. The remit of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing is to explore mechanisms of governance that could be applied in this area, covering germline and somatic genome editing. They are also trying to deal with ‘whistleblowing’, which is usually a problem internal to an institution and is

particularly challenging to tackle at an international level. In addition, they are looking at aspects of public engagement, notably what may constitute best practice. It is unlikely that there will be agreement around a single mechanism of governance, and to have any international law or convention is unrealistic. However, it is conceivable that a range of mechanisms could be employed to discourage bad practice. The final document is currently being produced and efforts are being made to include suggestions from the consultations. It will hopefully be published early next year.

4.8. The WHO has established a registry for somatic genome editing and is working towards a registry for research on genome editing on early embryos or gamete precursor cells. The latter will require collaboration from the scientific establishment.

4.9. A member queried who should be involved in promoting a dialogue about the wider ethical questions internationally. One member emphasised that the HFEA would first need political will to do it and a level of funding that is not currently available. The committee agreed that there would likely be international interest in the HFEA's regulatory model.

4.10. A member agreed with the categorisation and recommendation to limit the technology for these extreme situations but they questioned the clinical need. The most serious cases where the technology could be used, where couples were e.g. both homozygous for a recessive disease allele and had no other choice, are very rare in the UK. Pre-implantation genetic diagnosis (PGD) works well for couples who have a dominant or recessive condition in their family.

4.11. A member pointed out that genetic diseases often occur in clusters in specific regions of the world and it is in these places that frequencies of couples falling into the Commission's categories A and B would be much higher than in the UK.

5. Update on HFEA's work on treatment add-ons

5.1. Members of the Committee declared their interests:

- The Chair works in a clinic and contributed to papers that will be discussed
- Raj Mathur, Richard Anderson and Jane Blower are clinicians who work in clinics that offer treatment add-ons
- Joyce Harper and Daniel Brison have research interests in treatment add-ons

5.2. Dina Halai explained the work the HFEA has been doing since the last SCAAC meeting. We introduced a new audit tool, for use by clinics and HFEA inspectors, which will be used to review clinics' patient information relating to treatment add-ons and how they are delivered. Testing has received positive feedback, particularly when used to develop practices that are compliant with the consensus statement. All clinics are now expected to use the tool.

5.3. We have updated and published improved information on our treatment add-ons webpage about treatment add-ons, the traffic light rating system and the evidence base. The page now displays links to the SCAAC meeting minutes at which the evidence for treatment add-ons was reviewed.

5.4. We conducted an online survey to determine patients' understanding of information included in the website update. It is now closed and we are reviewing responses. The website will be updated in response to those findings.

5.5. We have developed a form to be used by health professionals, academics or patient organisations to request a review of evidence for an add-on if it is being offered to patients with the claim of increasing live birth rate or if there is concern about the safety of offered add-ons. Those review applications will be presented to SCAAC.

5.6. We continue to share information with the Competition and Markets Authority (CMA) to support their work developing guidance for clinics so that they understand their legal obligations under consumer law.

5.7. Two policy issues will be presented to the Authority in November for consideration:

5.7.1. The best way forward on green rated add-ons.

5.7.2. The approach to information provision for holistic/alternative therapies on the HFEA website

5.8. The HFEA's plans for future work were summarised. The treatment add-ons working group (TAG), made up of the signatories of the consensus statement are meeting in November to discuss priority work areas to bring about a culture change towards more responsible innovation of treatment add-ons. There will be communications with clinics to reiterate the principles of informed consent, in particular regarding the risks of add-ons. Next year the HFEA will consider developing information for clinicians around interpreting the evidence base and what data we would need to collect to establish an understanding of the use of treatment add-ons in the sector.

Action:

5.9. Share summary of the patient survey results with SCAAC via email when they are available.

6. Review of traffic light ratings from treatment add-ons

6.1. The Policy Manager gave the background of the traffic light rating system and defined the Committee's task.

6.2. The Committee was 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 should be considered in line with significant outcomes highlighted by the independent reviewer in their assessment of published RCTs.

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

6.4. The recommendations presented did not consider risks and concerns that are specific to a treatment add-on being used during the current COVID-19 pandemic.

6.5. Members were asked to:

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

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

6.5.3. 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 2019 so no new recommendation was given. The Committee agreed that it was highly unlikely a new RCT would be done due to ethical considerations.

6.7. SCAAC Recommendation: **Remains Amber**

Assisted hatching - Current rating: Red

6.8. No new RCTs were identified since the last review in 2019 so no new recommendation was given. Common practice is now using laser and the description should reflect that safety concerns were more associated with the use of acid.

6.9. SCAAC Recommendation: **Remains Red**

Elective freeze-all cycles - Current rating: Amber

6.10. Four new RCTs were reviewed and an amber rating was recommended by the external reviewer. The Committee discussed whether this section should be split for different indications; whether it is done for safety (such as in women with high ovarian reserve/PCOS) or to increase live birth rate. It is effective at reducing ovarian hyperstimulation syndrome but that treatment is not an add-on. For women who have normal to low ovarian reserve, evidence of effectiveness is conflicting. The Committee recommended clarifying the information on the 'Elective freeze-all cycles' webpage to ensure patients understand they may need elective freeze all for medical reasons eg to reduce risk of ovarian hyperstimulation syndrome

6.11. SCAAC Recommendation: **Remains Amber**

Endometrial scratching - Current rating: Amber

6.12. Three new RCTs were reviewed by Andy Vail who presented his literature review to the Committee, explaining his recommendation of an amber rating. The RCTs have generally been of poor quality in the past which has made the committee sceptical of the results. When looking at studies done in IVF and ICSI processes the trend is that early, poor-quality studies were very positive, later studies are closer to showing no effect. However, the latest four RCTs have high methodological standards and a meta-analysis shows a positive effect that is almost statistically significant. There is no detriment. There could be up to a 5% improvement in live birth rate. Of those four, Sarah Lensen's (an observer) study shows the least positive effect but it is slightly less controlled than the others. The individual patient data meta-analysis currently being undertaken may have the power to look into timing and subgroup effects so may be helpful. The Committee decided that evidence was still conflicting. From a clinical perspective, the committee discussed that although this is an intrusive procedure, it is not common for patients to have an infection after the scratch.

6.13. SCAAC Recommendation: **Remains Amber**

Hyaluronate enriched medium e.g. EmbryoGlue - Current rating: Amber

6.14. No new RCTs were identified since the last review in 2019 so no new recommendation was given. The committee discussed that many poor quality studies showed benefit but that this was not enough to support a green rating. The Committee agreed that it is highly unlikely any new RCTs will be made. A good meta-analysis or multi-centre study may still be helpful.

6.15. SCAAC Recommendation: **Remains Amber**

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

6.16. One new RCT was identified since the last review in 2019 and the independent reviewer recommended a red rating.

6.17. SCAAC Recommendation: **Remains Red**

Intrauterine culture - Current rating red

6.18. No new RCTs identified since the last review in 2019 so no new recommendation was given.

6.19. SCAAC Recommendation: **Remains Red**

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

6.20. No new RCTs identified since the last review in 2019 so no new recommendation was given. A member highlighted that there is no evidence to show that the treatment is unsafe and that should be reflected in the rating and patient information.

6.21. SCAAC Recommendation: **Remains Red**

PGT-A (day 3) – Current rating: Red

6.22. No new RCTs identified since the last review in 2019. Members agreed that PGT-A for day 3 embryos should remain on the HFEA's traffic light rated list of add-ons even though it is rarely offered.

6.23. SCAAC Recommendation: **Remains Red**

PGT-A (day 5) – Current rating: Red

6.24. No new RCTs identified since the last review in 2019 so no new recommendation was given. The Committee noted that there was an initial backlash to moving this to the red rating with several written complaints received by the HFEA. In light of that, the HFEA re-reviewed the evidence for other outcomes and published further explanation as to how the decision was reached.

6.25. SCAAC Recommendation: **Remains Red**

Reproductive Immunology – Current rating: Red

6.26. The independent reviewer has split his review of reproductive immunology into three for steroids, intravenous immunoglobulins and intralipids, recommending an individual traffic light rating for each. The recommendations presented at the meeting do not consider risks and concerns that are specific to a treatment add-on being used during the current COVID-19 pandemic.

Steroids – Current red rating under the umbrella term of reproductive immunology

6.27. There were nine new RCTs since the last review. Independent reviewer, Andy Vail, recommended a change in the rating to amber.

6.28. The members noted that there were 3 different treatments in the studies

- Glucocorticoids to improve implantation
- Androgens e.g. DHEA to improve ovarian response. They may need their own section and traffic light rating (not under reproductive immunology), as they have a different mechanism of action

- Glucocorticoid use to improve live birth rates in those without an immunological condition (eg lupus). This is what is considered reproductive immunology and should be the focus of this discussion/rating. Of those reviewed by the external reviewer, two studies were relevant to this.

6.29. The Committee agreed that the title 'Reproductive Immunology' is confusing for patients and as an umbrella term is unhelpful. They recommended that the uses of steroids should be separated and that immunological tests should be separated from the immunological treatments. There is little scientific evidence for the tests or for a causal link between abnormal test results, recurrent implantation failure and the treatments given for it. The Committee were not happy to give separate traffic light ratings at this stage for steroids, IV Ig and intralipids as they felt that the HFEA's information on reproductive immunology needed to be made clearer first.

Action:

6.30. The Executive will review the website information on reproductive immunology along with the survey findings.

Time lapse incubation and imaging - Current rating: Amber

6.31. There were eight new RCTs since the last review and the independent reviewer recommended it stay as amber. The committee agreed that although time lapse incubation and imaging can be used as a test and/or as a tool in a standard laboratory, this evidence review must be related to its effectiveness as a treatment add-on for improving live birth rate.

6.32. SCAAC Recommendation: **Remains Amber**

6.33. One member brought to the attention of the Committee the wording of the website information on DNA damage, suggesting that the word 'theories' be replaced with 'evidence' when describing the association between DNA damage and failed IVF attempts/miscarriage. The Chair stated that the link was an association, not cause-and-effect and so 'theory' was appropriate but there were differing opinions noted. The HFEA has previously chosen not to include a comprehensive set of tests including DNA fragmentation or comprehensively assess the evidence. The Committee recommended Sperm DNA damage be moved from the traffic lights page.

6.34. Throughout the discussion of the traffic light ratings, the Committee returned to the topic of how evidence of safety, or lack of, should be communicated to patients. Most of the studies used to review ratings are looking at effectiveness in improving live birth rate and frequently there is no evidence that a treatment is safe or unsafe. Some members expressed that the burden of proof should be on proving a treatment is safe before it can be used, such as in the NHS. It was acknowledged that there was an absence of trials that could prove safety. There are also differences in how much is known about safety of each treatment, for instance the risks of glucocorticoids are better understood. There was consensus that safety should be separated from effectiveness and individually commented on for each treatment, including safety to intended parent and safety to the unborn baby. The committee suggested that HFEA's information on treatment add-ons could include an overarching disclaimer to declare how it is hard to assess safety for most treatments, particularly the impact on the embryo and long-term development, hence the lack of evidence either way. The Committee recommended that future literature reviews of RCTs that look at outcomes of treatment should include outcomes related to safety e.g. duration of gestation, birth weight, gestation adjusted birth weight, congenital abnormalities.

Action:

6.35. The HFEA will consider how information about safety is presented within our add-ons information on our website along with the survey findings.

7. Any other business

7.1. The annual review of Committee effectiveness is to be carried out after the meeting. Members will receive an email about it.

7.2. The Chair wished to express his gratitude to Richard Scott on behalf of the Committee for his valuable contribution to the SCAAC meetings and congratulate him on his new appointment.

7.3. The Chair summarised the meeting and thanked the Committee and the guest speaker.

8. Chair's signature

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

Signature:

Chair: Yacoub Khalaf

Date: 25/01/2021