Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes – Treatment add-ons

Tuesday 25th July 2023, 1:00pm – 3:30pm

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

Authority members	Present	Tim Child (Chair) Frances Flinter Jason Kasraie (Deputy Chair) (online) Alex Kafetz Christine Watson
External advisors	Present	Richard Anderson (online) Kate Brian Alison Campbell Robin Lovell-Badge (online) Raj Mathur (online) Scott Nelson (online) Anthony Perry
	Apologies	Frances Ashcroft Zeynep Gurtin Kevin McEleny
Executive	Present	Dina Halai (Head of Regulatory Policy, Scientific) Ashley-Anne Brown (Meeting secretariat and Scientific Policy Officer) Anna Coundley (Policy Manager) Mina Mincheva (Policy Manager) Beth Lockwood (Policy Manager- Civil Service Fast Streamer) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information)
Invited speakers	Present	Andy Vail (External reviewer for treatment add-ons - University of Manchester) Paul Cannon (Expert medical librarian - University of Glasgow)
Observers	Present	Sharon Fensome-Rimmer, Georgia May and Caroline Street (HFEA) Izzy Passe (work experience) Amy Parsons and Kath Bainbridge (DHSC)

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. Apologies were received from Kevin McEleny, Frances Ashcroft and Zeynep Gurtin.

1.3. The Chair outlined the format of this add-ons discussion and the task of the committee to rate the fourteen add-ons using the new five-point rating system. He stated that certain add-ons to be rated have been prioritised and will be discussed first, after which the remaining will be rated.

1.4. Following the February 2023 SCAAC meeting the literature search methodology used to inform add-ons rating was refined as recommended by the SCAAC. This included:

1.4.1. The Executive working with an expert medical librarian, Dr Paul Cannon, to assemble a list of search terms and refine a methodology for searching for the literature.

1.4.2. A subset of SCAAC members reviewed the modified search terms.

1.4.3. The Executive conducted a literature search using the search terms. All SCAAC members were sent the list of search terms and papers for review, to confirm that all relevant evidence is captured. SCAAC members to highlight any missing papers to the Executive.

1.4.4. Papers were sent to the external reviewer, Professor Andy Vail, to analyse the quality of the evidence and make a recommendation for ratings.

1.4.5. The Executive refined the definitions and the decision tree as per the SCAAC's recommendations.

2. Review of ratings for treatment add-ons

2.1. Members were asked to:

2.1.1. Consider the quality of evidence for each treatment add-on based on the findings from an independent assessor;

2.1.2. Agree and recommend ratings for each treatment add-on based on the outcome of live birth rate (LBR) for the general population; and

2.1.3. Agree the recommend ratings for each additional outcome(s) and population (s) relevant to specific treatment add-ons.

2.2. ESHRE's draft guidelines and good practice recommendations for add-ons were highlighted to the committee for reference.

2.3. The committee raised that when updating the patient information on add-ons on the HFEA website, attention should be given where multiple ratings are allocated to an add-on to ensure that the explanations for each rating and why there are multiple ratings is clear for patients.

Artificial egg activation using calcium ionophore

2.4. SCAAC members discussed the expert reviewer rating recommended for artificial egg activation using calcium ionophore for each of the populations and subpopulations:

2.4.1. The Association of Reproductive and Clinical Scientists (ARCS) and the British Fertility Society (BFS) are due to publish guidelines on best practices for artificial egg activation.

2.4.2. The Director of Compliance & Information explained that artificial egg activation is an HFEA authorised process. The use of calcium ionophore is authorised for selected patients, e.g., patients with Phospholipase C zeta (PLCzeta) deficiency. It was also raised that depending on professional guidance due to be published later this year, artificial egg activation may need to be reviewed to determine if it is still appropriate for it to be classified as an add-on for most fertility patients. The committee therefore concluded it would be beneficial to await professional body guidance to avoid conflicting with it.

2.5. **Recommendation:** The committee recommended delaying allocating a rating for artificial egg activation using calcium ionophore until ARCS and BFS guidance is published to be in alignment with the professional bodies. In the interim, there should be a note on the HFEA website to explain why this add-on has not been updated.

Assisted Hatching

2.6. SCAAC members discussed the rating for assisted hatching:

2.6.1. The Chair raised whether it is more appropriate to separate out ratings for the use of assisted hatching in frozen oocytes, frozen embryos, fresh embryos and blastocysts but noted that ESHRE did not split assisted hatching by clinical scenario. Based on the scientific literature they were aware of and the expert review, the committee agreed not to separate out the ratings in this way.

2.6.2. The external reviewer recommended a grey rating as only one moderate/high quality study for LBR had been identified and no safety concerns were raised across a large number of studies, however the safety concerns resulting from multiple pregnancies, as raised by ESHRE, could indicate a red rating. The external reviewer noted that Cochrane review concludes unproven for live birth and contains many older randomised controlled trials (RCTs) in addition to those included here.

2.6.3. The committee noted that the ESHRE draft guidelines do not recommend the use of assisted hatching based on the lack of increase in LBR and the risk of increasing multiple pregnancy rate.

2.7. **Recommendation:** The committee agreed the following rating for assisted hatching:

- Grey for increasing LBR for most fertility patients

2.8. **Recommendation:** The committee agreed to consider separating out ratings for the use of assisted hatching in frozen oocytes, frozen embryos, fresh embryos and blastocysts at a later date. In addition, the committee will reconsider safety issues to determine if the rating should be red at a subsequent date.

Endometrial scratching

2.9. SCAAC members discussed the ratings for endometrial scratching:

2.9.1. The external reviewer commented on at 94% confidence level a 1-2% benefit at increasing LBR could be concluded, however the evidence is inconclusive at 95% (standard) confidence level and advised that the committee balance this against cost, inconvenience and pain of the procedure.

2.9.2. The Chair noted that older RCTs included are those that show the greatest success rates.

2.9.3. A member highlighted two studies that were published after the literature search had been carried out by the Executive to inform this discussion:

2.9.3.1. van Hoogenhuijze et al., published an individual participant data meta-analysis that suggested endometrial scratching has some small effect on live birth at an odds ratio of 1.25; and

2.9.3.2. a trial presented at the ESHRE 2023 conference that showed an effect in favour of endometrial scratching. However, the committee commented that we should be cautious of information published in abstracts from presentations as often the studies do not go on to be published in journals.

2.9.4. The group expressed caution as to the robustness of the evidence (identified in the literature search) that shows benefit.

2.9.5. The SCAAC agreed that a rating should be allocated for increasing LBR for most fertility patients *undergoing IVF/ICSI,* and that this would not include patients undergoing IUI given that many of the high-quality studies that were assessed were in populations undergoing IVF or ICSI.

2.9.6. The external reviewer commented that given there were no moderate/high quality studies explicitly for increasing LBR for patients with recurrent implantation failure (RIF) that it therefore could be rated the same as the general population as there is no evidence that effect for this subpopulation differs from the general. However the committee agreed that insufficient moderate/high quality evidence would result in a grey rating, as per the definition of the ratings.

2.9.7. The committee noted that the ESHRE draft guidelines do not recommend the routine use of endometrial scratching, and state there is not enough evidence for specific patient subgroups.

2.10. **Recommendation:** The committee agreed the following ratings for endometrial scratching:

- Amber for increasing LBR for most fertility patients undergoing IVF/ICSI. The committee concluded that there was insufficient evidence for a green rating, especially given the number of high-quality studies completed to date. The patient information on the HFEA website should emphasise that this rating does not apply to patients undergoing IUI and should also reflect the painful nature of this procedure.
- Grey for increasing LBR for patients with RIF.

Elective freeze all cycles

2.11. SCAAC members discussed the ratings for elective freeze all cycles:

2.11.1. The committee commented that there are some concerns that adverse obstetric outcomes may relate to embryo transfer in fresh and natural or artificial frozen cycles possibly due to differences in corpus luteum function, though this is yet to be proven.

2.11.2. The committee noted that the ESHRE draft guidelines do not recommend elective freeze all except where risk of ovarian hyperstimulation syndrome (OHSS) or endometrial pathology is increased and in pre-implantation genetic testing (PGT) cycles.

2.12. **Recommendation:** The committee agreed the following ratings for elective freeze all cycles:

- Amber for increasing LBR for most fertility patients given that there were conflicting findings from 4 moderate/high quality studies.

- Green for reducing risk of OHSS for most fertility patients as on balance there was consistent evidence.
- Green for reducing risk of OHSS outcomes for populations at increased risk of OHSS.
- Grey for improving obstetric/neonatal outcomes for most fertility patients as the studies were underpowered to evidence this.
- Grey for improving obstetric/neonatal outcomes for populations at increased risk of OHSS as the studies were underpowered to evidence this.
- Grey for increasing LBR for populations at increased risk of OHSS.

Time-lapse imaging and incubation

2.12. SCAAC members discussed the ratings for time-lapse imaging and incubation:

2.12.3. ESHRE draft guidelines highlight that TLI with or without embryo selection software has not been shown to improve LBR.

2.12.4. The external reviewer commented that there were 5 moderate/high quality studies with consistent results showing no improvements in LBR for most fertility patients when using automated or manual annotation.

2.12.5. A member commented that time-lapse imaging is offered at the clinic they work at, and they have internal data which shows benefit, but that these aren't published clinical or randomised trials. Another member highlighted a recent publication in the Lancet, published after the literature review carried out for this item had taken place, which also showed there to be no effect and supported a black rating.

2.12.6. Committee members discussed other benefits of using time-lapse imaging, including observation of late pro nuclei appearance, patients knowing how their embryos are developing and potentially feeling reassured and informed by this.

2.13. **Recommendation:** The committee agreed with ESHRE's recommendation that 'Time-lapse imaging has been shown to be a convenient and effective incubator which allows a continuous view of embryo development' and recommended similar wording be used in the HFEA's patient information. This should include that there could be other benefits for patients other than improving LBR.

2.14. **Recommendation:** The committee agreed the following ratings for time-lapse imaging and incubation:

- BLACK for improving LBR for most fertility patients when using automated annotation.
- BLACK for improving LBR for most fertility patients when using manual annotation.

Endometrial receptivity array

2.15. SCAAC members discussed the rating for endometrial receptivity array (ERA):

2.15.1. The external reviewer commented that there was only one high quality study, but concerns were raised by Cozzolino 2022 which reported that live birth rates were considerably lower with ERA and cumulative live birth rates were also lower.

2.15.2. The committee noted that ESHRE draft guidelines do not recommend endometrial receptivity tests.

2.16. **Recommendation:** The committee agreed that the wording of this add-on should be changed to 'endometrial receptivity *testing'* to be in line with NICE.

2.17. **Recommendation:** The committee agreed the following ratings for endometrial receptivity testing:

- RED for LBR for most fertility patients.

Hyaluronate enriched medium (eg EmbryoGlue)

2.18. SCAAC members discussed the rating for hyaluronate enriched transfer medium:

2.18.1. The external reviewer commented that at least three moderate/high quality studies with broadly consistent results showed that this add-on improves LBR.

2.18.2. However, the committee agreed that the Kleijkers 2016 study needed to be removed from the review as it looked at culture media and not hyaluronate enriched *transfer* medium. This meant that there was no significant study published since the add-on was last allocated an amber rating.

2.18.3. The committee noted that ESHRE draft guidelines recommend this add-on in single embryo transfer cycles.

2.19. **Recommendation:** The committee agreed that the wording of this add-on should be changed to 'hyaluronate enriched *pre-transfer culture* medium*'* to distinguish it from culture media.

2.20. **Recommendation:** The committee agreed the following rating for hyaluronate enriched pre-transfer culture medium:

- AMBER for improving LBR for most fertility patients

Intracytoplasmic morphologic sperm injection (IMSI)

2.21. SCAAC members discussed the ratings for IMSI:

2.21.1. The external reviewer stated that for this add-on there was very little evidence to show its benefit, and evidence lacked quality.

2.21.2. **Recommendation:** The committee agreed the following ratings for IMSI:

- GREY for improving LBR for most fertility patients.
- GREY for improving LBR for patients undergoing fertility treatment due to male-factor infertility.

Intrauterine culture

2.22. SCAAC members discussed the rating recommended for intrauterine culture:

2.22.1. The Chair commented that only one non-randomised study has been published about this add-on.

2.22.2. **Recommendation:** The committee agreed the following rating for intrauterine culture:

- GREY for improving LBR for most fertility patients.

Physiological intracytoplasmic sperm injection (PICSI)

2.23. SCAAC members discussed the ratings for PICSI:

2.23.1. The external reviewer commented that the well-designed and reported trial of Miller 2019 ruled out any major effect of PICSI, so the Committee could consider whether a black rating for improving LBR may be more informative summary information for patients despite not strictly fitting the current definitions for these grades.

2.23.2. The committee agreed that the Miller 2019 trial is definitive and that we are unlikely to see another significant trial like this again. The committee agreed that it was designed to investigate patients who needed ICSI ie patients that were undergoing fertility treatment due to male-factor infertility.

2.23.3. Members raised that it is important to give correct information to patients and although miscarriage was a secondary outcome in the Miller 2019 trial that there was evidence to show that in a selected group of older patients, where PICSI could reliably be used, the miscarriage rate was significantly reduced and felt that we should make an exception for this secondary outcome due to the high quality of the trial.

2.23.4. The committee noted that ESHRE draft guidelines do not recommend this add-on as a sperm selection method since it has been shown to have little or no effect on live birth or clinical pregnancy rates.

2.24. **Recommendation:** The committee agreed the following ratings for PICSI:

- Black for increasing LBR for patients undergoing fertility treatment due to male-factor infertility.
- Black for increasing LBR for older women (35+) undergoing fertility treatment due to male-factor infertility.
- Grey for reducing the chances of miscarriage for older women undergoing fertility treatment due to male-factor infertility because any evidence to support the use of PICSI for this outcome is based on secondary data.

2.25. **Recommendation:** The committee agreed that the patient information on the HFEA website should reflect that PICSI should *only* be used for those genuinely needing ICSI for male factor infertility.

Preimplantation Genetic Testing for Aneuploidy (PGT-A)

2.26. SCAAC members discussed the ratings recommended for PGT-A:

2.26.1. The external reviewer commented that several moderate/high quality studies consistently showed benefit of having PGT-A for reducing chances of miscarriage for most fertility patients. One significant study looked at live birth rate and time to birth for most fertility patients and showed that although live birth rate was higher following the first transfer, cumulative live birth rate was lower in the PGT-A arm, and time to conception resulting in live birth was also significantly longer.

2.26.2. Members agreed that a green add-ons rating using the new rating system does not mean we are encouraging patients to seek this treatment, but rather, this treatment can be considered where appropriate on an individual basis depending on a patient's personal circumstances and medical history.

2.26.3. A member highlighted that a publication in Cells, published after the literature review carried out for this item had taken place, shows that PGT-A can damage cells.

2.26.4. A member highlighted that the Kucherov 2023 study, published after the literature review carried out for this item had taken place, shows benefit in older patients.

2.26.5. The committee noted that ESHRE draft guidelines do not recommend routine use of PGT-A but noted that it may decrease time to pregnancy in specific patient groups.

2.27. **Recommendation:** The committee agreed that the Verpoest 2018 trial should not be included in this review as PGT-A was by polar body biopsy six to nine hours after ICSI, which constitutes a different class of intervention.

2.28. **Recommendation:** The committee agreed not to rate for the outcome of time to birth because the additional time taken to carry out this test would increase the time to birth in any case, and that there is not enough evidence for this outcome so it could be confusing for patients.

2.29. **Recommendation:** The committee agreed the following ratings for PGT-A:

- RED for improving LBR for most fertility patients.
- GREEN for reducing chances of miscarriage for most fertility patients. The committee agreed that the patient information should make it clear that although there could be a reduction in the possibility of miscarriage, there will also be a reduction in LBR and therefore this may not really be a benefit in the long term. The patient information should also be clear that there is still a possibility of having a miscarriage and having this add-on does not remove that risk completely.
- GREY for reducing chances of miscarriage in older women.
- GREY for improving LBR for older women.

2.30. **Recommendation:** The committee agreed that the patient information should be clear about the issues and implications concerning the use of PGT-A including:

2.30.1. Information about mosaicism and ranking embryos and that mosaic embryos, which can still result in a live birth, could be reported as being aneuploid and be discarded

2.30.2. Fertility treatment may take longer and will cost more than a routine IVF cycle

2.30.3. This add-on is an authorised process and what that means for clinics and patients.

Immunological tests and treatments for fertility – Intralipids

2.31. SCAAC members discussed ratings recommended for intralipids:

2.31.1. The committee agreed that although the safety concerns existed, they were not significant.

2.31.2. The committee noted that ESHRE draft guidelines do not recommend immunomodulating treatments including intralipids based on the absence of any rationale, documented side-effects, and no clinical benefit.

2.32. **Recommendation:** The committee agreed the following ratings for intralipids:

- GREY for improving LBR for most fertility patients.
- GREY for reducing the chances of miscarriage for most fertility patients.
- GREY for improving LBR for patients undergoing immunological testing.

- GREY for reducing the chances of miscarriage for patients undergoing immunological testing

2.32.1. **Recommendation:** The Executive to consider referencing the letter highlighting safety concerns of the use of intralipids from the President of the Royal College of Obstetricians and Gynaecologists (RCOG) within HFEA's patient information for this add-on.

Immunological tests and treatments for fertility – Intravenous immunoglobulin (IVIG)

2.33. SCAAC members discussed ratings recommended for IVIG:

2.33.1. The external reviewer commented that there were three RCTs providing moderate quality evidence, but the results were too imprecise to determine effectiveness.

2.33.2. The committee agreed that although the results were consistent between the three studies, that the confidence interval was too wide to conclude that there is a benefit from using this add-on.

2.33.3. Members agreed that the studies investigated patients who had previously had miscarriage(s) and not specifically patients with fertility issues therefore did not provide evidence for the general IVF population. However it was acknowledged that patients are being offered this treatment in fertility clinics.

2.33.4. The committee agreed that because this add-on concerns blood product, there will inevitably safety concerns associated with it. Members also agreed that this was an intrusive treatment with patients having to be injected regularly over a long period and that it is expensive. A member highlighted a paper by Guo et al., that highlights the adverse effects of IVIG.

2.33.5. **Recommendation:** Members agreed that the patient information for this add-on should explain the safety concerns associated with its use.

2.33.6. **Recommendation:** The committee agreed the following ratings for IVIG:

- RED for improving LBR for most fertility patients.
- RED for reducing the chances of miscarriage for most fertility patients.
- RED for improving LBR for patient undergoing immunological testing.
- RED for reducing the chances of miscarriage for patients undergoing immunological testing.

Immunological tests and treatments for fertility – Steroids (Glucocorticoids)

2.34. SCAAC members discussed ratings recommended for glucocorticoids.

2.35. **Recommendation:** Members agreed that the patient information for this add-on should explain the safety concerns associated with its use.

2.35.1. **Recommendation:** The committee agreed the following ratings for glucocorticoids:

- RED for most fertility patients.
- RED for reducing the chances of miscarriage for most fertility patients.
- RED for improving the chances of having a baby for patient undergoing immunological testing.
- RED for reducing the chances of miscarriage for patients undergoing immunological testing.

2.36. **Recommendation:** When the treatment add-ons application form and decision tree has been updated in line with the new treatment add-ons rating system, androgen supplementation should be reconsidered as an add-on. This is following SCAAC's discussion in June 2022.

3. Any other business

3.1. A member highlighted that NHS Scotland still perform PGT-A on day 3 embryos. The Executive informed that up until October 2020 SCAAC, the SCAAC had been allocating a red rating for day PGT-A on day 5 and day 3 embryos. At the October 2021 meeting of the SCAAC, it had been confirmed that this treatment add-on is presented as PGT-A on the HFEA website, rather than specifying Day 3 or 5.

3.2. The next SCAAC meeting will be held on Monday 2nd October 2023, and will be in person.

4. Chair's signature

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

Signature

Chair: Tim Child

Date: 20 September 2023