Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

6th June 2022

Teleconference (Zoom meeting)

Authority members	Present	Tim Child (Chair) Jason Kasraie (Deputy Chair) Frances Ashcroft Frances Flinter	Alex Kafetz Zeynep Gurtin
External advisors	Present	Richard Anderson Kate Brian Alison Campbell Yacoub Khalaf Raj Mathur	Kevin McEleny Scott Nelson Tony Perry
	Apologies	Robin Lovell-Badge	
Members of the executive	Present	Julia Chain (HFEA Chair) Victoria Askew (Meeting lead and Policy Manager) Ana Hallgarten (Meeting secretary and Public Policy Manager) Sonia Macleod (Scientific Policy Manager) Dina Halai (Scientific Policy Manager) Laura Riley (Head of Policy) Peter Thompson (Chief Executive) Rachel Cutting (Director of Compliance and Information) Nico Tilche (Senior Legal Adviser)	
Observers	Present	Rebecca Williams (Scientific Training Programme (STP) trainee)	

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. Apologies were received from Robin Lovell-Badge.

2. Matters arising

2.1. Minutes of the meeting held on 31st January 2022 were agreed remotely prior to the meeting.

2.2. The Scientific Policy Officer 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.

2.2.2. SCAAC members from ARCS and the BFS will relay any COVID-19 information from these meetings to SCAAC members.

2.2.3. Following the Committee's recommendation to consider androgen supplementation as a separate treatment add-on from immunological tests and treatments, a treatment add-on application form for androgen supplementation has been completed, for discussion at this SCAAC meeting.

2.2.4. The Committee requested amendments to take place to the workplan following SCAAC feedback, which has been completed.

2.2.5. At the October 2022 SCAAC meeting, consideration of whether further outputs on the impact of the microbiome on fertility are needed will be assessed as part of an agenda item.

2.2.6. SCAAC members were asked to send through suggested experts for the upcoming workplan agenda items. This continues to be a standing agenda item, and members are encouraged to highlight any suggestions to the Scientific Policy Team.

3. Chair's business

3.1. The chair thanked Gudrun Moore for her contribution to SCAAC over the years as Deputy Chair.

3.2. The Chair introduced Jason Kasraie as the new Deputy Chair of SCAAC.

3.3. The Chair introduced new members following the recent SCAAC recruitment process and as part of the recent Secretary of State for Health and Social Care appointments to the Authority.

- New SCAAC members that are also Authority members:
    - Professor Frances Ashcroft, Professor of Physiology at the University of Oxford
    - Mr Alex Kafetz, works in artificial Intelligence and health technology. Works at Beamtree and is a lay member for the NHS in East London
    - Dr Zeynep Gurtin, Lecturer at the EGA Institute for Women's Health at University College London
    - Professor Frances Flinter, Emeritus Professor of Clinical Genetics, King's College, London, Guy's & St Thomas' NHS Foundation Trust; member of the Nuffield Council on Bioethics

- New external experts:
    - Professor Anthony Perry, Professor at the Department of Biology & Biochemistry of the University of Bath
    - Professor Scott Nelson, Muirhead Professor of Obstetrics and Gynaecology at the University of Glasgow
    - Dr Alison Campbell, Director of Embryology, CARE Fertility

3.4. The Chair reminded SCAAC members that the HFEA will be publishing a list of members' Conflicts of Interest on the SCAAC webpage. Any updates should be sent to the Scientific Policy team.

4. Monitoring the effects of COVID-19 on fertility, assisted conception and early pregnancy

4.1. The Chair noted the 58 reports, papers and guidelines that had been submitted, shared, and discussed with the Committee in previous meetings.

4.2. The Committee discussed that it might be beneficial to broaden this topic to public health impacts on fertility, assisted conception and early pregnancy more generally.

4.3. It was agreed that limited information is emerging regarding the effects of COVID on fertility, and that other public health concerns are emerging including monkey pox, as well as increased Zika virus rates which merited monitoring by the Committee.

Action: The Committee will continue to monitor and share relevant literature regarding public health impacts on fertility, assisted conception and early pregnancy more generally.

5. Impact of Stress

5.1. The Policy Manager (VA) presented a literature review on the impact of stress on fertility treatment outcomes.

5.2. Patients undergoing fertility treatment frequently report high levels of stress and anxiety. Anecdotally, some patients have suggested that stress could play a role in their chances of having a successful treatment outcome.

5.3. However, when last discussed by the committee in February 2018, it was found that previous research results were mixed, and it was unclear how stress may impact a couple's chance of having a successful treatment cycle. The Committee concluded that the objective study on stress in patients in relation to fertility can be difficult because of confounding factors.

5.4. A literature review was undertaken which identified 15 studies published from March 2018 to May 2022. Five studies suggested that psychological distress, or the use of stress management, had some impact on fertility treatment outcomes. Ten studies suggested that psychological distress either had no impact, or conflicting impact, on treatment outcomes.

5.5. Despite the clear high levels of stress and anxiety in fertility patients, the research to date seems inconclusive on whether these increased stress levels have a negative impact on fertility

treatment outcomes. Study samples tend to be small, and psychological stress can be difficult to measure with many studies using self-reporting questionnaires. This subjective data collection could contribute to the conflicting results that are seen in the research on this topic.

5.6. One member mentioned Dr Alice Domar as a leading US expert in the field of stress and stress management in fertility treatment if further expertise were needed.

5.7. A member questioned whether patients being told that stress could reduce their chances of success would then further increase stress, and that this would be unhelpful in managing stress levels. The member felt that regardless of any impact on outcomes, reducing stress in patients is important and reinforcing a link between stress and outcomes would not necessarily be helpful.

5.8. The Policy Manager clarified that the HFEA recognises the importance of emotional support for patients during their fertility treatment. A piece of work had been undertaken to require clinics to have a Patient Support Policy and to give guidance on what good emotional support looks like. However, the evaluation of the evidence base in this area may help to establish more evidence-based principles for stress management.

5.9. A member made the point that fertility treatment is inherently stressful. If a link is established patients may feel more pressure to *not* experience stress during their treatment. The HFEA should also be conscious of treatment options available to patients that have a limited evidence base, including some fertility mindset coaches, and the potential for patient exploitation.

5.10. Another member noted that studies within the literature review which look at components of the personality trait neuroticism (namely anxiety and depression) did not find a correlation between stress and fertility treatment outcomes. However, those studies looking at patient's previous traumatic experiences did find a correlation. The member questioned whether there was more relevance for a patient's specific medical history, rather than more complex personality traits.

5.11. One member questioned whether counselling, which has previously been suggested as a stress management tool, has been proven to be effective at reducing stress. The member suggested looking for interventions where there was good quality evidence of stress reduction.

5.12. A member questioned whether a direct, causal relationship between stress and treatment outcomes could ever be established, due to different confounding factors. The member felt that there was a lack of evidence that counselling was able to reduce stress levels and clinics should not be mandated to offer patients counselling specifically for stress management.

5.13. The Policy Manager clarified that licenced clinics are required to offer all patients counselling to ensure that they meet the requirements in the HFE Act (1990) as amended of giving written informed consent, rather than for stress management, as outlined in the HFEA Code of Practice.

5.14. One member discussed potential methods of stress reduction, for example reducing costs and therefore reducing financial stress. The member outlined that there are several causes of stress that are outside of the clinic's control, for example relationship dynamics, and it would be difficult to suggested effective interventions for this.

5.15. The Chair discussed experiences of patients who had unsuccessful treatment outcomes expressing feelings of responsibility over an embryo not implanting due to stress. He

acknowledged the difference in reactions of patients to the same stressors. The Chair advised that stress does potentially impact patients' ability to return for subsequent treatment cycles.

5.16. The Chair asked members whether there is a need for the HFEA to produce transparent information for patients on the impact of stress on fertility treatment outcomes. Some members felt that as a clear link hasn't been established there is no need for individual information for patients, and that specific medical advice may fall outside of the HFEAs regulator remit.

Action: The impacts of stress on fertility treatment outcomes, and more specifically potential stress management tools, should remain as a medium priority topic of the SCAAC and be brought back to the committee for consideration at a future meeting.

6. Application form – Androgen supplementation

6.1. The Public Policy Manager (AH) presented an androgen supplementation add-on form.

6.2. The application was completed by the HFEA following the recommendation in October 2022 that androgen supplementation should possibly be considered a separate treatment add-on from immunological tests and treatments.

6.3. The evidence used in the form included a literature search of studies where live birth is the primary outcome.

6.4. Members were asked to recommend whether androgen supplementation should be considered an add-on and if so, given a RAG rating at the October or February SCAAC meeting.

6.5. Members agreed that androgen supplementation did not meet the criteria set out by the treatment add-ons Decision Tree.

6.6. However, SCAAC members were concerned about some of the language used within the decision tree and noted that as the Authority is considering possible changes both to the evidence base, and to how the evidence is presented, it would be beneficial to return to the decision tree in the future.

Action: The Executive will amend the treatment add-ons application form decision tree in line with the evolving treatment add-ons rating system.

7. Treatment add-ons Expansion of evidence base

7.1. The Chair introduced this item discussing the evidence base used for determining the robustness of the evidence around treatment add-ons as represented via the HFEA traffic light system, currently agreed by SCAAC to be restricted to evidence from RCTs.

7.2. The Scientific Policy Manager introduced the plan in considering expanding the evidence base, this included:

- An informal SCAAC workshop on the evidence (taking place the morning of the 6th of June)
    - This workshop considered evidence that other groups (including NICE and the MHRA) use
    - Researcher views on possible evidence types

- A discussion and **formal** recommendation at this SCAAC meeting
- A recommendation to be presented to the Authority in July 2022

7.3. The Scientific Policy Manager then highlighted the work on treatment add-ons rating that is taking place and three main elements:

1. Evolving the **presentational aspects** of treatment add-ons
2. Considering whether **outcomes other than live births** should be rated
3. Considering the **evidence base used to generate ratings**

7.4. When considering evolving the presentational aspects of treatment add-ons it was noted that the current main options being considered discuss the use of 'studies' rather than RCTs for rating, therefore the options for expanding the evidence base are not limited to RCTs only. Both options also have a category for situations where there is insufficient evidence available to rate the treatment add-on.

7.5. The Scientific Policy Manager then highlighted points for consideration within the discussion for using only RCTs going forwards or for using evidence beyond RCTs. They stated that either continuing with the status quo or changing the status quo would require justification.

7.6. The Chair advised the committee on the importance of all members participating in this discussion. As an advisory committee to the Authority, it is important to create a clear argument and reasoning behind any advice.

7.7. One member of SCAAC noted that Cochrane, the MHRA, and NICE are considered experts as regards the evaluating of scientific evidence. They stated that it would be a good for the HFEA to align itself with these experts, and that this would be a strong position.

7.8. Another member of SCAAC considered that RCTs are particularly important and useful metrics within the field of infertility. In research on chronic diseases there are multiple outcomes and dealing with relative conditions where interventions may have varying differences. In contrast, in infertility the factors that affect live birth rate have likely already been identified.

This member noted that NICE addresses a further range of issues, rather than just focusing on interventions, and therefore it is reasonable for them to widen their scope in a way that it might not be reasonable for SCAAC to do when rating treatment add-ons.

Additionally, the member argued that treatment add-on interventions are commercially charged-for to patients, in a way that other non-infertility related medical interventions are not. This commercial bias is present and visible in the literature, and therefore relying on *robust* RCTs can reduce the risk of using data that may not be reliable.

The member concluded that good and robust RCTs should *continue* to be the only evidence base considered in treatment add-ons rating.

7.9. A member considered that restricting the evidence base to RCTs is not only insufficient but means that the work being produced is not patient centred. They stated that when there are not enough good RCTs to make a rating, that SCAAC should consider additional data.

When considering Cochrane and NICE, they noted that the data being considered by an organisation should be dependent on the role of that body. For example, Cochrane does not give guidance, whereas the HFEA *does* provide guidance to the fertility sector. Cochrane therefore does not need to be as strict with the data they consider, as their work is for the research community. Members also noted that NICE assesses cost effectiveness and quality-adjusted life-years (QALYs) which are not considered by the HFEA.

The guidance that the HFEA publishes is with patient information in mind, and therefore the member thought it was important that when there are *no* RCTs other evidence is being used to ensure that the advice that is being provided *is* based on the best possible evidence.

When contemplating a system to determine when further work beyond RCTs should be considered, members stated that any sort of algorithm or decision tree used to determine the further evidence base should be developed using the judgement of an expert statistician, SCAAC, and the Authority.

7.10. A member commented on the value of RCTs and questioned what SCAACs position should be when there are *no* RCTs. Would a lack of RCTs mean that the treatment add-on is not addressed at all? Another member argued that the HFEA is not obligated to have an answer for every treatment add-on and that the use of 'bad' information would have a negative effect on patients.

7.11. It was noted by a member that the aim of the treatment add-ons system is to help patients. However, it is likely to be the case that patients will opt for treatment add-ons without all possible information available, or even against HFEA traffic light recommendations.

A problem with the current system is that there is a significant gap in which clinicians can tell their patients that not all trials (that may show positive effects) are included in our recommendations as a way to justify the treatment add-on use. If patients then hear that there is *some* positive evidence they may be inclined to choose a treatment add-on without understanding the importance of different levels of evidence.

The member also noted that given the small difference that some treatment add-ons provide to patients, it would be beneficial to possibly present cost/benefit analyses as part of the rating system.

7.12. A member agreed that it is necessary to go 'a bit further' than 'pure' RCTs as patients are regularly asking about HFEA opinions on treatment add-ons, and it would be beneficial for the HFEA to be able to provide a view even if using non-RCT data.

The member noted that there are many RCTs that can be both unhelpful and misleading. By using work beyond RCTs, it would provide scope to state what other research has taken place.

The member stated that considering work outside of RCTs should only take place if the RCTs available are not robust, or if there are no RCTs at all.

7.13. One member observed that the NICE guidance is often very straightforward, using terminology that scientists, clinicians, and patients are all able to understand fully. This ease of understanding was considered essential to the member, who felt that patients would need to have clear explanations regarding the change in evidence base, as well as explanations showing the different uses of evidence. They added that a threshold or bar would need to be highlighted to

patients when displaying non-RCT evidence, justifying what is considered ‘good enough’ evidence to be included.

7.14. It was argued that the balance of presenting information clearly without complexity, whilst accurately reflecting evidence would be a challenge. This would be even more complicated when presenting different ratings to treatment add-ons for different patient groups. One member presented two scenarios for the possible process to use when no good RCTs are available.

The first option is that in the absence of good RCTs the HFEA do not take a position. In this case patients would have to make decisions for themselves considering all the available information, without being able to refer to the HFEA analysis and recommendations. This may still be helpful to patients as it may empower them in discussions with their clinic.

The second option is that the HFEA considers other evidence besides RCTs and gives *some* opinion from this data. This second option would require very clear statements noting that the recommendations the HFEA considers evidence that is less thorough than in other treatment add-on ratings.

The member discussed how either option had potential negative implications for patients, therefore mitigating any such effects would be important. They posed the question, would it be better to have no guidance from the HFEA? Or would it be better to assess and use varying levels of evidence?

7.15. A member presented the possibility of a triangulation process for considering expanding the evidence base. They debated how having more than one approach for when certain pieces of evidence should be considered when assigning a treatment add-on rating would strengthen the process. Having two or three methodologies in place to support other data to be considered alongside RCTs would be helpful as if the additional data provides a stronger case for the rating that would be helpful, and if the additional evidence provides little further support then the RCTs can be considered sufficient.

This member also noted that as personalised medicine becomes more common, it may become acceptable to include studies with fewer patients as good evidence.

7.16. There was agreement regarding the possibility of using a triangulation method by another SCAAC member. An issue that is often present in RCTs within infertility research is the low number of patients available for research.

They argued that using observational studies and further work using triangulation approaches would give a stronger scientific basis for any recommendations given in the treatment add-on ratings.

Although triangulation should be considered key when there are no good quality RCTs, the member stated that triangulation could or should be used routinely, as data that proves similar effects to the RCTs could be a part of recommendations. The inclusion criteria could also, for example, make sure that the bias in some RCTs was being recognised.

7.17. One member questioned RCTs being considered a ‘gold standard’ in part due to how heterogenous the data sets presented in such studies are. This is sometimes due to ‘unknown unknowns’ in the research that may factor into results, thereby influencing them. One example

they gave was the ethnicity of participants, which may be an important factor within research and yet is not always acknowledged.

Due to possible confounding issues within RCTs, the member was surprised that animal studies were considered much lower on the expanding the evidence base tree. They argued that there is a great deal to be learnt from animal studies, as it permits an opportunity for scientific analysis outside of clinical applications.

7.18. A member expressed concern regarding new 'bright lines' about the evidence that SCAAC would accept. They felt that the current system was effective and simple, nonetheless that there is an obligation to help patients and not leave treatment add-ons as 'unclassified'.

Their worry was that in considering other data, there is no clear demarcation regarding which data should be used. They suggested that accepting evidence lower than an RCT could potentially suggest that the HFEA is effectively concluding that 'we don't know'. The benefits of expanding the evidence base would, however, allow more up-to-date information to be shared with patients.

They added that the use of a new evidence base would need to ensure that the body of work created was not too large for the HFEA to handle.

7.19. A member was interested in the use of the HFEA webpage for treatment add-ons and questioned whether it would be possible to perform IP address analysis to establish where and when the page was being used. They felt this was important, as SCAAC should be questioning the purpose and use of treatment add-ons when considering the best way forwards.

The member felt that an 'RCT plus' system would be beneficial, with the evidence base being expanded where other pieces of 'acceptable' evidence were available. They described the pitfalls of RCTs including the low number of RCTs available, and the resources required to run them. They argued that as data becomes increasingly democratised, as seen in large and crowdsourced data pools taking place in America, new questions and answers about evidence bases would be raised.

Others agreed that it was difficult to encourage patients to view the treatment add-ons page, and one member stated that their clinic does not charge for red treatment add-ons following the HFEA's recommendations and the desire to put patients first.

7.20. Members discussed the benefits of using evidence beyond RCTs for other factors including the long-term effects of treatment on children. Although congenital anomalies are often reported in RCTs, few RCTs consider long-term follow up. The use of observational studies would therefore be beneficial when considering outcomes other than live birth rates.

7.21. Members then discussed the reliance on RCTs and that although it would be 'safe' to focus mainly on RCTs, it would be acceptable to align the evidence base with the MHRA and Cochrane. Some members considered that relying on RCTs may be paternalistic, and not presenting all available data is unhelpful to patients. One member stated that given the use of a rating system, the best way forward would be to present all good data available with thorough explanations.

7.22. The Chair brought together the session by setting out some conclusions from the discussion between members.

- Although there was not a unanimous view, there was a majority view that under certain circumstances it would be considered acceptable to widen the evidence base that is used for treatment add-ons beyond RCTs.
- However, alternative evidence that is considered should be aligned with work that has already taken place, including that of NICE, Cochrane, and the MHRA.
- The quality of RCTs continues to be an important topic and therefore triangulation could be considered routinely even when there are meta-analyses and RCTs available.
- SCAAC will make a recommendation to the Authority that additional evidence should be considered for treatment add-ons when there are no robust RCTs or meta-analyses available.
- It would be helpful for an algorithm or flow chart to be developed to assist SCAAC when expanding the evidence base and choosing what research to include. There is a history of using flow charts/decision trees within the HFEA, and they are also used within NICE and Cochrane, therefore would continue this idea of aligning with other key bodies.

Action: Make a recommendation to the Authority that in the absence of good and robust RCTs or meta-analyses, expanding the evidence base may be necessary and helpful when assigning treatment add-on ratings.

8. Any other business

8.1. The Chair summarised the meeting and thanked the Committee for their contribution to the formal SCAAC meeting and the guest speakers for their informative presentations at the morning workshop.

9. Chair's signature

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

Signature 

Chair: Tim Child

Date: 18/08/2022