Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

Monday 6th February 2023, 11:00am – 3:30pm

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

Authority members	Present	Tim Child (Chair) Jason Kasraie (Deputy Chair) (present for items 1-7) Frances Ashcroft (online) Alex Kafetz
External advisors	Present	Richard Anderson (online) Kate Brian Alison Campbell Robin Lovell-Badge Raj Mathur (online) (present for items 1-6) Kevin McEleny Scott Nelson Anthony Perry
	Apologies	Frances Flinter Zeynep Gurtin
Executive	Present	Dina Halai (Head of Regulatory Policy, Scientific) Annabel Salisbury (Policy Manager) Zoe Constable (Policy Manager- Civil Service Fast Stream) Ashley-Anne Brown (Meeting secretariat and Scientific Policy Officer) Peter Thompson (Chief Executive) (present for items 8) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information) Sharon Fensome-Rimmer (Chief Inspector) (online)
Invited speakers	Present	Peter Rugg-Gunn (Guest speaker, The Babraham Institute) Andy Vail (External reviewer for treatment add-ons)
Observers	Present	Ana Hallgarten (HFEA) Beth Rowbottom (HFEA) Kazuyo Machiyama (HFEA) Abigail Ng (HFEA) Molly Davies (HFEA) Evgenia Savchyna (HFEA) Amy Parsons (Department of Health and Social Care)

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. Declarations of interest were received from Tim Child, Jason Kasraie, Alison Campbell, Kevin McEleny, Kate Brian, Scott Nelson, Richard Anderson, Frances Ashcroft, and Raj Mathur.

1.3. Apologies were received from Zeynep Gurtin, Frances Flinter, and Jason Kasraie (for the later part of the meeting).

2. Matters arising

2.1. Minutes of the meeting held on 3rd October 2022 were agreed upon prior to the meeting.

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

2.2.1. Assessment of further outputs for the impact of the microbiome and if it needs to be considered as a treatment add-on will be done as part of an agenda item at the June 2023 SCAAC meeting.

2.2.2. The Executive will make amendments to the treatment add-ons application form and decision tree in line with the evolving treatment add-ons rating system and present to SCAAC members at the June 2023 SCAAC meeting.

2.2.3. Following recommendations from the committee to the Executive, information for patients has been added to the HFEA website regarding a risk of hypertension in pregnancy following frozen embryo transfer in medicated cycles of fertility treatment. This information has been added to the HFEA website page that discusses the risks of treatment.

2.2.4. The committee agreed to consider a framework for assessing artificial intelligence (AI) technologies which fall within the regulatory remit of the HFEA. The October 2023 SCAAC meeting will next discuss AI. In the interim, the Executive will publish a Clinic Focus article for the sector on developments in the regulation of AI.

3. Chair's business

3.1. The Chair highlighted to members that the Executive would start planning soon for the HFEA's annual horizon scanning meeting to be held during the ESHRE conference and will contact the committee about this.

4. Relevant public health developments

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

4.2. No committee members had submitted a paper on this agenda item before the meeting.

4.3. A recent media discussion regarding COVID-19 vaccinations and their impact on fertility treatment outcomes was raised.

4.4. Papers investigating the impact of Covid-vaccinations on menstrual cycle regularity had shown a limited effect of the vaccine's impact; moreover, there does not seem to be a link between the vaccine and female fertility. For males, there seems to be a short-term impact on male fecundity that is restored. This slight decline in fertility initially following the vaccines is likely due to some patients being hyperthermic, thus reducing sperm count, but this is only temporary.

5. Prioritisation of issues identified through the horizon scanning process and the committee work plan

5.1. The horizon scanning process is an annual cycle that highlights relevant issues identified from journal articles, conference attendance, expert recommendations, and the Executive's Annual Horizon Scanning meetings.

5.2. The Policy Manager highlighted that the impact of long-term cryopreservation of gametes and embryos has been added to reflect new storage laws. The AI topic has been expanded to include robotics and automation to reflect better what is being included in searches of this topic. The topic of COVID-19 for fertility and early pregnancy has been removed based on previous SCAAC recommendations and instead will be captured in the agenda item of 'Relevant public health developments'.

5.3. The committee made the following comments and recommendations:

5.3.1. The topic of AI, robotics, and automation to be more specific.

5.3.2. Although the topic of the impact of the microbiome on fertility and fertility treatment is classed as a medium priority, we should be aware of the potential for companies to market supplements that claim to improve fertility based on the microbiome.

Action: The Executive to circulate the horizon scanning prioritisation process information to members.

5.3.3. There will be talks next month on synthetic embryo-like-entities at Third International Summit on Human Genome Editing (March 6th- 8th, 2023) and a member suggested that this should be shifted from medium-priority to high-priority.

5.3.4. Stressed the importance of still discussing low-priority topics reasonably regularly.

5.3.5. Recommended moving the topic of ectogenesis down the work plan.

Action: The Executive to switch ectogenesis and long-term cryopreservation in the current work plan.

6. Review of ratings for treatment add-ons

6.1. The Policy Manager (ZC) reminded the committee about decisions made at the July 2022 Authority and October 2022 SCAAC meetings.

6.2. Members discussed the new grey category and noted the following points:

6.2.1. The evidence for treatment add-ons is often conflicting, and it is essential to acknowledge that.

6.2.2. Presenting uncertainties and divergent views allows patients to make their own choices and informs their conversations with their healthcare professionals.

6.2.3. All points raised about the grey category are akin to the uncertainty caused by the current amber rating for add-ons.

6.2.4. Explaining clearly what each rating means for patients is important.

6.3. The Director of Strategy and Corporate Affairs reminded the committee that the external reviewer provides recommendations. The SCAAC are able to agree or disagree with those recommendations.

6.4. SCAAC members discussed the treatment add-on decision tree and its methodology and agreed that:

6.4.1. The NICE guidelines consider up to three studies for inclusion in their process and the HFEA have followed this.

6.4.2. It was noted that there may never be three studies for a particular add-on, especially where an excellent large RCT has already been published. Although some of these definitive studies are unlikely to be investigated again, there is potential for the subgroups in these studies that showed positive effects to be studied in the future.

6.4.3. The language in the decision tree means the quality of the evidence (GRADE criterion) and the quality of an individual study, which are two different things, are getting confused. The Chair concluded that given the expertise that had already informed the decision tree, it might not be appropriate to make new significant changes, but changes in the wording would be welcomed.

6.4.4. A GRADE methodology classification of medium or high quality could be met without an RCT. There can be high-quality evidence from cohort studies alone and compelling evidence does not have to come solely from RCTs.

6.4.5. The Cochrane meta-analysis identified more studies about assisted hatching than those identified by the HFEA.

6.4.6. There is always a risk that data will be outdated when the HFEA publish the ratings online, given the dynamic nature of research. The committee suggested publishing the review period dates with the add-ons information. In addition, it is important that patients are made aware of the reasoning behind each decision the committee makes.

6.4.7. That key search terms do not always capture the topic depending on the searchable terms used by authors, and that is something we should be cautious of.

6.4.8. The Committee prefers not to include pre-prints as part of the evidence base, as they may never get published; or abstracts, given their lack of information.

6.4.9. Inclusion of a forest plot in the report provided by the external reviewer would not help to identify varied reliability of studies; additionally, it would not be able to identify a large cohort study that has been poorly designed.

6.4.10. The committee agreed actions to ensure completeness of our literature review methodology.

Action: The Executive will approach an expert librarian to assemble an initial list of search terms and recommend a methodology for searching for the literature.

Action: Some members of the SCAAC to review the search terms.

Action: The Executive will conduct a literature search using the search terms.

Action: All SCAAC members should review the resulting list of literature to confirm that all relevant data, i.e. the evidence, is being captured. SCAAC to highlight any missing papers to the Executive, and SCAAC to take ownership of the list of papers.

Action: Send papers to the external reviewer to analyse the evidence base's quality and make a recommendation for ratings.

Action: Next SCAAC meeting will be dedicated to discussing add-ons and allocating new ratings.

Action: Update website information on treatment add-ons to include details on the methodology and the range of dates within which publications have been reviewed.

Action: The Executive to refine the definitions and the decision tree and circulate to the SCAAC for input.

Physiological intracytoplasmic sperm injection (PICSI)

6.5. SCAAC members discussed the expert reviewer rating recommended for physiological intracytoplasmic sperm injection (PICSI) for each of the populations and subpopulations:

6.5.1. The PICSI study (Miller, 2019) is an example of a trial that has one large high-quality study but does not align with the current decision tree. The Chair highlighted that in the presence of one large high-quality definitive RCT that is unlikely to be replicated, it may be appropriate to make a decision on the basis of this evidence.

6.5.2. A trial could be considered as definitive if there are no other trials registered that could be more definitive, we could justify by stating that *we are aware of x trials around the world, but at present, this is the most definitive hence why we took x stance.*

6.5.3. It was decided that for PICSI, the SCAAC would be willing to make a recommendation based on a single significant-high-quality study.

6.5.4. A new subgroup of patients may benefit from PICSI, those with high DNA damage, but it was also highlighted that the data presented in this study was for most patients and not a subgroup analysis.

6.5.5. The authors suggest there is no difference to live birth rate for most patients. Older patients did show an improvement in live birth rate – although this data was examined retrospectively.

6.5.6. It was noted that the paper states that the study was not statically powered to investigate miscarriage. However, the data may indicate a genuine effect on miscarriage and the findings of a difference in miscarriage rates may lead to further investigations in subsequent studies.

6.5.7. Power calculations suggest that the difference between older women and the most fertility patient's subgroup is relatively comparable.

6.5.8. How the information showing no increase in live birth but a potential decrease in miscarriage might come across as confusing from a lay perspective; the committee cautioned that there is a need to explain this appropriately in the HFEA's website information.

6.5.9. The committee agreed the following ratings for PICSI:

- Black for live birth rate for most fertility patients
- Grey for live birth for older women
- Grey or Black for live birth rate for male-factor infertility patients
- Grey for miscarriage rate for most fertility patients
- Grey for miscarriage rate for male-factor infertility patients
- Grey for miscarriage rate for older women

6.5.10. A suggestion was made to rate Black for the live birth rate for male-factor infertility patients, but this was not concluded at the meeting and will be discussed again at the next meeting.

6.6. The Chair stated that following any modifications made in the upcoming weeks, the ratings proposed for PICSI must be reassessed to align with updated definitions.

Time-lapse imaging and incubation

6.7. SCAAC members discussed the expert reviewer rating recommended for Time-lapse imaging and incubation for each of the populations and subpopulations:

6.7.1. The variability of time-lapse given the use of time-lapse with selection algorithms, as an incubator, or both. That in the draft ESHRE guidance, they had split time-lapse into three as suggested by the expert advisor.

6.7.2. The consequence of rating time-lapse imaging and incubation, given that the incubators are widely used in clinics.

6.7.3. If machine learning from timelapse systems was encompassed in this add-on.

6.7.4. The Committee decided to return to review this add-on at a later date.

7. Synthetic embryo-like-entities

7.1. The Scientific Policy Officer presented a literature review on synthetic embryo-like-entities (ELEs) which identified thirty-nine studies published between November 2021 and December 2022. The HFEA has been considering the topic of synthetic ELEs since June 2018, when it was decided that given the complex developmental potential of some of these structures, synthetic ELEs should continue to be part of the annual horizon scanning process for the Authority to continue to monitor any developments.

7.2. The Chair welcomed guest speaker Dr Peter Rugg-Gunn from the Babraham Institute to speak on new developments in integrated and non-integrated stem-cell-based embryo models to date.

7.3. The committee discussed developments in the field of synthetic embryo-like-entities:

7.3.1. It is essential for the committee to understand these models' capabilities to ensure new regulations can appropriately capture the evolution of these models. The speaker believes there are no intrinsic reasons why models could not become more sophisticated; however, for this to happen, it will take more time and research. Moreover, in humans, it is impossible to know what the developmental potential is. Currently, there are similarities between these models and the human embryo but also apparent differences; blastoids cannot develop in the same way as embryoids.

7.3.2. Researchers who work in embryoid body models have produced precursors of practical lineages, such as early blood cells, for several years.

7.3.3. To reassure society that there are specific scientific goals for doing this work on embryo models, the speaker suggested a form of an oversight committee to investigate the reasoning for research and the type of research allowed in these models.

7.3.4. The building blocks required to make blastoid models are less well understood in non-human primates, and this understanding would come over time.

7.3.5. For specific model types, they are relatively poor at modelling the human embryo in terms of efficiency.

7.3.6. The speaker complimented the current regulation for human embryo research regulation and suggested that the regulation of stem cell-based embryo models may want to follow a similar methodology. Moreover, due to this research's complex and specialised nature, the HFEA may not be the best regulator to oversee these models. The speaker talked of Australia, where blastoids are considered embryos (the only country that classifies blastoids in this way), thus requiring an embryo license to work with blastoids. The speaker highlighted that in terms of regulation, a committee for embryo models should oversee all model types irrespective of the cells they are derived from.

7.3.7. The MRC stem cell bank currently does not regulate induced pluripotent stem (iPS) cells; thus, models derived from these stem cells require no oversight. Due to the different considerations of each model type, the speaker suggested having two committees with oversight, one for embryo models and the other for stem cells (such as those that use iPS cells).

7.4. The Head of Policy noted that the HFEA's consultation work to prioritise recommendations for change with the HFE Act includes a question on whether the Act should be future-proofed to accommodate scientific developments that could benefit patients.

8. Any other business

8.1. A member suggested engaging with Genomics England to ensure their feedback is included in SCAAC discussions where relevant.

8.2. A paper titled *Leukocyte telomere length in children born following blastocyst-stage embryo transfer* was raised by a committee member prior to this meeting. The paper concluded that the transfer of blastocyst-stage embryos was associated with shorter leukocyte telomere length (LTL) in children than in the transfer of cleavage-stage embryos, explaining the shorter LTL in children

conceived by ART than by spontaneous pregnancy. The Chair noted that the SCAAC will discuss the topic of Health outcomes in children covered by ART at a future meeting; thus, this paper will be addressed at this time.

9. Chair's signature

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

Signature

Chair:

Date: 12 April 2023