Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

Monday 2nd October 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) Alex Kafetz Frances Flinter Christine Watson (online)
	Apologies	Zeynep Gurtin
External advisors	Present	Robin Lovell-Badge Kevin McEleny Richard Anderson (online) Anthony Perry Scott Nelson (online) Alison Campbell
	Apologies	Kate Brian Raj Mathur
Executive	Present	Julia Chain (Chair of HFEA Authority) Peter Thompson (Chief Executive) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information) Mina Mincheva (Policy Manager) Ana Hallgarten (Public Policy Manager) Molly Davies (Scientific Policy Officer; Committee Secretariat)
	Apologies	Dina Halai (Head of Scientific Policy)
Invited speakers	Present	Rod Mitchell (University of Edinburgh) Suzannah Williams (University of Oxford)
Observers	Present	Hannah Sladen (HFEA Senior Legal Advisor) Jane Saxton (HFEA Scientific Inspector) Janki Bhatt (Civil Service FastStream) Emily Staricoff (Civil Service FastStream) Kath Bainbridge (Department of Health and Social Care)

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed members to the meeting.

1.2. The Chair reminded members of the advisory role of the SCAAC, highlighting that members should advise the HFEA on any significant implications for licensing and regulation arising out of scientific and clinical developments in assisted conception, embryo research and related areas.

1.3. A declaration of interest was received from Scott Nelson following a new affiliation with Alife Health.

2. Matters arising

2.1. The Executive updated the Committee on the matters arising from the meeting:

2.1.1. Assessment of further outputs for the impact of the microbiome and whether this needs to be considered as a treatment add-on is to be discussed at this meeting.

2.1.2. The Executive are in the process of amending the treatment add-ons application form and decision tree in line with the updated treatment add-on ratings system. Following this, the application for androgen supplementation as a treatment add-on will be brought to a future meeting of the SCAAC for reconsideration.

2.1.3. The Committee agreed to consider a framework for assessing artificial intelligence (AI) technologies which fall within the regulatory remit of the HFEA. AI will be discussed by the SCAAC in February 2024. In the interim, the Executive will publish a Clinic Focus article for the sector on developments in the regulation of AI.

2.1.4. Following the review of ratings for treatment add-ons at the July 2023 SCAAC meeting, the Executive is updating the patient-facing website information on treatment add-ons. The anticipated launch date for the updated website content is early October 2023. This will be accompanied by a communications campaign informing both the public and fertility sector of the changes and a joint letter from the SCAAC Chair and HFEA Chief Executive directly to the Person Responsible (PRs) at all HFEA licensed clinics.

2.1.5. As agreed at the July 2023 SCAAC meeting, three HFEA Authority members together with a SCAAC advisor will visit Newcastle Fertility Centre in December 2023 to hear about the organisation and staffing of the Mitochondrial Donation Programme in more detail.

3. Chair's business

3.1. The Chair welcomed Mina Mincheva as the Executives new Policy Manager and Molly Davies as the Scientific Policy Officer and Secretariat for SCAAC.

3.2. The Chair reminded the Committee of the upcoming Committee Effectiveness Review in which members will be asked to provide confidential feedback by email on the effectiveness and activity

of the Committee for discussion at the February 2024 SCAAC meeting and presentation at the March 2024 Authority meeting.

4. Relevant public health developments

4.1. At the June 2020 meeting, the SCAAC agreed to take on a monitoring role looking at the effects of COVID on fertility, assisted conception and early pregnancy. At the June 2022 meeting the Committee agreed to expand this standing agenda item to discuss relevant public health developments.

4.2. No papers were raised for discussion.

4.3. The Committee discussed whether papers of interest outside the scope of public health developments should be raised as an additional agenda item going forwards.

5. Health outcomes in children born from ART (including culture media)

5.1. Health outcomes in children born from ART was last discussed by the SCAAC in February 2020. The topic has since been expanded to include the impact of embryo culture media, which was last discussed by the SCAAC as an independent subject in February 2021.

5.2. The literature review identified 114 studies published between January 2020 and September 2023. The literature review indicated that there has been an increase in the number of follow-up studies on developmental outcomes during childhood and adolescence; particularly with relation to cardio-metabolic health, mental, social and cognitive development.

5.3. The Executive highlighted the current HFEA guidance on information which should be provided to patients regarding a proposed treatment as detailed by paragraphs 4.8 and 4.9 of the Code of Practice (version 9.3).

5.4. The Executive noted that the composition, quality and safety of culture media is not within the regulatory remit of the HFEA, falling within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). However, SCAAC monitor the effect of culture media in the context of its safety for the embryo, and the health of any children born following assisted conception.

5.5. The Committee discussed developments in the research:

5.5.1. The Committee highlighted the need for longer-term follow up studies looking into health outcomes in adults conceived using assisted reproductive technologies (ART), with particular weight put upon the need to establish the cause of differences between cohorts, should these be identified.

5.5.2. It was noted that performing linkage studies using health data from more recent cohorts of individuals conceived using ART is limited by prohibitions in the UK legislation and HFEA framework. The Committee recommended that the Executive consider moving towards improving

outputs for linkage studies from the UK database, although it was noted that this will not be possible retrospectively.

5.5.3. The Committee discussed the opportunity to evaluate outcomes with reference to performance difference of culture media specifically; however, it was highlighted that it would be difficult for research groups to identify causation due to many inherent confounding factors (eg stimulation protocols, incubators, ambient environment). It was noted that *in vitro* studies using human material is limited by the 14-day rule, although combining data recorded on the type of culture media with data held on the HFEA Register (ie perinatal outcomes such as preterm birth) could enhance outcome data on studies looking into the effects of culture media in humans.

5.5.4. Concerns were raised around the collection of commercial data contributing to product marketing.

5.5.5. SCAAC discussed the use of the HFEA Register data and data that could be collected from clinics on a voluntary basis. The burden and appetite for enhanced reporting was raised as a concern and the Committee suggested that for this to be productive it would be appropriate for SCAAC to define the clinical questions that could be addressed through the submission of specified data (ie what is known and may be relevant). It was suggested that robust data known to be associated with long-term outcomes could be prioritised in the first instance (eg baseline parameters such as body mass index).

5.5.6. Following the embedding of the Patient Register Information System (PRISM), due to complete in summer 2024, the Executive raised the possibility of expanding the data dictionary with guidance from the Committee.

5.6. The Committee made the following recommendations:

5.6.1. In time, the Executive to consider the appropriateness of collecting voluntary data on culture media as part of the HFEA Register data. A small working group of Committee members could be established to define the clinical questions to be addressed and the appropriate data that could be submitted to the Register in order to answer these questions. This could be discussed in due course with the Licenced Centres Panel (LCP) and could also look into the possibility of improving utility of future UK ART data for linkage studies.

6. *In vitro* derived gametes

6.1. Members were reminded that the Human Fertilisation and Embryology (HFE) Act 1990 as amended prohibits the use of *in vitro* derived gametes in treatment; however, they can be used in research licenced by the HFEA. Human in vitro gametes (unfertilised and not generated into an embryo) fall within category 1b research as described by the Guidelines for Stem Cell Research and Clinical Translation (2021).

6.2. It was noted that during the most recent horizon scanning process discussed in February 2023, the topic was recognised as a medium priority area for the SCAAC.

6.3. The Chair welcomed guest expert Professor Rod Mitchel from the University of Edinburgh to speak on the new developments in *in vitro* spermatogenesis:

6.3.1. Professor Mitchell introduced the different methodologies used to generate sperm *in vitro*, overviewing the developments in current research using embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and spermatogonial stem cells (SSCs). While these have been successfully used in some animal models to generate functional gametes (resulting in offspring), there has been very limited success in humans.

6.3.2. Professor Mitchell further outlined the ongoing challenges related to human *in vitro* spermatogenesis that include testing for gamete functionality, safety concerns over correct genetic and epigenetic make-up, efficiency of generating spermatozoa *in vitro*, and ethical acceptability. He concluded with suggested areas that *in vitro* spermatogenesis research should focus on: *in vitro* culture models, cryopreservation techniques and culture media composition.

6.4. Professor Suzannah Williams from the University of Oxford was then invited to present on in vitro oogenesis:

6.4.1. Professor Williams introduced the methods of *in vitro* oogenesis, highlighting the importance of these gametes as model systems to study germ cell development and as an alternative source of gametes for reproduction. She elaborated on the challenges of generating *in vitro* derived oocytes: the appropriate culture media, the use of correct transcription factors, the source of supporting cells, and consideration of accurate timing of all these parameters that require thorough understanding of ovarian biology. Professor Williams referred to issues and concerns with generating oocytes *in vitro* arising from murine studies that may also need to be considered when attempting human *in vitro* oogenesis. Among others, she mentioned impaired meiosis, gamete developmental incompetence, success rate of gamete production and potential health implications for resultant offspring.

6.4.2. She also noted that there are several private companies currently known to be working on developing human fertility treatments, including the development of a whole ovary cryopreservation for reimplantation and *in vitro* oocyte generation and development.

6.4.3. Professor Williams concluded that the technology to support the generation of *in vitro* derived oocytes is imminent and highlighted concerns regarding the current gap in regulation to respond to the rapid advancements in the field. She noted that there are a number of legal and ethical challenges for the regulation of the process of *in vitro* oogenesis.

6.5. The Chair highlighted that draft proposals for Modernising Fertility Regulations had been presented at the September 2023 Authority meeting. The Chief Executive commented that, although the proposals do not explicitly detail the scientific advancements, proposals should be developed to clearly emphasise the urgent need for regulatory oversight of these new 'categories' of cells.

6.6. As indicated by the speakers, clinical potential for these techniques is becoming increasingly near. Concern was raised regarding the timeline for legislative change and the rapid progress of research in this field of research.

6.7. The Committee and speakers discussed the developments in the field of *in vitro* derived gametes:

6.7.1. A member indicated that progress towards *in vitro* culture of human spermatogonial stem cells was limited by difficulties deriving a culture system which accommodates slow replication. The speaker (RM) agreed that progress in culturing of isolated or dissociated spermatogonial stem cell

was distant, however development of cells may be progressed by providing support through introducing somatic cell component as whole tissue or organoids. Concerns were raised around the use of interspecies somatic cells for the development of human spermatogonial stem cells in culture and the resultant ethical and clinical considerations.

6.7.2. A member asked the speaker to provide further information on the source of somatic stem cells being used for in vitro oogenesis. The speaker (SW) noted that the research is currently focused on the requirement for theca and supporting cells.

6.7.3. The speaker (SW) noted that, with relation to *in vitro* oogenesis, ongoing conservation research has allowed similarities and differences between species to be better understood. The speaker agreed that use of interspecies supporting cells for the development of human gametes with clinical applications would be concerning due to the existing unknowns.

6.7.4. A member raised the possibility of restoring fertility potential through the transplantation of preserved pre-pubertal testicular tissue. The speaker indicated that there are at least three international centres who are in the process of preparing applications to allow for testicular tissue to be transplanted back to patients. The Policy Manager (MM) highlighted that a centre in Belgium has received ethical approval to begin transplanting pre-pubertal tissue back to adult male survivors of childhood cancer. In the UK, this will involve HFEA approval to test functionality of resultant gametes.

6.7.5. The Committee considered the definition of a reliable indicator for human functional assays. It was noted that more work is required to establish appropriate methods to test functionality of *in vitro* derived sperm. A member noted embryos need to be cultured beyond 14-days to understand early development of tissues, epigenetic factors, etc.

6.7.6. It was noted that the techniques of *in vitro* spermatogenesis or transplantation of tissue back to the patient will not correct the underlying cause of infertility for patients who cannot produce sperm *in vivo*. It is likely that further intervention (such as genome editing) would be required to fully restore function.

6.7.7. A member highlighted that, whilst the potential to generate XX cells from XY induced pluripotent stem cells (iPSCs) may be possible, the generation of XY cells from XX iPSCs is highly unlikely.

6.8. The Committee agreed that patients will soon be able to access treatments involving the generation of *in vitro* derived gametes and therefore the Authority will need to consider how regulation of these 'other categories of cells' may be defined in future legislation.

6.9. It was noted that the breadth of methodology in this field raised a variety of legal and ethical questions. The Executive should strive to understand what may already be considered by existing legislation and what techniques are more likely to be realised in the near future.

6.10. The Committee made the following recommendations:

6.10.1. The Executive to continue to keep abreast of the ongoing research and advances in the area. This work should continue to reflect upon the legal hurdles and ethical considerations.

6.10.2. The Executive to communicate the rapid scientific advances and researchers' concerns regarding the lack of oversight with the Department of Health and Social Care as part of the Executives work on reforming the HFE Act.

7. The impact of the microbiome on fertility treatment outcomes

7.1. Due to unforeseen circumstances, SCAAC members agreed to provide feedback on this item via email following this meeting. Recommendations and comments received are noted below.

7.2. The Executive circulated a literature review highlighting 120 studies published between February 2019 and September 2023 investigating the possible relationship between the human microbiome and fertility or fertility treatment outcomes. As noted by the paper, this topic was classed as a medium priority area for the SCAAC at the February 2023.

7.3. The Committee acknowledged that there has been a substantial increase in published literature on the effects of vaginal and endometrial microbiota on fertility outcomes, highlighting that the research is moving from testing towards the development of treatments.

7.4. The Committee members provided feedback on the recent developments on the topic:

7.4.1. A member noted that the research indicates that vaginal and endometrial microbiota could influence pregnancy outcomes for IVF patients, highlighting that bacterial vaginosis may affect 20-50% of women of reproductive age and thus could be a risk factor for infertility. It was also noted that levels of specific *Lactobacillus* species in the vaginal microbiota seem to be associated with IVF success rates and could be a useful guide for the timing of IVF cycles.

7.4.2. A member noted that there appears to be a growing public interest in the role of the microbiota on fertility outcomes and patients are beginning to use private companies for microbiota testing. In addition, both male and female microbiome supplements are currently being marketed by private companies to patients, with the suggestion that they will be able to “optimise fertility”.

7.4.3. A member mentioned that as microbiota can be modulated with probiotics and antibiotics the use of these treatments in fertility treatment may also need to be considered going forward. However, it was noted that in animal studies it has been difficult to alter a pre-existing microbiota with supplementation only, which would require using strong antibiotic treatments to disadvantage resident microbiota.

7.4.4. A member noted that, at present, the uptake of testing and/or use of treatments by patients remains limited, having too low a risk to warrant an add-on rating by the Committee at this time.

7.4.5. A member highlighted that it may be pertinent to consider the potential importance of the wider microbiome and the effects on hormone production, for example the gut microbiome and its impact on the hypothalamus and subsequent production of pituitary hormones.

7.5. The Committee made the following recommendations:

7.5.1. The Committee suggests that interventions which claim to modulate the vaginal and/or endometrial microbiome should not be considered for inclusion on the add-ons list due to limited uptake of these treatments and insufficient evidence to warrant rating by SCAAC at this time.

7.5.2. The Committee to continue closely monitoring the development of marketed supplements and treatments that claim to improve fertility based on the microbiome.

8. Review rating for artificial oocyte activation add-on

8.1. The Executive reminded the Committee that artificial oocyte activation using calcium ionophore was introduced to the HFEA's traffic light rated list of add-ons in February 2017, when it was assigned an amber traffic light rating by the Committee. It was noted that artificial oocyte activation using calcium ionophore sits on the authorised process list for use only selected patients, for example, those with a phospholipase C zeta (PLCzeta) deficiency.

8.2. The Committee were reminded of the definition of an add-on, as agreed by the Authority in July 2022.

8.3. During the review of treatment add-ons, undertaken at the July 2023 SCAAC meeting, the Committee recommended delaying the allocation of a rating to artificial oocyte activation using calcium ionophore until the Association of Reproductive and Clinical Scientists (ARCS) and the British Fertility Society (BFS) had updated the best practice guidelines. The use of ICSI in ART: evidence for practice was published in August 2023.

8.4. The Deputy Chair of the SCAAC and supervising author of the best practice guidelines, summarised the evidence and recommendations:

8.4.1. Artificial oocyte activation should not be used routinely with ICSI as its safety, in terms of potential developmental consequences and birth outcomes, has yet to be established.

8.4.2. ICSI with artificial oocyte activation may be used where two previous routine ICSI cycle(s) have resulted in <30% or no fertilisation.

8.4.3. Where artificial oocyte activation is used, patients should be advised that safety, in terms of the potential developmental consequences and birth outcomes, has not been established.

8.4.4. Patients should be provided with safety data relating to the specific artificial oocyte activation technique used.

8.5. The Deputy Chair noted that, when developing the guidelines, the authors considered the evidence of safety cautiously. Although no evidence of harm was identified, long-term effects of this technique have not yet been established; Therefore, appropriate counselling, consent, and provision of safety data to those offered this technique is required.

8.6. The authors considered appropriate use of the technique to be limited to patients with evidence of low or no fertilisation, as evidenced by 8.4.2. In the absence of PLCzeta testing, which may not be accessible to all patients, two routine cycles of ICSI were considered suitable to identify patients who would benefit from this process.

8.7. The supervising author commented that, when developing the guidelines, the consensus between authors of the paper was consistent.

8.8. One member raised whether the authors has considered the use of this technique for poor blastocyst or embryo development. It was noted that the authors were aware of this research but wanted to take a cautious approach, not permitting the technique for other indications until further evidence is available.

8.9. The Director of Compliance and Information highlighted that should the recommendation change, impartial patient information explaining the professional body guidelines would be made available through the HFEA website.

8.10. One member noted that the guidelines were consistent with the recommendations from the European Society of Human Reproduction and Embryology (ESHRE) good practice recommendations.

8.11. **The Committee made the following recommendations:**

8.11.1. The Committee determined that artificial oocyte activation using calcium ionophore would not meet the HFEA criteria for treatment add-ons as it should not be offered to the general population. The Committee agreed that that artificial oocyte activation using calcium ionophore should be removed from the HFEA's add-ons list.

8.11.2. The Committee agreed that the removal of the technique from the add-ons list should be accompanied by signposting to the professional body guidelines. A summary of the relevant background information which led to the decision should be highlighted on the add-ons webpage.

9. Any other business

9.1. Prior to the meeting, the Executive had circulated the following papers to the Committee for consideration:

1. Risk of Stroke Hospitalization After Infertility Treatment - PMC (nih.gov)

2. Complete human day 14 post-implantation embryo models from naïve ES cells | Nature

9.2. In relation to the paper on the risk of stoke hospitalisation, a member commented that findings do not show a worrying trend for ischaemic stroke but a slightly increased risk of haemorrhagic stroke. It was noted that patients in the study had a slightly higher average age and that no account was taken as to the cause of the infertility. Members concluded that this falls outside of the remit of the HFEA.

9.3. With regards to the paper on 14-day embryo models, a member commented that this work demonstrates the need to extend the 14-day limit. This raises a number of challenging ethical issues regarding the status of embryo models, whether these should fall within the remit of the HFEA, and whether embryo-like models should be treated differently to embryos.

9.4. It was noted that, in order to validate embryo-like models against embryos created from *in vivo* derived gametes, both embryo-like models and embryos will need to be grown beyond 14 days. The question of the time limit to which they may be grown will need to be established.

9.5. A member highlighted two additional reports of interest, indicating that both support a 28-day limit with conditionality and nuance:

1. Public dialogue report on research involving early human embryos (published 24th October 2023)

2. The 14-day rule in the Dutch Embryo Act (published 31st October 2023)

9.6. The next SCAAC meeting will be held on Monday 5th February 2024, and will be in person.

10. Chair's signature

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

Signature

Chair: Tim Child

Date: 30 November 2023