Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

Monday 5th February 2024, 11:00am – 3:00pm

Microsoft Teams

Authority members	Present	Tim Child (Chair) Alex Kafetz Frances Flinter Christine Watson
	Apologies	Zeynep Gurtin
External advisers	Present	Jason Kasraie Kate Brian Raj Mathur Robin Lovell-Badge Anthony Perry Scott Nelson Alison Campbell
	Apologies	Kevin McEleny Richard Anderson
Executive	Present	Julia Chain (Chair of Authority) Peter Thompson (Chief Executive) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information) Dina Halai (Head of Scientific Policy) Mina Mincheva (Policy Manager) Emily Staricoff (Policy Manager) Molly Davies (Scientific Policy Officer; Committee Secretariat)
Speakers	Present	Ana Hallgarten (Department of Health and Social Care, former HFEA Public Policy Manager)
Observers	Present	Kath Bainbridge (Department of Health and Social Care) Ruby Relton (HFEA Social Research Manager) Dharmi Degui (HFEA Policy Officer) Kezia Quarrie-Jones (HFEA Social Media & Digital Communications Officer) Amy Charles (HFEA Inspections and Logistics Officer) Liliane Ingabire (HFEA Payables and Receivables Administrator)

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed the Committee and introduced the standing observer representing the Department of Health and Social Care.

1.2. Apologies were received from Zeynep Gurtin, Richard Anderson, and Kevin McEleny.

1.3. 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.

1.4. No declarations of interest were received in relation to the meeting agenda.

2. Matters arising

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

2.1.1. Following the October 2023 meeting, members ratified their recommendations on the topic of 'The impact of the microbiome on fertility treatment outcomes' via email, stating that interventions to modulate the vaginal and/or endometrial microbiome should not be considered for inclusion on the add-ons list at this time.

2.1.2. The Executive are in the process of amending the treatment add-ons application form and decision tree for considering applications for additional add-ons 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 previously agreed to consider a framework for assessing artificial intelligence (AI) technologies which fall within the regulatory remit of the HFEA. The topic of 'AI, robotics and automation in fertility treatment' was discussed at this meeting under item 9.

2.1.4. Following the review of ratings for treatment add-ons at the July 2023 SCAAC meeting, the Executive has updated the patient-facing website information on treatment add-ons, publicised by an accompanying communications. Based on feedback received from the sector, the Executive will make minor changes to the patient information on our website to make information more explicit.

2.1.5. As agreed at the July 2023 SCAAC meeting, three HFEA Authority members together with a SCAAC External Adviser visited Newcastle Fertility Centre to hear about the Mitochondrial Donation Programme in more detail. The Committee Chair provided an update on the visit under item 5 of this meeting.

3. Chair's business

3.1. The Chair noted that this will be Raj Mathur's final SCAAC meeting and thanked Raj on behalf of the Committee and Executive for his valuable contributions to the SCAAC during his 10 years as an External Adviser.

3.2. The Chair noted that the HFEA are in the process of recruiting three new External Advisers to the SCAAC. The Committee will be informed as these appointments are made.

3.3. The Chair informed the Committee that following the end of this term of office as an Authority member, Jason Kasraie will continue to serve as an External Adviser to the SCAAC until January 2025.

3.4. The Chair thanked the Committee for their recommendations on the interim paper detailing revision to the Authorised processes list and decision tree for authorising, reviewing and deauthorising processes, which was circulated to the committee by email between meetings.

3.5. In summary, the Committee supported the recommendation to change the SCAAC Standing Orders to make it the sole decision-making committee for applications regarding authorised processes. The Committee were notified that the Statutory Approvals Committee (SAC) had also been consulted on this proposal and are in support of the new process, pending Authority approval.

3.6. An External Adviser noted that, should the Authority agree to the proposed amendments to the decision tree for authorising, reviewing and deauthorising processes, the Executive should consider whether the name of the SCAAC should be amended to reflect the change from an 'advisory' Committee.

3.7. The Chair informed members that the proposed modifications to the revised authorised processes list will be presented at the March Authority meeting.

4. Relevant public health developments and research findings

4.1. During the October 2023 meeting this item was expanded to include research findings outside the scope of public health developments which are relevant to the interests and role of the SCAAC.

4.2. Prior to the meeting, a member had highlighted the following text to the Committee for consideration:

- Introduction - In Vitro–Derived Human Gametes as a Reproductive Technology - NCBI Bookshelf (nih.gov)

4.3. As this text has been included in the horizon scanning literature search, the Committee was asked to consider this summary with relevance to item 6.

4.4. No further papers were raised for discussion.

5. Mitochondrial donation programme update

5.1. The Chair informed the Committee that three Authority members (Tim Child, Frances Flinter, Jason Kasraie) and one External Adviser to the SCAAC (Anthony Perry) visited Newcastle Fertility Centre in December 2023 to hear about the organisation and staffing of the mitochondrial donation programme in more detail. The visit was not an inspection but a visit of support by representatives of the HFEA, organised to understand the current status of the programme.

5.2. During the visit, members were given a comprehensive update on the programme and were reassured that the programme was functioning well. The Chair and an Authority member present for the visit relayed details of the clinical programme:

5.2.1. Of the patients referred to the programme, approximately half of the patients have undertaken preimplantation genetic testing (PGT) cycles and the remaining had gone onto pursue pronuclear transfer (PNT) treatment cycles. All patients have at least one counselling session ahead of treatment.

5.2.2. Members of the SCAAC had constructive discussions with the team about how some of the challenges might be addressed.

5.2.3. A shortage of donor eggs specifically for PNT treatment programme was noted.

5.2.4. To date, 9 patients have completed the programme. There remains a relatively low number of patient referrals, with 32 applications approved by SAC to date.

5.2.5. At present, the storage and treatment licence held by Newcastle covers mitochondrial donation treatment using PNT only. At a research level, the team are addressing a number of limitations associated with mitochondrial donation technologies and are investigating maternal spindle transfer (MST) treatments to approach mitochondrial disease.

5.3. Concerns around the lack of publication having the potential to propagate inappropriate use of this technology internationally and impact on Newcastle's ability to secure further research finding were raised.

5.4. The Chair highlighted that there are no requirements set out by the law which relate to the publication of research and therefore it is not possible to incorporate this provision into the Licence Conditions.

5.5. A member highlighted that two embryologists were currently being trained on the technique and that the team at Newcastle were aware of the need to increase the number of practitioners capable of performing the procedure. The Committee recognised that the time commitment required of practitioners to the programme is a constraint to training and retaining staff.

5.6. The team at Newcastle will be invited to a future SCAAC meeting to give an update.

6. Prioritisation of issues identified through the horizon scanning process (including review of Committee workplan)

6.1. The Committee was reminded that the horizon scanning process is an annual cycle that highlights relevant issues in fertility treatment and embryo research identified from journal articles, conference attendance, and expert recommendations from January - December 2023. The frequency at which topics are discussed by the Committee is determined by their priority. The Committee were asked to be mindful of the role and function of the SCAAC when considering topic prioritisation and workplan.

6.2. The Committee agreed to the renaming of the following topics:

- Artificial intelligence (AI), robotics and automation **in fertility treatment** (previously named 'artificial intelligence (AI), robotics and automation')
- **Emerging** technologies in embryo and gamete testing (previously named 'new technologies in embryo and gamete testing')
- **Germline/heritable** genome editing (previously named 'genome editing')

- **Stem cell based** embryo models (previously named 'Synthetic embryo-like entities')

6.3. The Committee agreed that 'Testicular tissue transplantation to restore fertility in males' is considered as a distinct topic from 'In vitro derived gametes' due to recent developments in immature testicular tissue transplantation to restore fertility in adult males who are survivors of gonadotoxic treatment in pre-puberty. In addition, the Committee agreed that 'metabolomic profiling' be incorporated into the topic of 'Emerging technologies in embryo and gamete testing'.

6.4. In relation to the topic prioritisation, the Director of Strategy and Corporate Affairs noted that should members feel that there have been limited publications relevant to a specific topic, which therefore do not warrant further discussion, the workplan may be adjusted to postpone the discussion of a topic.

6.5. The Committee made the following comments and recommendations:

6.5.1. Overseas mitochondrial donation is being investigated as a treatment for infertility (not mitochondrial disease). Although this is not legal in the UK, but given discussion of future changes in the Act, Members agreed that this should be maintained as a high-priority topic with discussion in October 2024.

6.5.2. Recommend moving 'Impact of stress on fertility treatment outcomes' down the workplan if needed.

6.5.3. The Committee agreed that discussions on the topic of 'Scientific considerations relevant to the 14-day rule' and 'Stem cell based embryo models' should be held at the same meeting due to their relevance to one another.

6.5.4. The Executive noted that these topics will be of relevance to concurrent work on modernising the HFE Act. Due to the timeframe of this work and anticipated outputs from external organisations, such as those from Cambridge Reproduction, it is most appropriate to schedule these topics for October 2024 to allow for a full discussion. The Chair invited Robin Lovell-Badge to attend the October meeting as an expert to contribute to these discussions, as his term as an External Adviser will have ended by then.

6.5.5. An External Adviser queried how the Executive determined the prioritisation criteria for 'Would there be high patient demand/clinical use if introduced' on the topics of 'Germline genome editing', 'Alternative methods to derive embryonic and embryonic-like stem cells' and 'Testicular tissue transplantation to restore fertility in males'. They also questioned the timeframe for clinical introduction of in vitro derived gametes, highlighting that some companies are stating that these will be available imminently. The Committee recommended that the Executive use less binary terminology when prioritising topics.

Action: The Executive to review Annex C: Topic prioritisation table.

6.6. The Policy Manager informed the Committee that topic of 'Treatment add-ons' has been separated from the horizon scanning process as the literature review of treatment add-ons is performed independently of the horizon scanning process. The Committee were asked to consider the frequency of review for treatment add-ons with the Executive proposing every three or five years. Between reviews, the Committee and the Executive should continue to actively monitor and highlight relevant publications that could change the rating of an add-on, and an ad-hoc review can be carried out for a particular add-on should this arise.

6.7. A member highlighted that, due to expertise of those on the Committee, the SCAAC can be confident that members will be aware of any substantial developments in research relevant to the treatment add-ons between reviews. Furthermore, they highlighted that Cochrane reviews are also not usually updated within five years of publication. Another External Advisor highlighted that the current NICE review of the Fertility Guideline will include information on add-ons, therefore updating the HFEA's add-ons information every five years is appropriate.

Recommendation: The Committee agreed that the review of treatment add-ons ratings should be carried out every five years, publishing recommendations at every 5-year mark.

Action: Members to highlight research developments relevant to the add-on ratings to the Committee under the standing item: 'Relevant public health developments and research findings'.

Action: Executive to update the wording on the HFEA website to reflect that the agreed review frequency and process.

6.8. An External Adviser suggested that patients should be informed that the Authority continue to monitor research relevant to treatment add-ons between the full rating review of treatment add-ons.

6.9. An External Adviser proposed that work should commence ahead of 5 years to allow review of add-ons ratings to be considered and published at the 5-year mark, i.e. publication date for the next review of ratings for treatment add-ons should be October 2028.

6.10. The Executive invited the Committee to email recommendations for additional External Advisers to support the Committee on an ad-hoc basis as relevant to specific topic discussions.

7. The impact of long-term cryopreservation of gametes and embryos

7.1. The Committee was reminded that this topic was introduced to the SCAAC in February 2023 following the amendments to the storage laws bought in by the Health and Care Act 2022. In relation to this item the Committee is asked to monitor any safety or viability concerns relating to the keeping of gametes or embryos in long term storage.

7.2. Jason Kasraie, began the discussion by summarising the recent developments presented by the literature:

7.2.1. Of the notable research which present data from retrospective cohort studies, there is conflicting evidence on whether there is or isn't a detrimental effect of cryopreserving gametes or embryos for increased periods. Of the research that indicated there is an effect arising from increased storage time, approximately 70,000 patients made up the cohort, in comparison to approximately 54,000 patients showing no effect.

7.2.2. There is no significant emerging evidence that long term storage results in birth defects or concerning neonatal outcomes in children born following long-term vitrification.

7.2.3. A number of confounding factors may additionally contribute to these results, for example the differences in cryoprotectant used, improvements in vitrification-thaw procedures over time, differences in the skill set of embryologists, closed vs. open cryopreservation systems, liquid vs.

vapour phase methods, etc. Other external factors which may affect embryo viability include audits, are temperatures dropping/rising during auditing.

7.2.4. It is important to establish the mechanism by which harm is happening (if it is happening). One small genetic study suggests there may be a potential difference in the way microRNA is expressed, yet a different study indicates there is no difference in DNA methylation profiles.

7.2.5. Currently there is not sufficient evidence to be confident that there is a detrimental effect of long-term cryopreservation. However, it may be appropriate to highlight to patients that the safety of long-term cryopreservation is yet to be established.

7.3. The Committee discussed the developments on this topic:

7.3.1. It was noted that agreed that external factors, including differences in audit practices and storage systems, are difficult to control for making it challenging to determine whether increasing storage time is the factor resulting in reduced embryo and oocyte viability. It was suggested that if guidance was provided by the Authority to clinics, it would be in relation to external practices.

7.3.2. It was noted that there are no safety concerns in relation to neonatal outcomes for the resultant child, indicating that the main concerns relate to the viability of material with increasing storage durations.

7.3.3. It was noted that due to the number of variables it may not ever be possible to be conclusive. From current research it was not possible associate mechanisms which would be responsible for a drop in viability that is not responsible for a drop in safety.

7.3.4. The Committee agreed that due to insufficient evidence it is not possible to determine that long-term storage has no effect on the viability of gametes or embryos at this time. The Committee will continue to monitor the literature on this topic with high priority.

7.3.5. The Committee advise that should further evidence be published which confirms there is a detrimental effect arising from the length of cryopreservation on viability of embryos or gametes, this should be communicated to patients who are storing material for increased durations. The Committee agreed that this remains a way off.

7.3.6. It was noted that patients are encouraged to freeze eggs younger to increase availability of material should they wish to begin treatment later. This is in conflict with viability concerns, however, if patients freeze eggs in their 20s, on balance this remains the sensible choice with the evidence available at this time.

7.3.7. It was noted that should the viability concerns be realised, this will have the most significant impact on patients who are storing material due to cancer treatment or for social reasons. As highlighted by the paper, only a small number of these patients return to thaw gametes and embryos.

7.3.8. An External Adviser highlighted the editorial by George and Keefe (2023) on the paper by Yan et al. (2023), stating the conclusions support the need for further studies controlling for confounding factors.

7.3.9. The Committee went onto agree that the Authority should take a cautious yet reassuring approach, explaining to patients and the sector that there is an absence of conclusive data on the impact of long-term cryopreservation of gametes and embryos rather than evidence of effect. This

should highlight that the Committee are not concerned about the impact of long-term cryopreservation on safety.

Action: The Executive to update patient-facing website information on long-term storage to highlight to patients that there is a lack of evidence regarding the impact of long-term storage on viability of embryos. The wording will be agreed with select members of the Committee.

8. Heritable Genome Editing

8.1. The Committee were reminded that the HFE Act does not permit interventions in the nuclear DNA of gametes or zygotes for the purpose of germline genome editing in reproduction. Genetically modified embryos are currently only permitted in research and cannot be grown in culture for more than 14 days.

8.2. It was noted that the most recent discussion on the topic of 'Genome editing' was held in October 2020, with horizon scanning outputs examined in 2021 and 2022.

8.3. The Committee provided feedback on the recent developments on the topic:

8.3.1. An External Adviser commented that the World Health Organization are still developing recommendations made by the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. This work is predominantly focused on issues of equity and access of somatic genome editing.

8.3.2. At present the most interesting methods in the field are base editing and prime editing which are thought to be much safer than methods relying upon non-homologous end joining or homology-direct repair. These techniques are being applied in trials for somatic gene therapy but there is limited work using these techniques for embryo germline editing. Research has to be done on embryos, therefore the data from trials for somatic gene therapy are not transferrable. However, an External Advisor had the view that relevant research will progress at pace.

8.3.3. Another External Adviser agreed that it is unlikely that CRISPR-Cas9 systems will be used for early genome editing due to their potential to induce catastrophic off-target effects.

8.3.4. It was noted that at present there is no recent research into the application of other techniques – such as prime editing – for heritable germline editing which have made concerns more pressing for the Authority. Experience from somatic gene editing trials will go some way to inform understanding, however further research on embryos or gamete precursors (in vitro derived) is required to fully understand the application of genome editing techniques on the germline.

8.3.5. The Committee agreed that it is currently unsafe to proceed with heritable genome editing for clinical practice, as prohibited by the HFE Act. Should the Executive wish to release a statement, the Committee recommend the following wording:

"The HFE Act does not permit interventions in the nuclear DNA of gametes or zygotes for the purposes of germline genome editing in reproduction. The last SCAAC review of studies using genome editing techniques on human and animal embryos was presented to the committee in February 2024. Significant further scientific research into improving the accuracy of genome editing technologies is required before germline applications can be considered."

It should be made clear that for genome editing to be applied to the germline for use in clinical practice, changes to the HFE Act will be required.

8.3.6. The Committee recommended that scientific advances in techniques and what is technically feasible for germline editing should be the focus of future Committee discussions.

8.3.7. An External Adviser noted that, should methods of germline genome editing be shown to be safe there will likely be the requirement for the Authority to respond rapidly (due to demand) and the Executive should remain mindful of this when developing Act proposals.

8.3.8. Concerns were raised about the possibility of genome editing techniques to modify the epigenome or mitochondrial DNA of early embryos, which is not prohibited by the current wording of the HFE Act. Although the Committee are not aware of specific applications of this technology, the possibility of this was highted to the Executive.

Action: The Executive to consider consulting an expert on epigenetics to comment on techniques of modifying the epigenome of the early embryo.

8.3.9. The Chief Executive noted that should the Department of Health and Social Care take forward proposals for modernising the HFE Act this will be considered as part of this work.

9. Artificial intelligence (AI), robotics and automation

9.1. A summary of the paper highlighting the key developments in the application of AI, robotics and automation as part of fertility treatment was presented to the Committee. Notable advancements in basic science, clinic facing advancements, and robotics and digital health were overviewed. The Committee's attention was drawn to specific policy developments relevant to the use of AI in healthcare, for example guidance published by the Medicines and Healthcare products Regulatory Agency.

9.2. The Committee were reminded that this topic was last discussed in October 2022.

9.3. The Committee praised the quality of the paper presented, highlighting the value of the paper in itself as a useful resource for the sector.

9.4. A member commented that the topic of AI in the context of HFEA regulation needed to be refined further, suggesting that digital health interventions, such as provision of patient health information and use of apps, should be considered separately. To develop the focus the Executive may wish to consider the specific remit of the Authority in relation to each of the headings set out in the paper: Developments in basic science; clinic facing advancements; AI models to predict or improve treatment outcomes; uses of AI in male fertility, semen and sperm assessment; advancements in robotics. For example, the bias present in models of machine learning as trained by humans or machines.

9.5. A member suggested that an appropriate output from the Authority may be a statement to the sector noting that innovation in this field is moving faster than regulation. An External Adviser noted that lay summaries of the paper would additionally be of benefit to clinical staff and patients.

9.6. It was noted that in the next 12 months we are likely to see a much greater use of machine learning models for outcomes predictions, therefore it will be pertinent for the sector to ensure that the models will be built on good quality patient data and appropriately verified to ensure

consistency. These tools should be applied to support the expectations of patient seeking treatment and feedback on their use from patients and professionals should be sought to ensure that their use is appropriate. The External Adviser noted that there is potentially a place for the Executive to provide guidance to clinics who are considering adopting these prediction models, for example guidance which highlights the appropriate questions to ask developers.

9.7. In addition, clinic staff will need appropriate training on the interpretation of commercial models and ways to communicate outputs with patients.

9.8. Prediction models for individual and group clinics have already been developed by Univfy using the clinics own data with outputs of these models being dependent upon the quality of data and the data collected by clinicians. There is not a standardised agreement for what is seen to be a good quality dataset. Input data should be of high quality and be tested and validated and given to patients in the right way.

9.9. An External Adviser shared an image highlighting the potential areas of application for AI in assisted reproductive technology. Noting, that these interventions can be introduced to clinics without further regulation. The sector requires more robust evidence to support the validity of these technologies and there may be a role for the Authority to encourage trials to be performed. A good example is the soon to be published VISA study.

9.10. The Chief Executive confirmed that it would be useful for the Executive to clarify where AI technologies are being applied in assisted reproduction and whether these technologies should be considered add-ons to treatment. An External Adviser explained that many of the AI tools may be considered as add-ons to treatment (whether charged for directly or indirectly) as they have not been shown to improve live birth outcomes. However, there are benefits to using AI tools, such as reproducibility.

9.11. It was noted that often these systems are introduced to clinics for all patients, therefore, to consider the technology an add-on may be dependent upon the way in which the system had been implemented and whether there is an associated cost or patient choice. Technologies should only be considered as part of the add-ons rating if there is patient choice and a direct cost involved.

9.12. Not all uses of AI will be concerning to the Authority, although where grey areas exist (e.g. clinical decision support) the Committee suggested that the Executive hold further discussion to establish relevant outcomes. The Chair noted that although some AI models may have a small effect individually, the cumulative effect of many technologies should be considered.

9.13. An External Adviser went onto state that large language models, such as Google Health's AMIE, are likely to transform the field rapidly.

9.14. The Chair noted that regulation of AI is legally stated and at this time we may only suggest areas in which the Authority feel technologies should move into our regulatory remit, considering the wider government view.

9.15. An External Adviser noted that future uses of robotics may take several years to implement and therefore isn't a high priority at this time.

9.16. In relation to the ask on which aspects of AI, robotics and automation in fertility that the Executive should focus on, the Committee recommends the Executive prioritise understanding and

emphasising the importance of model validation before systems are offered in practice. The focus should be on exploring technologies with patient-facing application.

Action: The Executive have had a watching brief on developments in the uses of AI within clinics, including regular engagement with other relevant regulatory bodies, for some time. The Executive is considering outputs needed going forward, including communication activities aimed at the clinical and research communities.

10. Committee effectiveness review

10.1. The Annual Review of Committee Effectiveness was led by the Chair. A summary of feedback was recorded by the Executive for presentation at the March 2024 Authority meeting.

11. Any other business

11.1. The Chair highlighted to the Committee that the Executive will soon start planning for the HFEA's annual horizon scanning meeting held during the ESHRE conference. The Committee will be contacted about this as required.

12. Meeting summary and close

12.1. The next SCAAC meeting will be held as hybrid, in person and via Microsoft Teams on Monday 3rd June 2024.

12.2. The Chair closed the meeting by once again thanking Raj Mathur for his outstanding contributions to the SCAAC.

13. Chair's signature

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

Chair: Tim Child

Date: 20 March 2024