

Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

10 June 2019

Derwent Room, 1st Floor, 10 Spring Gardens, London, SW1A 2BU

Authority members	Present	Yacoub Khalaf (Chair) Gudrun Moore (Deputy Chair) Kate Brian	Ermal Kirby Anne Lampe
External advisors	Present	Richard Anderson Andy Greenfield Joyce Harper Raj Mathur Kevin McEleny (phone)	Richard Scott Shankar Srinivas
	Apologies	Jane Blower Daniel Brison Sheena Lewis Robin Lovell-Badge	
Members of the executive	Present	Dina Halai (Meeting lead and Scientific Policy Manager) Rasheda Begum (Meeting secretary and Scientific Policy Officer) Peter Thompson (Chief Executive) Laura Riley (Head of Regulatory Policy) Amanda Evans (Research Manager) Jennifer Rogers (Research Manager) Stevan Cirkovic (Policy Officer) Catherine Burwood (Senior Governance Manager) Moya Berry (Committee Officer) Paula Robinson (Head of Planning and Governance)	
Invited speaker	Present	Cristina Hickman	
Observers	Present	Dafni Moschidou (DHSC) Jazmin McCalla-Bedward (MHRA)	

1. Welcome, apologies, declarations of interest

- 1.1. The Chair welcomed the Committee and noted that there were new members to the Committee including a new Authority member (Ermal Kirby) and 4 new external advisers (Richard Anderson, Kevin McEleny, Richard Scott and Shankar Srinivas).
- 1.2. Apologies had been received by Robin Lovell-Badge, Sheena Lewis, Daniel Brison, Jane Blower.
- 1.3. The Chair acknowledged that SCAAC is now made up of 11 external advisers and five Authority members which in line with the updated [Standing Orders](#).
- 1.4. The Chair highlighted upcoming events including the HFEA 2019 Annual Conference and HFEA's annual horizon scanning meeting.

2. Role of SCAAC

- 2.1. The Chair outlined the functions of SCAAC as per the Standing Orders:
 - make recommendations to the Authority on the safety and efficacy of scientific and clinical developments (including research) in assisted conception, embryo research and related areas;
 - make recommendations to the Authority on patient information relating to those scientific and clinical developments;
 - advise the Authority on significant implications for licensing and regulation arising out of such developments and;
 - where required, work with the Authority members to consider the social, ethical and legal implications arising out of such developments.
- 2.2. The Chair listed the current priority items that the SCAAC decide ahead of each year. The prioritised items inform the Committee's workplan. The priority items are emerging or ongoing issues in fertility treatment and/or research that the SCAAC keep an eye on and discuss at regular intervals in order to inform the HFEA of any developments that may require a response from the HFEA.

3. New HFEA Strategy 2020-2023

- 3.1. The Head of Planning and Governance joined the meeting and provided an overview on the new proposed HFEA Strategy for 2020-2023. The HFEA operates under an Act and has certain statutory powers and duties to carry out inspections and provide information.
- 3.2. A consultation period for the strategy has begun by means of an [online survey](#). Consultation will run through the summer and the feedback will be considered at the Authority meeting in November. This will eventually lead to the publication of the final strategy in April. The strategy has been presented to other HFEA stakeholder groups, where it has received positive feedback.
- 3.3. The new strategy consists of three key areas, each with an aim and two objectives:
 - The best care - high quality care informed by evidence. The main objective is for treatment to be safe, offered responsibly with a visible evidence base to help patients make informed

choices. Clinics should also be well-led and the HFEA have been working with PRs around leadership. The HFEA's activities will continue to focus on the ways we regulate as well as engagement with the sector and other bodies to go beyond regulation and compliance to define a gold standard clinic. In encouraging more research, the HFEA will work towards supporting researchers and encourage more funding to be made available for fertility research including clinical research and register research that uses HFEA data. The second objective focuses on the lack of information on male infertility therefore the HFEA could add this to their website and signpost to other sources.

- The right information - accessing the right information at the right time. A significant issue that has been raised by patients is that they do not receive appropriate information in the early stages of seeing their GP, as GPs may not be knowledgeable about infertility or be aware of the HFEA. The HFEA are looking to target GPs and nurses by working with the relevant Royal Colleges to ensure that the information reaches primary care providers and nurses. Another output will be to develop materials to support patients in early treatment decisions.
- Shaping the future - being prepared for likely future changes. The last review of the HFEA Act was in 2008, which increases the probability of a new review although there is no clear timeline for when the review will happen. The HFEA must be prepared to assist and provide information for parliamentary debate. Any changes will need to be implemented by working with the sector. We expect a rise in [opening the register \(OTR\)](#) requests, particularly from 2023 when the first donor-conceived people turning 18 will be able to apply to HFEA to access identifying information about their donor. The HFEA will need to ensure they have the capacity and capability to deal with the volume of requests that will be received. Associated issues arising from this, such as the current managed system of anonymity around donors, donor-conceived people and their close genetic relatives, will be addressed with consideration also to the implications of commercial DNA testing kits and websites. Another aspect concerns the scientific developments in genomics and artificial intelligence (AI). The HFEA wants to lead debates in the sector around these developments as well as providing up-to-date information to patients on significant developments in DNA testing and AI. Many disease sub-types are being considered by the Statutory Approvals Committee (SAC) for approval for preimplantation genetic diagnosis (PGD) testing, and the HFEA will consider how to deal with the complexity and increasing number of applications.

3.4. The Committee were asked for initial feedback on the proposed strategy. The Chair asked whether there has been a trend in the increase of OTR requests. The Chief Executive answered that the number of applications is expected to increase in the next strategy period¹, and the HFEA will need to consider capacity to process applications should the number increase greatly.

3.5. A member asked what the process is for making changes to the Act. The Chief Executive explained that the decision to reopen the Act for review lies with the government. The HFEA will need to consider what provisions in the Act need to be focused on if a review is opened.

3.6. A member asked how the HFEA intends to encourage research, and if this involves commissioning or paying for research. The Chief Executive outlined that the HFEA does not fund research, however it does hold a large dataset that is underexploited, therefore there has been work carried out to migrate the dataset into a more stable structure that is more amenable for use in research. Clinics can also add their own data to [the HFEA register](#). A member raised that

¹ In 2021, for the first time, donor conceived children who turn 16 will have access to non- identifying information about their donor and in 2023 when they turn 18, they will have access to identifying information and will be able to contact their donor

access to the Register requires someone from the HFEA to process the data before it can be used by researchers which is a rate limiting step. The new Register structure will rectify this issue.

- 3.7.** A member asked about the way in which patient information will be made available. The Head of Planning and Governance outlined that this can be through the HFEA website which already provides patient information as well as signposting to and from other online sources. The new strategy aims to improve information provision about male fertility. Another member asked how standards can be set for provision of information to patients within clinics. The Chief Executive explained that the HFEA often sets out principles about provision of information in its guidance, such as in the [Code of Practice](#).
- 3.8.** A member noted that the best care needs to include treatment that is effective in addition to being scientifically and ethically robust.
- 3.9.** A member asked why add-ons can be used if evidence shows they are not effective. The Chief Executive answered that the HFEA does not have explicit powers to prohibit most add-ons, and for instance has no powers to regulate drugs. Another member raised that when novel processes are considered, an approval leads to the procedure being added to the [authorised process list](#) and there is no explicit mechanism to approve the novel process for research only and not treatment. The Chair raised that the evidence for add-ons has been assessed in a pragmatic way to support patients and that is the maximum that the Committee and Executive is able to do.
- 3.10.** A member raised that a review of the Act should include protecting patients who are paying for treatment privately in the same way NHS patients are protected, and that patients paying for fertility treatment are less well protected.
- 3.11.** A member asked what percentage of patients going through fertility treatment look at the HFEA website and whether a revision of the Act could allow the HFEA to extend its regulatory oversight to add-ons. The Chair responded that the HFEA monitors visits to the website in general (but not specifically visits by patients). A member raised that add-ons should be restricted to research only and patients should not pay to have them used in their treatment. Another member raised that some patients may be desperate to use some add-ons which may cause distress if they are restricted therefore there should be a balance where patients are provided with the best evidence. Patients should be made aware that where a treatment needs more evidence, this could mean that more evidence, when it exists, could show that the treatment does not work.
- 3.12.** The Chair addressed that carrying out the required level of research requires significant funding which is difficult to obtain therefore most of the evidence available is from small studies. The Chief Executive highlighted that the Committee is an advisory one which is not able to commit the resources of the HFEA, however they can advise what they feel that the Authority should prioritise. The Chair said that discussion on treatment add-ons can be continued at the October meeting.

4. The 2017 Fertility Trends report

- 4.1.** The Research Manager presented the key trends and themes from the [Fertility Trends report](#) that was published in May 2019. The Fertility Trends report is an annual report that provides an overview of the fertility sector such as treatment numbers, success rates, patient age and funding. The audience for the publication includes patients, clinicians, researchers and the media. In 2017

there were ~50,000 patients that went through fertility treatment and this consisted of ~70,000 treatments.

- 4.2.** Key findings on patient characteristics were presented. Most patients (~91%) had male partners, the rest had same sex partners, no partner or were surrogates. The number of patients with male partners has been declining as a proportion since 2007. Patients with same-sex partners has risen by 12% in the last year. There had been a 22% rise in surrogates and 4% rise in partners with no partners in the last year. Potential reasons for the numbers include more acceptance of the LGBTQ community and fertility education.
- 4.3.** In 2017, the most common fertility treatment was in vitro fertilisation (IVF) accounting for 93% of treatment cycles (n=69,822). The remaining 7% consisted of donor insemination (n=5,603). There has been a rise in IVF cycles and a rise of 11% in use of frozen embryos. Use of ICSI has plateaued. Potential reasons for rise in IVF could be due to late family starting, as the average age of an IVF patient is 35.5 years. Rise in use of frozen embryos could be due to rise in single embryo transfers.
- 4.4.** The IVF live birth rate was 22% per embryo transferred which was the highest on record rising from 18% in 2012. Donor insemination birth rate was 14% per treatment cycle, rising from 13% in 2012. The highest births are for women under 35 at 30% per embryo transferred. Success rates for frozen embryos have become more comparable with fresh embryos. Possible reasons for rise in success rate could be because of single embryo transfer usage. The rise in success rates for frozen embryos could be due to improvement in storage techniques. Further considerations could be that the natural limit has been reached for IVF. Where patients used their own eggs, success rates decline with age, however if a patient uses donor eggs, the rates are maintained with age.
- 4.5.** Multiple birth rates have declined from 28% in 2008 to 10% due to the HFEA's Multiple Births campaign which encouraged use of single embryo transfers. Further considerations could be whether the rate needs to be reduced to lower than 10%.
- 4.6.** NHS funding of assisted reproduction treatment (ART) has increased in Scotland in the last 5 years from 42% to 62%. In Northern Ireland funding remained steady at ~50%. In Wales, funding has fluctuated and is now at 39%. In England, funding has slowly declined from 39% to 35%. There has been major reduction in NHS funded DI cycles which could be due to changes in clinical commissioning groups (CCGs).
- 4.7.** One member noted that the possible reasons for the numbers cannot be determined as the HFEA does not collect the relevant information such as reasons for egg freezing.
- 4.8.** A member asked for clarification on whether fresh embryo usage has declined and whether rates of freeze-all cycles have increased. The rate of fresh embryo usage has declined slightly, there would need to be further analysis on freeze-all cycles where the intention of treatment was to freeze embryos.
- 4.9.** A member asked whether the Authority has a view on whether rates should be displayed as per embryo transferred or per treatment cycle. The Chief Executive highlighted that a decision was made to have the main rate displayed on Choose a Fertility Clinic (CAFC) as per embryo transferred. Birth rates in the Fertility Trends reports are for per embryo transferred however rates for per treatment cycle are available in the underlying data for the report.

5. Matters arising

- 5.1.** Minutes of the February 2019 meeting were agreed remotely prior to the meeting.
- 5.2.** At the previous meeting, the Executive were asked whether they will make a statement on the genetically edited babies that had been created in China. The regulatory framework in the UK does not allow for genetically edited offspring and therefore has not been raised as an area of concern that the HFEA need to respond to. The HFEA will continue to monitor the area of genome editing.
- 5.3.** The expertise amongst Committee members has been reviewed and new members have been recruited.
- 5.4.** A journal paper on use of intracytoplasmic sperm injection (ICSI) is currently being reviewed by the Chair and will require updating by the HFEA.
- 5.5.** Committee members have raised issues with the lack of evidence supporting the safety and efficacy of the intrauterine culture device that is currently an approved novel process. Members have recommended that the device should only be used in a research setting. The Executive will revisit intrauterine culture with the Statutory Approvals Committee (SAC) who approve novel processes.
- 5.6.** The authorised processes list is to be reformatted so that novel processes are displayed separately and are distinguished from the historic authorised processes.

6. Issues and opportunities of artificial intelligence (AI) in the fertility sector

- 6.1.** The Committee were joined by Dr Cristina Hickman, who is a lecturer at Imperial College London and Chief Scientific Officer at a commercial fertility care provider called Apricity. Dr Hickman was invited to provide a presentation on issues and opportunities of AI in the fertility sector. Dr Hickman considered the four criteria for embryo selection (accessible, non-invasive, consistent and predictive of outcome) and commented that AI could meet these, especially consistency and diagnostic power. AI could be used to determine any data driven process within fertility, including determination of the most appropriate treatment protocol patients should be having to increase the chances of live birth, for hormonal treatment optimisation, improving embryo selection through prediction of live birth, improving follicle scans interpretation and impact of stress. Dr Hickman gave a summary of how AI is currently used clinically for IVF. It is used for formulation of embryo selection algorithms in time-lapse systems, semen analysis in computer assisted sperm analysis (CASA) systems, follicle recognition in ultrasound scanners, PGT assessment, and gamete donation programmes (image recognition and matching of donor and recipient). Dr Hickman emphasised that AI should be applied across the whole IVF process, not just embryo selection.
- 6.2.** Dr Hickman has been involved in research around optimising embryo selection. She commented that the three current methods of embryo selection (morphology, time-lapse and preimplantation genetic testing, PGS) do not fulfil four basic criteria of an embryo selection system. A study was carried out by her team where 395 time-lapse images of blastocysts were sent to five embryologists in different countries. Agreement on embryo quality by all 5 embryologists was found in only 89 of the images. Dr Hickman highlighted that time-lapse images contain a large

amount of data and that only a subset of the data is currently analysed for embryo selection. She suggested that AI could redefine evidence-based medicine by processing multiple types of data at once.

- 6.3.** A study by Khosravi et al., 2019² was presented. This study involved classification of embryos into good, fair and poor quality based on outcome. AI training was carried out based on the good and poor embryos. The trained AI was then used to reclassify the fair embryos. The AI achieved a 98% accuracy prediction of morphology.
- 6.4.** A study by Zaninovic et al 2018³ created an AI that could annotate the number of cells in a cleaved embryo image, resulting in automated annotation. Two independent studies^{4,5} have used AI to predict implantation of embryos and have found levels of accuracy of over 90%. Studies looking at AI prediction of live birth have shown accuracies in the region of 78%⁶. AI can also be used to predict live birth using time-lapse and proteomics⁷.
- 6.5.** AI technology has been used to seek patterns within the HFEA publicly available data ⁸ in order to make the HFEA data set more visible to patients. Apricity has also developed a patient facing app, using AI to make complex fertility information simple for patients to understand their treatment, Dr Hickman noted this approach makes data more transparent and accessible to empower patients to make their own decisions.
- 6.6.** There has been an increase in AI research in the last couple of years. Published research consists of studies looking at embryo classification and prediction of clinical pregnancy. AI research that has appeared at conferences include prediction of live birth and image recognition during egg collection. AI research has also been carried for oocyte identification and diagnosis. Dr Hickman suggested future research areas could possibly include follicular monitoring, follicular stimulation protocols, key performance indicator (KPI) assessments, robotics, assisted micromanipulation and quality control (QC) assessment.
- 6.7.** Dr Hickman highlighted other uses for AI other than embryo selection, including optimising treatment design, assisting monotonous tasks, chatbots to distribute protocols within the clinic, mining medical records, and virtual health assistants. These functions show AI can be used for organisation of data as well as prediction.
- 6.8.** Dr Hickman addressed the opportunities for AI, which included reducing risks of current practice, standardisation of clinical decision making, empowering of patients as AI can simplify complex data so that patients can understand their treatment better, processes can be made leaner and more cost effective.

² <https://www.nature.com/articles/s41746-019-0096-y>

³ [https://www.fertstert.org/article/S0015-0282\(18\)31597-8/abstract](https://www.fertstert.org/article/S0015-0282(18)31597-8/abstract)

⁴ Tran D, Cooke S, Illingworth PJ, Gardner DK. Deep learning as a predictive tool for fetal heart pregnancy following time-lapse incubation and blastocyst transfer. *Human Reproduction*. 2019 May 21;34(6):1011-8.

⁵ Rocha C, Nogueira MG, Zaninovic N, Hickman C. Is AI assessment of morphokinetic data and digital image analysis from time-lapse culture predictive of implantation potential of human embryos?. *Fertility and Sterility*. 2018 Sep 1;110(4):e373.

⁶ Zaninovic N, Rocha CJ, Zhan Q, Toschi M, Malmsten J, Nogueira M, Meseguer M, Rosenwaks Z, Hickman C. Application of artificial intelligence technology to increase the efficacy of embryo selection and prediction of live birth using human blastocysts cultured in a time-lapse incubator. *Fertility and Sterility*. 2018 Sep 1;110(4):e372-3.

⁷ IVI: The study of the collective proteins expressed in a cell, tissue or organism

⁸ On the [Apricity website](#), it says the results from the fertility predictor are generated using the HFEA database from 2010-2016

- 6.9.** Dr Hickman noted the risks that may be associated with AI, including data bias (due to geographical differences in types of fertility patients, as well as differences in clinical practice) causing certain AI algorithms to lack generalisation, which raises the importance for clinics to collaborate in order reduce bias. Data security data, data access and ownership were also noted as risks. Dr Hickman commented that patients should own their data and have full access to their data. Other risks were poorly validated interpretations, digital know-how of doctors and embryologists, and prediction of inappropriate outcomes (such as social characteristics) that may need to be regulated.
- 6.10.** Dr Hickman highlighted the obstacles that need to be overcome for introducing AI, including digitisation of the IVF process, completeness of data, compatibility of data, access to data and regulation.
- 6.11.** Dr Hickman ended the presentation by outlining a system called SUBSTRA that is a block-chain platform being used in French clinics to allow AI development within health data in compliance with information governance, ethics and international regulations regarding healthcare data handling.
- 6.12.** The Committee were asked for any questions on the AI presentation. A member asked whether embryos are affected by time-lapse. Dr Hickman has not seen evidence to show time-lapse harms embryos and exposure to light is lower and quoted commercial research demonstrating the safety of light exposure from time-lapse machines
- 6.13.** A member asked whether studies will be carried out in a randomised controlled trial (RCT) setting to compare outcomes for AI and non-AI practice. Dr Hickman commented that RCTs are not the best way to test AI, as the potential for many AI technologies is not to increase live birth rather to increase diagnostic power. Time to live birth could potentially be improved through AI approaches to embryo selection if the information coming from AI leads to change in clinical practice i.e. changing the timing of transfer or the number of embryos transferred. Assessment of the efficacy of diagnosis would be an experimental design more suitable to the abilities of AI.
- 6.14.** The Chair noted that the Committee looks at tangible benefits of technologies for patients and that AI technology will have significant cost that clinics will need to invest. Dr Hickman raised that the technology can be inexpensive for clinics as they can use embryo images from local microscopes to build an AI. AI can be developed to be an innovation that reduces the cost of IVF, making IVF more accessible.
- 6.15.** The Chief Executive outlined that the IVF sector broadly consists of an NHS funded section of medium sized clinics, small standalone private clinics and private groups. The Chief Executive asked whether the size of a clinic matters for a clinic to take up AI. Dr Hickman answered that AI requires diversity of data, including the data from small clinics. Clinics that are not prepared to share data will therefore trail behind from research and development. A member asked whether bias could be introduced if clinics carry out different measurements. Dr Hickman answered that with large enough data sets in a global scale, differences can be controlled for, and that the aim for a diverse set of data is to create an infrastructure that can be used for several decision-making purposes within the IVF process, not just embryo selection.
- 6.16.** Members discussed the AI presentation and many agreed that improved live birth should be the main outcome for the technology, however one member raised that some patients may value reduced miscarriage rate or time to live birth. A member raised that they would have preferred

more time to ask questions for the AI presentation, the executive will consider whether the committee meeting format should revert back to having a longer meeting, having trialled a shorter meeting this time around, at SCAAC members' request.

- 6.17.** A member highlighted that AI networks are used in radiology for cancer detection, which still involves radiologists however the amount of work is reduced by the AI excluding clear cases where a tumour is not present. A member emphasised that AI research is not particularly unique therefore should be treated with the same scrutiny as other types of research. A member suggested that there should be structured questioning on different aspects of AI such as the research itself and the scientific validity of it as well as how the technology will impact the sector.

Action: Executive to revisit the topic of AI at a future SCAAC meeting and to consider inviting an academic speaker who is an expert on AI.

Recommendation: The SCAAC did not make the Executive aware of any other developments in AI.

7. Embryo culture media update

- 7.1.** The Chair noted that the last discussion that SCAAC had on embryo culture media highlighted an RCT that suggested that embryo culture may lead to higher birthweight. The exact impact of higher birthweight is unclear. There have been no additional papers that confirm or refute previous findings. Members were asked if they are aware of any additional literature.
- 7.2.** A member noted that one of the studies identified in the literature review found no difference in cardiovascular development in 9-year-old children and asked why this would be measured. There has been previous research to show that cardiovascular development is different in children born from ART.
- 7.3.** The Chair raised that embryo culture media components are unknown which does not provide a clear basis for implications to clinical practice. A member commented that digitisation of IVF would be difficult if the contents of embryo culture are still largely unknown.

Recommendation: SCAAC did not make the Executive aware of any other developments on embryo culture media

Recommendation: SCAAC did not advise any communication to be made to the MHRA

Agree hot topics for 2019 Horizon scanning meeting

- 7.4.** The annual HFEA horizon scanning meeting was due to take place at ESHRE 2019. As part of the agenda for the meeting, the below listed hot topics were proposed to be discussed at the meeting:
- Genome editing
 - Artificial intelligence
 - Pre-implantation genetic testing
 - Direct to consumer DNA testing and anonymity
 - Mitochondrial donation for non-disease related purposes

- Surrogacy

7.5. A member noted that acupuncture is a highly requested add-on and asked whether this add-on along with other holistic treatments can be discussed at the horizon scanning meeting. The Chief Executive highlighted that the list of add-ons on the HFEA website are the ones that are prioritised by the HFEA, however discussion can be considered for add-ons outside of the list.

Recommendation: SCAAC agreed with the above list of hot topics.

8. Any other business

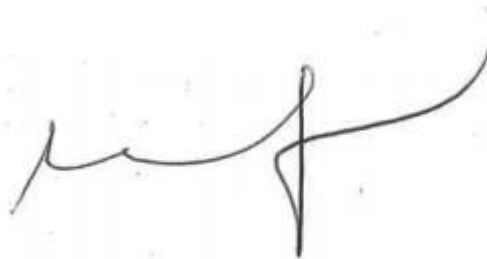
8.1. The Chief Executive raised that the evidence for add-ons must be from RCTs, however there is no indication that many RCTs are being carried out. The Committee were asked whether a conversation could be had at the next SCAAC meeting to consider different types of evidence. Members agreed that as there are not many RCTs being carried out it is therefore essential to consider alternative evidence in this circumstance. A member raised that a genetic testing company have claimed to test their products on 200,000 embryos whereas RCTs on PGS often only have a sample of less than 500 embryos. The Chair raised that RCTs should remain to be held as the only objective way to assess whether an intervention works, however acknowledged that RCTs are difficult to carry out and suggested that a non-bias speaker such as an epidemiologist should be invited to a SCAAC meeting to provide insight about how evidence should be assessed.

8.2. The Chief Executive apologised for technical issues that occurred for those dialling-in during the meeting.

9. Chair's signature

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

Signature

A handwritten signature in black ink, appearing to be 'Yacoub Khalaf', written over a light blue grid background.

Chair: Yacoub Khalaf

Date: 14 October 2019