Scientific and Clinical Advances Advisory Committee (SCAAC) - minutes

5 February 2018, 11.00am – 4.00pm

Derwent Room, 10 Spring Gardens, London SW1A 2BU

Authority members	Present	Yacoub Khalaf Kate Brian Andy Greenfield Sally Cheshire	
	Apologies	Tony Rutherford Anne Lampe	
Members of Executive		Anna Quinn (lead) Rasheda Begum (secretary) Hannah Verdin Peter Thompson Clare Ettinghausen	Nick Jones Niamh Marren
External advisors	Present	Melanie Davies Joyce Harper Robin Lovell-Badge Gudrun Moore	Jane Blower Daniel Brison (on phone)
	Apologies	Sheena Lewis Raj Mathur	
Invited speaker		Mark Grumbridge	

1. Welcome, apologies and declarations of interest

1.1. The Chair welcomed the Committee members to the meeting and welcomed Clare Ettinghausen, the new Director of Strategy and Corporate Affairs at the HFEA.

1.2. Yacoub Khalaf declared interests as he is a co- investigator and co-applicant of the HABSelect trial as well as a co-author of the paper currently being written on the results of the trial. Daniel Brison also declared the same interests.

2. Matters arising

2.1. The minutes from the previous meeting were agreed remotely prior to the meeting.

2.2. The Scientific Policy Manager gave an update on outstanding actions from previous meetings. An action from the February 2017 meeting was a request for the horizon scanning spreadsheet to be reformatted so that all studies went under one tab. The spreadsheet has been modified so that all the papers are arranged under a single tab which has been sent to the Committee members for comment.

2.3. The Scientific Policy Manager is working with the Communications team to redraft the ICSI patient information, specifically to amend the section on miscarriage risks.

2.4. At the June 2017 meeting, it was discussed to write up the ICSI paper as a journal paper, this is currently with Committee members to provide suggestions on revising the paper.

2.5. Also at the June 2017 meeting, it was agreed that a letter would be sent to the MHRA setting out the Committee's concerns about regulation of embryo culture media. A letter was sent in November 2017 and a representative of MHRA will be present at the meeting to speak with the Committee.

2.6. At the October 2017 meeting, the Committee discussed new patient information for DNA fragmentation, PICSI and IMSI. An independent expert in evidence assessment has agreed to peer review the traffic light ratings for the three add ons. The traffic light ratings are set to be finalised for the June 2018 meeting.

2.7. One member enquired about making the traffic lights on the HFEA website accessible to colour blind users. The colour of the traffic light rating is now named alongside the traffic light symbol on the website.

3. Chair's business

3.1. The Chair gave an overview of the results from the HABSelect trial, which compared sperm selection using hyaluronic acid with standard ICSI. The trial was presented at the BFS meeting in Liverpool in January and currently being prepared for publication. David Miller is expected to present the results at the June 2018 meeting.

3.2. An annual review of the Committee is in progress, the Committee members were thanked for their contribution.

4. Regulation of embryo culture media

4.1. The Committee welcomed Mark Grumbridge, Senior Clinical Advisor at Medicines and Healthcare Products Regulatory Agency (MHRA), to the meeting.

4.2. The Scientific Policy Manager outlined that embryo culture media is a high priority standing item for SCAAC. The Committee considers a literature review every year and papers and minutes related to embryo culture media are provide to the MHRA for information. The Committee last discussed embryo culture media at the June 2017 meeting. At the meeting, the Committee considered evidence suggesting that culture media has an impact on birth weight of children born from assisted reproduction. The Committee raised concerns that manufacturers are not obliged to disclose the exact composition of their products. In order to better understand the regulation of embryo culture media and reporting obligations of manufacturers, a letter was sent by the SCAAC Chair and HFEA Chief Executive to the Chief Executive of the MHRA. Members of the Executive will also visit the MHRA to meet the Devices team to discuss the strategic relationship between the HFEA and MHRA.

4.3. The Chair began the discussion by highlighting studies on embryo culture media that have shown impact on the health of the offspring, mainly birth weight. The Chair also highlighted the importance of expert assessment to assure the validity of such studies, including review by independent statisticians.

4.4. Mr Grumbridge explained that medical devices that are to be CE marked need to go through a conformance check by a Notified Body, the MHRA is responsible for monitoring Notified Bodies. There are five Notified Bodies in total in the UK, one of which are BSI who are currently the only notified body to have provided CE certification for IVF products. Audits are done twice a year at BSI by the MHRA. At an audit, compliance from both the manufacture and Notified Body is assessed. The MHRA will randomly pick devices and perform checks to ensure that the Notified Body have considered the relevant clinical and technical data.

4.5. A CE certificate is usually valid for five years. When the five years are coming to an end, the manufacturer has to apply for a new certificate. It is the responsibility of the Notified Body to consider post market data that would include, adverse events, any post market studies and reports of any technical changes the devices.

4.6. A member asked for clarification on what happens when the composition of a culture medium changes. Mr Grumbridge responded that the manufacturer is obliged to inform the notified body of such changes. A member asked what kind of changes are notifiable, such as qualitative and quantitative changes. Mr Grumbridge reiterated that any change is to be reported. Mr Grumbridge also described that a product with a CE certificate is under post-market surveillance which may be done by a post market clinical study however these clinical studies are not regulated by the MHRA, instead they are required to have ethics committee approval.

4.7. The Committee asked if the MHRA would be able to provide a list of culture media that has been approved. Mr Grumbridge explained that there is no list kept by the MHRA, however the BSI could be approached to provide a list. Mr Grumbridge clarified the role of the MHRA is to regulate the Notified Body. It was also noted that a CE marked product may be overseen by a Notified Body in a different country within the EU. Competent Authorities in each member state must

cross-audit each other as required by the European Commission. A manufacturer can go to any Notified Body to get a CE certificate.

4.8. The Committee discussed the use of experts by Notified Bodies when they consider applications for CE certificates. When a Notified Body requires specific expertise, they will approach a relevant clinician who will review the clinical and technical information submitted by the manufacturer. The Committee asked if there is any transparency in who Notified Bodies consult for expertise and Mr Grumbridge responded that the list of experts is usually confidential and the recruitment of such experts is overseen by MHRA where CVs are reviewed to ensure competency, for UK-based Notified Bodies only.

4.9. On the subject of post market surveillance, Mr Grumbridge outlined that customer feedback would sometimes be the basis for obtaining information on whether a product works properly. There are also accessible databases with reports of incidents. In 2017, there were 12 reports to MHRA relating to IVF media. These reports come from either the manufacturer or users. A Notified Body is expected to ask manufacturers about post surveillance when renewing a CE certificate. One Committee member suggested there needs to be set standards for post market surveillance in the IVF sector.

4.10. The Committee has been aware of evidence showing that culture media has potential to alter birth weight. The reliability of recent evidence of culture media's effect on birth weight was discussed, including the recent prospective randomised controlled trial and the independent review it received, as well as the clinical significance alterations in birth weight. Mr Grumbridge agreed that registry data could be useful however cautioned that any connections made between culture media and adverse events are made properly taking into account all possible variables.

4.11. A member asked if an audit of all Notified Bodies that have regulated culture media could be carried out at EU level. Mr Grumbridge mentioned that there is an EU Commission body called Notified Bodies Operational Group (NBOG) who could be approached.

4.12. The Chief Executive raised that the new register structure does allow for clinics to voluntarily submit additional information for each cycle such as information about culture media. Outcomes could then be compared between those clinics. A member noted that findings from a subset of clinics reporting culture media data would be subject to bias.

4.13. Mr Grumbridge agreed to investigate specific products named in the literature and approach the relevant Notified Bodies.

Action

4.14. This item will be followed up at a meeting between the HFEA and MHRA and discussions from the meeting will be fed back to SCAAC.

5. Review of novel process applications

5.1. The Scientific Policy Manager gave a brief overview of the authorised process list and explained that there is a standard operating procedure (SOP) for considering novel process applications when a clinic wants to add a new process to the authorised process list. Part of the SOP requires that the applying centre must submit an outcomes report on safety and efficacy of the novel process two years after approval. The report is then presented to SCAAC for information to discuss whether any new information raises cause for concern and if the process should remain

on the authorised process list. Removal from the list for any novel process would require a decision from the Statutory Approval Committee.

Intrauterine culture

5.2. Two previous novel processes were discussed, the first being intrauterine culture. This novel process was considered by SCAAC in 2015 and was approved by the HFEA Statutory Approvals Committee. A paper was provided to the Committee with an outcomes report from the applying centre. The Committee was asked to consider the outcomes report and advise if there any concerns that intrauterine culture should be removed from the authorised process list.

5.3. There was discussion on how it can be known whether other centres besides the applying centre are using the novel process. The inspectors would have this information.

5.4. The Committee reviewed the outcomes report provided by the centre, and it was raised that there was a lack of hypothesis and the data was insufficient. Members noted that the protocol used in the outcomes report is different from the protocol described in the original application, and raised that there are risks in using the device in inseminated oocytes up to pro-nuclei check.

5.5. The Committee agreed that it would be useful to get in touch with the applying centre and ask if they are still using the device. If the Committee have further questions, a representative from the centre should be invited to the next SCAAC meeting to provide their rationale if they are continuing to use the device.

Action

5.6. The Scientific Policy Manager will liaise with the centre for more information.

Egg activation using calcium ionophore

5.7. The Scientific Policy Officer gave an overview of gamete activation using calcium ionophore as a novel process. As the process was added to the authorised list before the current SOP was put in place, there is no applying centre that can provide an outcomes report. As an alternative, HFEA Inspectors asked for feedback on the use of calcium ionophore at inspections in the months prior to the Committee meeting. Out of the 13 inspections carried out during this time, two clinics reported using calcium ionophore. The reports were provided to the Committee. The Committee were asked to consider a literature review and reports from the Inspection team and advise whether there was any information that raised concern on calcium ionophore as a novel process.

5.8. The Committee agreed there is no evidence to suggest calcium ionophore is unsafe. The Chair suggested to keep the process on the list until there is new evidence in the literature to suggest otherwise.

Action

5.9. The authorised process list will be reviewed to ensure process are listed correctly.

6. Prioritisation of issues during the horizon scanning process

6.1. The Scientific Policy Manager and Officer reviewed scientific journals and identified studies from the last year that had relevance to the Authority's work. A spreadsheet of references has been provided. The Committee were asked for comments on the new format of the spreadsheet and

additional references to add. One comment was made on the inclusion of the New Scientist, as it is not a scientific journal.

6.2. There was discussion on general prioritising of topics, where high priority items should be those of most clinical relevance. It was suggested to review the horizon scanning process, to ensure that high priority is given to long standing items such as treatment outcomes as well as new innovations such as SHEEFs.

6.3. The four suggested high priority items for 2018 were discussed.

Mitochondrial donation

6.4. In 2016, the Authority made the decision to approve mitochondrial donation techniques so that clinics were able to apply for a variation to their licence to carry out mitochondrial donation in treatment. A licence variation was granted to Newcastle Fertility by the Licence Committee allowing them to carry out pro-nuclear transfer. The first patient specific applications have been considered and approved by the Statutory Approvals Committee.

6.5. The Committee agreed that it would be useful to invite Mary Herbert to a future meeting to talk about her team's experience of carrying out mitochondrial donation in practice.

SHEEFs

6.6. There has been an increase in research showing that scientists can use stem cells to create embryo-like structures. Synthetic human entities with embryo-like features (SHEEFs) have received attention from the wider community, for instance this topic was raised at the PET conference in December 2017. Research on SHEEFs have prompted questions on the definition of an embryo and the 14-day rule. SCAAC discussed SHEEFs at the June 2017 meeting where comments were made on poor efficiency of techniques and the need for research to be reproduced. The Committee were asked if they would like a wider literature review on SHEEFs and if any specialist speakers should be invited.

6.7. The Committee discussed the name "SHEEFs" which some felt was not an appropriate term. There was discussion on the paper from which the term "SHEEFs" originated (Aach et al., 2017[1]) on application of the 14-day rule to SHEEFS.

6.8. The Committee were happy to keep SHEEFs on the workplan and were keen to invite international researchers to attend SCAAC to discuss research in this area.

Impact of stress on fertility treatment outcomes

6.9. Patients undergoing fertility treatment often undergo stress, however it is unclear how stress may impact a couple's chance of having a successful treatment cycle. There has been research with mixed results. A study by Massey et al. 2016, assessed short term stress by measuring cortisol levels in saliva and long-term stress by measuring hair cortisol levels. The study found no relationship between salivary cortisol and treatment outcomes. Lower levels of cortisol in hair was predictive of clinical pregnancy. This could invite suggestions for interventions aimed at reducing stress in the months before treatment could possibly have a benefit to patients. The Committee were asked if this is an area that should be explored in more detail and if any speakers should be invited to SCAAC.

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[1] Aach, J. et al, 2017. Addressing the ethical issues raised by synthetic human entities with embryo-like features. *Elife*. Available at https://doi.org/10.7554/eLife.20674.

6.10. Members expressed that this area was important and referred to the Fertility Network UK survey. The Head of Regulatory Policy suggested the emotional support project could be relevant. This project is being carried out by a Policy Manager at the HFEA to improve the emotional experience of treatment and donation before, during and after treatment Members agreed that objective study on stress in patients in relation to fertility can be difficult because of confounding factors. The Chair of the HFEA mentioned that there will be a session on supporting patients at the HFEA annual conference which could factor in the issue of stress on patients and suggested a separate literature review should be carried out.

Action

6.11. The Scientific Policy Manager will speak with the project manager for the emotional support project to see if SCAAC's work on impact of stress can be aligned with emotional pathways.

The impact of the microbiome on fertility and fertility treatment

6.12. Some research has suggested that the microbiomes of the male and female reproductive tract could have an impact on fertility and fertility treatment outcomes. The Committee were asked if they agree with the high priority rating and if they had any suggestions for speakers.

6.13. Members agreed that the research on microbiomes in relation to fertility treatment is in its infancy. Feedback from one member's colleagues will be collected to provide guidance on whether this should remain a high priority item for SCAAC.

7. Committee work plan 2018/19

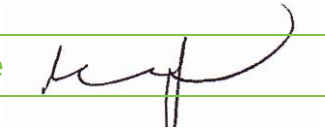
7.1. The Scientific Policy Manager presented the draft work plan for 2018/19. Proposed agenda items for upcoming meetings were put forward. Items will be finalised in due course.

8. Any other business

8.1. The Scientific Policy Manager informed the Committee that the Executive has been working with the Statutory Approvals Committee to identify suitable experts to advise the Committee on the patient specific applications for mitochondrial donation. There is a list of experts who can be approached to be a peer reviewer who can comment on the application, or they can be an expert advisor who attends the Committee meeting to provide advice on the day. The Committee were shown the list of experts and gave suggestions on additional experts who may be approached.

9. Date of next meeting

9.1. Monday 18 June 2018, HFEA Offices

Signature 

Name Yacoub Khalaf

Committee chair	
Date	02/05/2018