

# Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

04 February 2019

Keith Peters room, Francis Crick Institute, London NW1 1ST

Authority members	Present	Yacoub Khalaf (Chair) Gudrun Moore (Deputy Chair)	Anne Lampe Kate Brian
External advisors	Present	Robin Lovell-Badge Jane Blower Melanie Davies Joyce Harper	Sheena Lewis Raj Mathur Andy Greenfield
	Apologies	Daniel Brison	
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) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Laura Riley (Head of Regulatory Policy) Hannah Carpenter (Policy Officer) Amanda Evans (Research Manager) Jennifer Rogers (Research Manager) Sandrine Oaks (Inspector) Nicola Lawrence (Inspector)	
Invited speaker	Present	Channa Jayasena	

## 1. Welcome, apologies, declarations of interest

- 1.1. The Deputy Chair welcomed the Committee members to the meeting.
- 1.2. The Committee was introduced to Dina Halai who is the new Scientific Policy Manager at the HFEA and will be overseeing the management of the Committee. The Committee was also introduced to several new staff who were observing the meeting including two Research Managers in the Research and Intelligence team, two new inspectors on the Inspectorate team and a Policy Officer in the Policy team.
- 1.3. Apologies had been received by Daniel Brison.

- 1.4. In relation to the agenda, Sheena Lewis declared interests related to sperm DNA fragmentation and Raj Mathur and Melanie Davies declared that they work in private practice.
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## 2. Matters arising

- 2.1. The Scientific Policy Manager went through outstanding actions from past meetings. The first action was updating the treatment add-ons page of the HFEA website. The Committee members were thanked for their input on the content. The updates went live on 15 January 2019 which was the same date that the consensus statement on the responsible use of treatment add-ons<sup>1</sup> in fertility services was released.
- 2.2. The second action was for a discussion to be arranged on including fertility investigations in the HFEA's traffic light rating system. The Scientific Policy Manager proposed for this action to be followed up at a future meeting or offline. The Chief Executive highlighted that the Authority has a position on treatment add-ons (optional extra treatments which claim to improve chances of live birth) and that the list at present focuses on the treatment add-ons most commonly offered in clinics. He continued that the list has not been expanded to include diagnostic tests (investigations or assessments of fertility) which may be used to inform the course of treatment recommended to a patient, as this may become confusing for patients. Any change to the framework of treatment add-ons, such as to include diagnostic tests would need to go to Authority for discussion.
- 2.3. A member highlighted that reviewing the treatment add-ons annually doesn't allow for updates to the add-ons list if new evidence from clinic trials is published before the next review is due. The Chief Executive emphasised that HFEA's resources are limited and that new evidence cannot always be assessed straight away because external assessors outside of HFEA are used to assess the evidence. However, he added that if the Executive become aware of compelling evidence that would change an existing traffic light rating for an add-on, then it would aim to investigate this earlier than the next review date.
- 2.4. An action from the June 2017 meeting was to reformat a literature review on the use of ICSI into a journal article. The document is currently with the SCAAC Chair for review. It is likely that the literature review will require updating, the HFEA will await the Chair's comments and then will action accordingly.
- 2.5. In the October 2018 meeting, Prof Nick Macklon presented to the Committee on intrauterine culture. Prof Macklon sent slides on new data regarding the technique that had been presented at the Fertility 2019 conference, however the Chair suggested that additional data is needed, therefore Prof Macklon will be requested to provide this to allow for SCAAC to review whether intrauterine culture should remain on the list of approved novel processes.
- 2.6. The last action was on reviewing the HFEA authorised process list<sup>2</sup>. This was referring to two processes on the list which are novel processes, however the list does not make it clear that they are novel processes, so the list will be reformatted to reflect this. The Scientific Policy Manager will liaise with the Compliance team to review the authorised processes list.

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<sup>1</sup> <https://www.hfea.gov.uk/media/2792/treatment-add-ons-consensus-statement-final.pdf>

<sup>2</sup> <https://portal.hfea.gov.uk/knowledge-base/other-guidance/authorised-processes/>

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### 3. Chair's business

- 3.1. Gudrun Moore had accepted the position of SCAAC Deputy Chair, taking over from Andy Greenfield who will remain on the Committee as an external advisor.
- 3.2. Invitations for new SCAAC members have been sent out and the Committee standing orders have been amended to allow increasing the number of external advisors on the Committee to cover specific areas of expertise. Those who accept are expected to attend the June meeting as their first meeting.
- 3.3. The Deputy Chair acknowledged the new venue for the meeting which had previously been held at HFEA offices which is based within NICE's office building. However, because of limited capacity to book rooms via NICE, the SCAAC meeting was being held at the Francis Crick Institute because of the favourable Crick location for various members. There were some issues with the Crick reception arrangements because attendees were required to wait to be escorted to the meeting room. This will be rectified with the venue for any future meetings at the Crick.

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### 4. Prioritisation of issues identified through the horizon scanning process

- 4.1. A paper was circulated to the Committee on high priority items identified through horizon scanning. The Scientific Policy Manager highlighted that horizon scanning feeds into the HFEA strategy and in turn the HFEA strategy should feed into how issues are prioritised by the Committee. The Committee were provided with an overview of the total criteria list for considering and prioritising issues that the Committee and the Executive should focus on for the year. It was set out that: High priority issues are within the HFEA's remit and meet at least two other criteria in the list. Medium priority issues are within the HFEA's remit and meet at least one other criteria. Medium priority can also be given to issues that are not within the HFEA's remit if they meet at least two other criteria.
- 4.2. The Committee were presented with the list of issues that had been identified by the Executive as high priority for 2019/2020 through the horizon scanning process. A new addition to the list was artificial intelligence. The other items on the list were recurring items. Two items that had been considered as high priority the previous year had been recategorised as medium priority which were the impact of stress on fertility and the impact of the microbiome on fertility. This was due to these items not being within the HFEA's remit, but they do meet at least two other criteria and the HFEA are keen to continue their awareness of these issues.
- 4.3. The Committee were asked to comment on the list of high priority issues proposed.

### Genome editing

- 4.4. The Committee discussed recent events where a researcher had announced at the Second International Summit on Human Genome Editing to have created genetically edited babies, which has attracted controversy. There were also reports that a US group are planning to carry out research into genome editing where the genome editing technology will be injected into testes and volunteers had been recruited and the research is to take place in Ukraine. The Executive were asked if there will be a statement from the HFEA now that a few months have passed since the announcement on the gene edited babies was made.

- 4.5. Several organisations in the scientific community will be carrying out an evaluation on the scientific aspects of the case of the genome edited babies, and this will feed into work that will be done by the World Health Organisation (WHO) to look at governance aspects.

**Action: The Chief Executive and the HFEA Chair will consider whether the HFEA should release a statement on genome editing.**

## Mitochondrial donation

- 4.6. The Committee discussed cases around patients entering the UK to have PGD or mitochondrial donation treatment. The Chief Executive outlined that clinics providing these treatments to international patients would not be prohibited from a regulatory standpoint, though recognised that follow-up of patients would be more difficult for international patients.
- 4.7. A member raised that in 2016 the mitochondrial expert panel established by the HFEA recommended that mitochondrial donation treatment should not be used to treat infertility.

## Treatment add-ons

- 4.8. The SCAAC Chair proposed that interventions or tests which a patient may be offered can also be considered as treatment add-ons. Examples of interventions that the Chair felt the Committee should revisit for the purposes of including on the list of regularly reviewed treatment add-ons included: routine heparin, routine steroids, intrauterine hCG, routine thyroxin, hysteroscopy, and in vivo culture. Tests included endometrial receptivity array (ERA), NK killer cell testing, DNA fragmentation, sperm aneuploid testing, genetic carrier or expanded carrier screening, mitochondrial DNA levels for embryo scoring, microbiome testing, routine measuring of anti-phospholipids antibodies, thyroid antibody testing and vitamin D testing. A member noted that fertility MOT should also be considered as a test. The Chief Executive reiterated that the inclusion of tests, to the current treatments add-ons<sup>3</sup> will require a policy discussion at Authority level.
- 4.9. The Chair noted that the HFEA's remit to regulate use of gametes and embryos in treatment and research would not extend as far as considering add-on procedures that are tests or investigations for infertility issues. There was a suggestion that these procedures would be more suited to the scientific committees of the Royal College of Obstetricians and Gynaecologists or British Fertility Society who have a remit that is more relevant.
- 4.10. A member proposed that the HFEA collect information at inspections on what treatment add-ons clinics have provided and their costs. Another member raised that this would add burden to clinics and the work may not be justified as treatment add-ons are not regulated by the HFEA.
- 4.11. A member commented that there is a lack of representation in the SCAAC Committee from the private sector, however the discussion concluded that other SCAAC members already have experience working in private practice. The consensus statement has not received response from the private sector, however the HFEA will be contacting all Persons Responsible (PRs) at licensed clinics about the consensus statement.
- 4.12. A member commented that some issues discussed by the SCAAC Committee require bioethical considerations.

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<sup>3</sup> <https://www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons/>

**Action:** Executive to consider the level of bioethics expertise in the Committee

**Decision:** The Committee agreed with the proposed list of high priority issues for 2019/2020 and suggested that, for clarity, mitochondrial donation should include mitochondrial replacement and also that health outcomes in women should also be considered in addition to health outcomes in children.

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## 5. Committee workplan

- 5.1. The Scientific Policy Manager presented the proposed workplan to the Committee with suggested items for future meetings. The Committee were asked to comment on the workplan and make suggestions for speakers for each topic.
- 5.2. The Chair noted that culture media has been a standing item and often the conclusion made by SCAAC from reviewing the literature is that more follow-up of children born is required and that there may not be an interest to carry out follow-up or it may be too expensive.
- 5.3. The Committee discussed artificial intelligence in relation to lab process automation. Suggested speakers included Laura Rienzi and Christina Hickman. A member can also get in contact with Chris Holmes at the Turing Institute.
- 5.4. The Committee suggested a speaker from Newcastle Fertility Centre to talk about their research on mitochondrial donation.
- 5.5. The Committee suggested Ali Brivanlou from The Rockefeller University as an expert speaker on embryo-like entities.
- 5.6. The committee suggested that Catherine Racowsky be invited next year to inform on new non-invasive methods technologies in embryo testing as she considered this area in a horizon scanning presentation in Fertility 2019.

**Action:** The Committee workplan to be finalised by the Executive.

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## 6. Impact of the microbiome on fertility and ART outcomes

- 6.1. The Scientific Policy Officer introduced a paper on the subject of the microbiome and its impact on fertility and ART outcomes. A literature review had been carried out, which indicated that research into the microbiome is growing, but has yet to produce findings that capture any feasible relationship between the microbiome and fertility.
- 6.2. The Committee was joined by Dr Channa Jayasena, a Consultant in Reproductive Endocrinology and Andrology from Imperial College London, who was invited to provide insight into the field of research revolving around the role of the microbiome in infertility.
- 6.3. Dr Jayasena described two types of techniques used to study the microbiome. The first was culture-based techniques which are widely available and affordable providing functional information including the importance of some microbiota and antibiotic sensitivity. However, only a minority of microbes can be cultured using traditional means and culture-based screening can lead to misclassifications.
- 6.4. The second technique described was next-generation sequencing (NGS) which can resolve the biases associated with culture-based techniques. NGS allows for quantification of microbiome

DNA but does not provide functional information. Also, NGS is highly sensitive therefore more likely to detect contaminants.

- 6.5. Dr Jayasena highlighted studies<sup>4,5,6,7,8,9,10,11,12,13</sup> that have shown association of vaginal microbiota with preterm birth. The studies have indicated that increasing diversity in a lactobacilli dominant microbiome was present in patients who had pre-term births.
- 6.6. Dr Jayasena then spoke about the vaginal and uterine microbiome. A study by Babu et al., 2017<sup>14</sup> was summarised, which used traditional culturing techniques. The study compared the microbiome between healthy women and women with infertility. Lactobacillus dominant microbiome was significantly associated with healthy women. Candida and enterococcus were more common in women with infertility problems.
- 6.7. A dendrogram from Ravu et al., 2011<sup>15</sup> was presented where microbiota of individual women were organised into clusters and grouped accordingly which can be used to make inferences about what types of bacteria dominate certain subgroups.
- 6.8. Dr Jayasena gave an overview of three systematic reviews that look at studies on bacterial vaginosis. He explained that there is a high heterogeneity amongst these studies and reviewers have classed the strength of the evidence as low.
- 6.9. Dr Jayasena then moved on to the male microbiome. Studies have identified a dominance of lactobacillus in semen. Two further dendrograms were shown to show clustering of male microbial communities. One from Weng et al., 2014<sup>16</sup> suggested that an increase in diversity in the microbiome is present in men with fertility problems, though Dr Jayasena acknowledged that whether this is causal is yet to be verified.
- 6.10. The findings from a study by Boeri et al., 2018<sup>17</sup> were shown. The study investigated whether human papillomavirus (HPV) impacted male fertility. High-risk HPV status was associated with increased impaired sperm progressive motility and sperm DNA fragmentation.
- 6.11. Dr Jayasena concluded his presentation by noting that many studies are descriptive and that the field is not yet at a stage to be translated into clinical significance. There is a potential role but no proof of causalities. There is no current role for consideration around the microbiome to be taken into account in the management of infertile couples.

<sup>4</sup> Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science*. 2014 Aug 15;345(6198):760-5.

<sup>5</sup> Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *The lancet*. 2008 Jan 5;371(9606):75-84.

<sup>6</sup> Gravett MG, Witkin SS, Haluska GJ, Edwards JL, Cook MJ, Novy MJ. An experimental model for intraamniotic infection and preterm labor in rhesus monkeys. *American journal of obstetrics and gynecology*. 1994 Dec 1;171(6):1660-7.

<sup>7</sup> Gravett MG, Hummel D, Eschenbach DA, Holmes KK. Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. *Obstetrics and gynecology*. 1986 Feb;67(2):229-37.

<sup>8</sup> Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, Cotch MF, Edelman R, Pastorek JG, Rao AV, McNellis D. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. *New England journal of medicine*. 1995 Dec 28;333(26):1737-42.

<sup>9</sup> Donders GG, Van Calsteren K, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I, Van Lierde S. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2009 Sep 1;116(10):1315-24.

<sup>10</sup> Hill GB. Preterm birth: associations with genital and possibly oral microflora. *Annals of Periodontology*. 1998 Jul;3(1):222-32.

<sup>11</sup> Menard JP, Mazouni C, Salem-Cherif I, Fenollar F, Raoult D, Boubli L, Gannerre M, Bretelle F. High vaginal concentrations of *Atopobium vaginae* and *Gardnerella vaginalis* in women undergoing preterm labor. *Obstetrics & Gynecology*. 2010 Jan 1;115(1):134-40.

<sup>12</sup> Holst E, Goffeng AR, Andersch B. Bacterial vaginosis and vaginal microorganisms in idiopathic premature labor and association with pregnancy outcome. *Journal of clinical microbiology*. 1994 Jan 1;32(1):176-86.

<sup>13</sup> Pararas MV, Skevaki CL, Kafetzis DA. Preterm birth due to maternal infection: causative pathogens and modes of prevention. *European Journal of Clinical Microbiology and Infectious Diseases*. 2006 Sep 1;25(9):562-9.

<sup>14</sup> Babu G, Singaravelu BG, Sri Kumar R, Reddy SV. Comparative Study on the Vaginal Flora and Incidence of Asymptomatic Vaginosis among Healthy Women and in Women with Infertility Problems of Reproductive Age. *Journal of clinical and diagnostic research: JCDR*. 2017 Aug;11(8):DC18.

<sup>15</sup> Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, Karlebach S, Gorle R, Russell J, Tacket CO, Brotman RM. Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Sciences*. 2011 Mar 15;108(Supplement 1):4680-7.

<sup>16</sup> Weng SL, Chiu CM, Lin FM, Huang WC, Liang C, Yang T, Yang TL, Liu CY, Wu WY, Chang YA, Chang TH. Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. *PLoS one*. 2014 Oct 23;9(10):e110152.

<sup>17</sup> Boeri L, Capogrosso P, Ventimiglia E, Pederzoli F, Cazzaniga W, Chierigo F, Pozzi E, Clementi M, Viganò P, Montanari E, Montorsi F. High-risk human papillomavirus in semen is associated with poor sperm progressive motility and a high sperm DNA fragmentation index in infertile men. *Human Reproduction*. 2018 Dec 4;34(2):209-17.

- 6.12. A member commented that the microbiome has been studied for a long time, however is now becoming more prominent because of advancement in technology.
- 6.13. A member highlighted that the gut microbiome can also have a significant effect on reproduction.
- 6.14. The Chair raised that there needs to be more research in this area to understand the biology involved.

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## 7. Any other business

- 7.1. The Committee discussed developments in germline genome editing. This included genome editing of spermatogonia (or perhaps later stages of spermatogenesis) via the testes or of zygotes in the oviduct which involves injecting CRISPR complexes directly into these locations. While this may affect gametes or embryos, this may not fall under the HFEA's remit.

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## 8. Date of next meeting

- 8.1. Monday 10 June 2019, HFEA Offices

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## 9. Chair's Signature

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

### Signature



**Chair:** Yacoub Khalaf

**Date:** 02/05/2019