

Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

6th June 2020

Teleconference (Zoom meeting)

Authority members	Present	Yacoub Khalaf (Chair) Gudrun Moore (Deputy Chair) Kate Brian	Ermal Kirby Anne Lampe
External advisors	Present	Richard Anderson Jane Blower Daniel Brison Andy Greenfield Joyce Harper	Sheena Lewis Robin Lovell-Badge Raj Mathur Kevin McEleny Shankar Srinivas
	Apologies	Richard Scott	
Members of the executive	Present	Dina Halai (Meeting lead and Scientific Policy Manager) Victoria Askew (Meeting secretary and Policy Manager) Laura Riley Sally Cheshire Peter Thompson Clare Ettinghausen Rachel Cutting Nora Cook-O'Dowd Victoria Brown Bernadette O'Leary Emily Tiemann	
Observers	Present	Dafni Moschidou (DHSC) Tracy Moore (CMA)	

1. Welcome, apologies, declarations of interest

- 1.1. The Chair welcomed the Committee members to the meeting. The Chair explained that there would be a condensed agenda and that the meeting was being held remotely using Zoom due to the COVID-19 pandemic.
- 1.2. Apologies were received from Richard Scott.
- 1.3. Declarations of interest were received from Daniel Brison.
- 1.4. The Chair introduced Tracey Moore from the Competition and Market Authority (CMA) to the Committee who was observing the meeting as part of the [CMAs wider work](#). The HFEA's Director of Strategy and Corporate Affairs, Clare Ettinghausen, explained that the CMA had launched a [project](#) in February 2020 to produce consumer law guidance for the fertility sector as part of their work on consumer protection legislation. This work will be beyond the remit of the HFEA investigating price transparency, the miss-selling of add-ons and how success rates could confuse consumers. The HFEA is helping the CMA develop their approach and facilitating discussions with sector and patient groups.
- 1.5. A draft report by the CMA is due to be published in the autumn of 2020 for public consultation and patient guidance is due to be published in spring 2021. The HFEA hopes this guidance will help inform sections of the Code of Practice.
- 1.6. The Chair highlighted that when conducting this work the CMA would need to take into account how evidence is assessed for different interventions and that this links with the work of SCAAC. Ms Ettinghausen agreed and said that the CMA would also like to observe the October 2020 SCAAC meeting to listen to the discussion on reviewing the evidence base of treatment add-ons. Tracey Moore confirmed the CMA's approach.

2. Matters arising

- 2.1. Minutes of the meeting held in February 2020 were agreed remotely prior to the meeting.
- 2.2. Policy Manager, Victoria Askew, updated the Committee on matters arising. Two actions from the February 2020 meeting were completed; for the HFEA to revise the workplan and prioritisation list as agreed in the workplan discussion and to send the Committee the exact wording in the Code of Practice for genetic counselling and incidental findings. The information requested by the Committee were included as appendices to the matters arising document.

3. Chairs Business

- 3.1. The Chair proposed that there could be an important role for the HFEA monitoring the research into the effects of COVID-19 on reproduction or early pregnancy as we are not yet aware of the impact of this viral infection. It was suggested that the Committee should have a standing agenda item to discuss recently published research into COVID-19 and communicate between meetings if members become aware of significant research. The Chair invited the Committee to consider this suggestion.
- 3.2. One member highlighted that research into the effects of COVID-19 on reproduction and pregnancy is developing rapidly. There are now several groups in the UK and Europe who are

trying to collect this information, including the UK obstetrics surveillance system (UKOSS) and the European Society of Human Reproduction and Embryology (ESHRE). One group have applied for funding to the National Institute for Health Research (NIHR) to set up a register that monitors the outcomes of patients that are COVID-19 positive.

- 3.3.** It is important to capture data on early exposure of COVID to patients that are pregnant. Some evidence suggests that exposure around the periconceptual period, including the first trimester, may be different to exposure to 2nd or 3rd trimester. The member agreed that Committee should have a standing agenda item for COVID-19 research.
- 3.4.** A member informed the Committee that there is evidence that the ACE2 receptor is expressed in testicular cells including Sertoli cells. There is also suggestion that the influence of androgens on the level of expression of the ACE2 receptor more generally in tissues may affect male fertility as well as the severity of the disease in males. The Chair asked if this is an explanation as to why men are more likely to be severely affected by the virus than women? The member explained that it is one possibility but there are many potential explanations.
- 3.5.** One member asked how the Committee could do this review with accuracy and reliability. The Chair suggested that this would be a collective responsibility of members to review the literature and use their expertise to select the papers that are robust and could affect the information that the HFEA provides to clinics and patients.
- 3.6.** One member raised whether the Committee had the relevant expertise to analyse the literature. Although the Committee contains experts in ART there are no virologists or immunologists. The Chair suggested that if additional expert advice was needed then the Committee could invite a relevant expert to input into the meeting.
- 3.7.** A member informed that Committee that the British Fertility Society (BFS) and the Association of Reproductive and Clinical Scientists (ARCS) writing group that produce their policy documents are relying on the Royal College of Obstetrics and Gynaecology (RCOG) writing Committee to keep their guidance up to date. The member suggested that the Committee could invite a member of the RCOG writing Committee to input to COVID-19 conversations.
- 3.8.** The Chair highlighted that at the October 2020 SCAAC meeting the Committee is due to discuss the review of [treatment add-on traffic light ratings](#) so there will not be space on the agenda to discuss COVID-19 from an obstetric point of view. This could be considered for future meetings.
- 3.9.** One member also suggested that if the application to the NIHR for a national COVID-19 registry is successful, that could be linked to the HFEA register so the HFEA could be directly involved in the linkage study for ART outcomes.
- 3.10.** Ms Ettinghausen explained to the Committee that she Chairs the HFEA register research panel and that the HFEA is aware that several researchers are interested in linking COVID-19 data to the HFEA register. Ms Ettinghausen explained that, due to the regulations, this is not an easy process. However, there are plans to compile a list for the HFEA website of research projects that are looking at HFEA data and COVID-19 related issues so anyone interested can consult with the existing projects.

Action:

- 3.11.** The HFEA will update the Committee about COVID-19 research using HFEA data later in the year and update on any outcome studies further into the future.

Recommendation:

- 3.12.** The Committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research in a standing agenda item.
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4. PGT-A

- 4.1.** The Director of Compliance and Information, Rachel Cutting, summarised the feedback that had been received by the HFEA in response to the [change of the red-amber-green \('RAG'\) traffic light rating](#) for pre-implantation genetic testing for aneuploidy (PGT-A) on day 5 embryos from amber to red. Although the comments raised varied, there was a common argument that the exclusive focus on live birth rate in the traffic light assessment process meant that other suggested benefits of PGT-A, including a reduction in the chance of miscarriage or reduction in the time to pregnancy, particularly in older women, had been ignored.
- 4.2.** The HFEA had commissioned a revised assessment from the independent expert in systematic reviews, of the quality of evidence looking at findings additional to live birth rate that have been reported in the randomised controlled trials (RCTs) already reviewed by SCAAC at their October 2019 meeting. These additional outcomes were the secondary outcomes of these RCTs, so the reliability of their conclusions may be less than those of the primary outcome, pregnancy or live birth rate. The Committee were asked to consider the assessment and then give a recommendation on whether the HFEA website information on [PGT-A](#) should be updated to inform patients of the evidence for these alternative outcomes.
- 4.3.** One member raised that, taking into consideration the [good practice recommendations for PGT](#) recently published by ESHRE, the traffic light ratings adopted by the HFEA were too narrowly focused. The member was aware of clinics that were asking patients to disregard HFEA advice because it lacks comment or ratings based on other criteria than live birth, leaving patients confused. The member felt that there seemed to be evidence that both miscarriage and time to pregnancy could be decreased when using PGT-A.
- 4.4.** Another member commented that the ESHRE's guidance mainly provides information on pre-implantation genetic testing for monogenic disorders (PGT-M) and pre-implantation genetic testing for structural re-arrangements (PGT-SR). The guidance given for PGT-A is vague so has little effect on the HFEA traffic light rating. The member also clarified that there is a clear distinction between PGT-M/PGT-SR, which are diagnostic tests, and PGT-A, which is a screening technique. The member felt that the contextual information provided to patients on the HFEA traffic lights webpage does not contain enough detail and should be expanded to include information such as outcomes other than live birth rate that might be relevant. The member noted that there have been no published RCTs that show PGT-A can either reduce the time to pregnancy or reduce miscarriage rates as their primary finding.
- 4.5.** One member raised concerns that the rating change of PGT-A to red was causing clinics to tell patients to ignore traffic light ratings and that some patients were so confused they were requesting aneuploid embryos be used in their treatment. The member felt this was a failing of the clinics to adequately counsel their patients, rather than a failure of the HFEA.

- 4.6.** Other members felt that a positive aspect of the traffic light system was its simplicity and that patients might be further confused by adding multiple traffic light ratings for the same add-on treatment for alternative outcomes than live birth.
- 4.7.** The Scientific Policy Manager explained that the Executive were working on updating the treatment add-ons webpage to include more information about why and how SCAAC decide the traffic light rating of treatment add-ons in relation to live birth rate and why RCTs are the gold standard of evidence in determining the RAG rating used. The update will highlight more clearly that the existing traffic light ratings are based on live birth rate alone. The HFEA was also considering whether there should be additional RAG ratings for outcomes other than live birth rate and how this could be presented in a clear, patient-friendly manner. Continuing, the Scientific Policy manager said that the Executive would also conduct user acceptance testing for these website updates to determine patients' understanding of the information presented to them. The issue at the meeting today was solely to discuss whether the Committee would recommend additional information be added to the website for PGT-A around research findings of reduced miscarriage rate or reduced time to pregnancy.
- 4.8.** Ms Cutting mentioned the treatment add-ons audit tool which was due to be introduced during clinic inspections in Autumn 2020 to gather information about the add-ons clinics are providing. Ms Cutting explained that if the traffic light rating system for treatment add-ons was to have more sophistication in future, such as including ratings for alternative outcomes than live birth or for potential harms then it would be easier to inspect against in a clinic.
- 4.9.** Another member noted that the advice from the independent expert concluded that the combined evidence suggested a reduction in miscarriage rate, but that it was not possible to draw this conclusion from a single study. The independent expert also concluded that all of the current available RCTs look at single treatment cycles so are not able to compare time to pregnancy.
- 4.10.** One member commented that there is a distinct difference between adding traffic light ratings for outcomes other than live birth rate and being clear about the quality of the evidence for those alternative outcomes. The Committee should be clear that RCTs are the gold standard of research and explain why it is unwise to rely on evidence produced from non-RCT research. Some of the feedback received about PGT-A is from people who feel that the Committee should consider alternative sources of evidence than RCTs.
- 4.11.** The Chair highlighted that there are no professional bodies that recommend the routine use of PGT-A with the current evidence base available, including the American Society of Reproductive Medicine (ASRM), ESHRE and BFS. The Chair questioned whether the treatment add-on traffic light rating system should include secondary outcomes from RCTs. Although some randomised controlled trials may have shown subtle decreases in miscarriage rate there have been no studies with a primary outcome of miscarriage rate or time to pregnancy.
- 4.12.** One member suggested that at the next SCAAC meeting the Committee should agree which, if any, outcomes in addition to live birth should be reviewed for when determining the RAG ratings for treatment add-ons in future. The member acknowledged that this may vary for different add-ons and the Committee could consider each add-on separately to highlight its key issues.
- 4.13.** The HFEA Chair reflected on the discussion. The Committee seemed to have reached a consensus that the introductory text on the HFEA website should make it more clear that the traffic light ratings are solely given for the outcome of live birth rate. The Committee also seemed

to feel that for PGT-A, contextual information should be expanded to include that there is some secondary evidence from RCTs that suggests a reduction in miscarriage rate, but that this evidence is not conclusive, and that as always, patients should discuss their specific circumstances with their clinic.

- 4.14.** One member was concerned that updating the patient information to include conclusions from less reliable evidence would encourage patients to use PGT-A. The Committee agreed that the wording should explain that the evidence was not conclusive and only applies to certain categories of patients, if at all.

Recommendation:

- 4.15.** The introductory text of the webpage should be updated to make it more clear that the current traffic light ratings are based on evidence from RCTs where the primary outcome was live birth rate. The PGT-A section of the website should also be updated to include that secondary outcomes of RCTs have shown a potential decrease in miscarriage rate but that these findings are less reliable than primary outcomes and patients should seek advice about their personal circumstances from an expert.

Action:

- 4.16.** The Executive will circulate the updated introductory text for the treatment add-ons webpage to the Committee.

5. Novel process application – IVF using the AneVivo device in inter-partner and standard egg donation

- 5.1.** The Scientific Policy Manager outlined to the Committee that the HFEA had received a novel process application for the use of intrauterine culture, using the AneVivo device, in inter-partner and standard egg donation. As a novel process application had not been received for some time the Scientific Policy Manager reminded the Committee of the standard operating procedure for these applications. There is a list of authorised processes available on the HFEA website organised by which licensable activity they involve, dictated by the HFE Act 1990. This includes processes such as procuring gametes, processing gametes and storing gametes. If a centre wishes to use a process that is not included in this authorised list, they must seek permission from the HFEA by submitting a novel processes application.
- 5.2.** The Authority has delegated the authorisation of novel processes to the Statutory Approvals Committee (SAC), advised by the opinion of SCAAC on whether there is evidence that the process is not safe or not effective. The SAC will use this opinion, along with the information in the application form, to decide whether to approve, reject or adjourn the approval of the novel process.
- 5.3.** This application is an extension to the currently authorised process, intrauterine culture of gametes and embryos (including insertion into the woman's uterus and removal of device, followed by transfer of embryo(s) to the same woman), to allow the device to be used between different women. This would allow eggs donated by a partner or donor to be inserted into a second partner or recipient for incubation for a short time in the womb. The Committee had previously raised concerns about the lack of available data on the effectiveness and safety of intrauterine culture, based on the original application. The Committee was asked to give their

recommendation on whether there was evidence that the extended use of the process, between different women, was not effective or not safe.

- 5.4.** The Chair highlighted that the process had been used in the UK before it was authorised by the HFEA. The Scientific Policy Manager explained that when the HFEA inspector became aware of the unauthorised use of the process they informed the centre that the use of the device between women was not included in the original application and was therefore not authorised. In response the centre submitted a novel application form.
- 5.5.** The Committee discussed that at the [October 2018 SCAAC meeting they had heard from a representative of the clinic that submitted the application to use](#) intrauterine culture device. He suggested there was a psychological benefit to patients from using this process, although he did not provide any evidence to support this claim. A member suggested that there was a possibility of the process causing more psychological burden as patients may feel that if they did not opt to use it (and there was a financial cost) then they were not 'good' parents. Other Committee members agreed, stating that although it was beneficial for both partners to feel involved in the treatment, this was an expensive and invasive procedure.
- 5.6.** One member explained that there is evidence that the source of the embryo, whether donor eggs, sperm or embryo, has no impact on how the baby is appreciated and brought up within the family. They felt that a claim of potential psychological benefit for this device was not a sufficient justification for its use.
- 5.7.** Another member felt that, taking into consideration that this process had been previously approved by SAC, it was difficult to see how the extension for use in donor recipients and in same sex couples could be rejected.
- 5.8.** The Chair highlighted that the Committee needed to determine from the evidence whether the use of this process in two women, compared to its use in one woman, posed any increased risk. The Chair felt there was not enough evidence provided by the applicant to answer this question.
- 5.9.** Members discussed that the previous rationale for the use of the process given to the Committee had been that it was able to replicate a more natural environment than culture media. The intrauterine device was designed for embryos to access the uterine environment including growth factors and cytokines. However, members were not persuaded by this argument incubation is not taking place in the natural environment: it is the fallopian tube where embryo development takes place, not the uterus.
- 5.10.** One member questioned whether the Committee needed advice from an external expert as to whether there was any risk involved in transferring embryos from one uterus to another. Some members felt that the movement of the embryo from one woman to two was a marginal difference and therefore they had no major concerns with the extension request.
- 5.11.** One member questioned whether this process had any evidenced benefit to the embryo. This member felt that this should be taken into consideration alongside any psychological benefit for the parent.
- 5.12.** Another member highlighted that in previous meetings there were concerns about the loss of the device whilst inserted into the uterus. The Committee were unable to establish the likelihood of this occurring. The member was also concerned that using the device in two women doubles the

chances of infection. It was acknowledged that the applicant appeared to have provided evidence that there is no increased risk, but this evidence is limited.

- 5.13.** One member raised that at the October 2018 meeting the SCAAC requested that the representative bring additional data which the Committee had not yet seen. The Committee were aware that the device is being used in other countries, including Spain, so felt that there should be more evidence of its safety and effectiveness available.
- 5.14.** The Committee felt that if this extension was approved then there should be a strict follow up on asking for additional evidence from the applicant to be provided to the Committee for their consideration after a certain number of procedures within an appropriate length of time.
- 5.15.** One member highlighted to the Committee that this extension to the approved process does not advance the benefit of the device, but it does increase the risk. This alters the risk-benefit ratio. There is evidence from animal models that increase manipulation of embryos around the time of transfer causes programming effects in offspring. There have been studies to show that if an embryo is flushed out of one mouse and implanted into another changes in offspring birth weight and long-term development are seen. Although this is not a definite risk in humans it indicated that the risks may be increased by increasing manipulation.
- 5.16.** The Committee agreed with this statement and questioned whether, if the applicant returned and requested the extension of the process into further women, when the Committee would feel that the risks were excessive.

Recommendation:

- 5.17.** The Committee made a recommendation to SAC that there appears to be no evidenced benefit extending the use of this device into more than one woman. Until a clear benefit has been established, the Committee would not recommend proceeding with this extension as there are potential risks that cannot be quantified due to a lack of evidence.

6. In vitro derived gametes – literature review

- 6.1.** Policy Manager, Ms Askew, gave an overview of the literature review to the Committee which focused on key research findings into in vitro derived gametes since October 2016. Legislation in the UK prohibits the use of in vitro derived gametes in the treatment of humans. Researchers in the UK must hold a HFEA research license if they wish to investigate whether in vitro derived human eggs or sperm could undergo fertilisation and the early stages of embryo development. It is therefore important that the HFEA is aware of progress in this research area.
- 6.2.** There appeared to have been some promising developments in animals, with researchers successfully producing fertile offspring from in vitro derived spermatid like cells and replicating the entire process of oogenesis in vitro. Nuclear quality of in vitro derived gametes appears to be unaffected and researchers were able to replicate an intact blood-testis barrier in vitro. However apoptotic and autophagic pathways seemed to be altered and the production of gametes in vitro is inefficient.
- 6.3.** In humans it has only been possible so far to replicate germ cell development to an early stage and meiosis has been difficult to achieve in vitro. It is difficult to compare protocols between studies due to the variety of culture approaches used and studies often took place on small

sample sizes. Protocols may need to develop a step wise approach that replicates key phases of germ cell development. Although there are questions over the applicability of findings in animal studies to humans, there are major ethical and safety concerns about conducting this research in humans.

- 6.4.** The Chair asked the Committee to comment on the latest research findings in this area. Members commented that there were few developments and that progress in this research area is slow and developments may take a while.
- 6.5.** One member highlighted that in humans the recapitulation of meiosis in vitro appears to be the biggest challenge for in vitro gametogenesis. The Committee discussed that there doesn't seem to be a particular reason why the recreated of meiosis in humans is more difficult than in animals, where it has been achieved. However, oogenesis is a particularly long process. Culture needs to be maintained for many months which is technically difficult, but as techniques develop this may not be necessary.
- 6.6.** The Committee discussed the four-month long protocol outlined by [Yamashiro et al. \(2020\)](#) as part of the paper set which involved co-culture of human cells with fetal gonadal somatic cells from the mouse. The Committee noted that there is significant progress being made in the generation of fetal gonadal somatic cells in humans so it should be possible to recapitulate the protocol described by Yamashiro et al. (2020) in humans without the need for mouse gonadal somatic cells. However, as previously highlighted there is currently difficulty progressing beyond the oogonial stage in humans and research has been unable to proceed into meiosis. A member suggested that it may be necessary for a succession of different advancing stage gonadal cells to be used during culture.
- 6.7.** One member informed the Committee that, in mouse models, primordial germ cell like cells, derived from induced pluripotent stem cells and embryonic stem cells, which are co-cultured with early post-natal testes can undergo gametogenesis with reasonable efficiency. However, this research has not yet been conducted with human tissue.
- 6.8.** The Committee discussed when it is likely that in vitro derived gametes would become clinically relevant. They concluded that this would still be some time away, with a need that any eggs or sperm produced in vitro could be fertilised to produce normal embryos, and that the tissue derived from these embryos was also normal. Culture would also need to continue for long enough to determine that the epigenetics were correct. However, if in vitro derived gametes in humans were to successfully take place in another country then HFEA would need to act on this to regulate its use in the UK.
- 6.9.** A member highlighted that clinical application of in vitro derived gametes could be an alternative to genome editing. If patients were finding it difficult to undergo successful PGT-M then in vitro growth has been suggested as an alternative treatment. In vitro gametogenesis, although further from clinical application, could also be used as an alternative treatment in this situation.
- 6.10.** One member commented that there is a distinction between in vitro growth, deriving mature gametes from cells that had already differentiated into the line of oocytes or spermatogonia, and in vitro gametogenesis, which derives cells from alternative sources such as embryonic stem cells which then undergo the whole process of gametogenesis. Both in vitro processes would require a HFEA license, but in vitro growth is closer to the stage of clinical application.

- 6.11.** A member suggested that the 14-day rule of embryo culture for research makes it impossible to culture embryo resulting from your in vitro derived gamete to a point where it is possible to derive primordial germ cells and other tissues from those embryos. The tissues would need to be tested for their epigenetic changes before in vitro derived gametes could be used safely in humans.

Recommendation:

- 6.12.** The SCAAC did not make any recommendations for outputs from the HFEA that would be required addressing the use of in vitro derived gametes.

7. Any other business

- 7.1.** A member requested an update regarding the relaxation of the 10-year storage limit in relation to the COVID-19 pandemic. The member noted that this appeared to be a change to the existing legislation. Ms Ettinghausen explained that parliament had passed regulations that enabled patients whose gametes or embryos are currently in storage to extend storage for an additional two years, allowing for a total allowance of 12 years. This would require active consent from patients or donors. The Committee asked for clarification as to whether this extension also applied to embryos stored for research purposes.

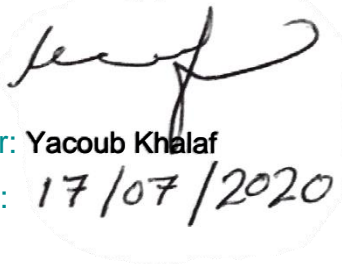
Action:

- 7.2.** The executive will circulate information to the Committee about the recent extension to stage limits and will clarify if this law change applies to embryos stored for research purposes.
- 7.3.** A member was asked to update the Committee on the progress of the commission report on human genome editing and when it might be published. A draft has been sent for peer review comments. These comments will be sorted with a response within around a month. This report will be shared publicly in August 2020, subject to any impact of COVID-19 on the publication date.
- 7.4.** The Chair informed the Committee of the Horizon Scanning meeting taking place on 9 July 2020 in line with the ESHRE 2020 virtual conference. The Chair then summarised the main discussion points of the meeting and informed the Committee of the next SCAAC meeting date.

8. Chair's signature

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

Signature



Chair: Yacoub Khalaf

Date: 17/07/2020