

Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes

3rd February 2020

St Martin's Hall, St Martin-in-the-Fields, Trafalgar Square, London,
WC2N 4JH

Authority members	Present	Yacoub Khalaf (Chair) Gudrun Moore (Deputy Chair) Kate Brian	Anne Lampe
	Apologies	Ermal Kirby	
External advisors	Present	Richard Anderson Jane Blower Andy Greenfield Robin Lovell-Badge Raj Mathur Kevin McEleny	Richard Scott Shankar Srinivas
	Apologies	Daniel Brison Joyce Harper	Sheena Lewis
Members of the executive	Present	Victoria Askew (Meeting lead and Scientific Policy Officer) Emily Tiemann (Meeting secretary and Policy Officer) Laura Riley Amanda Evans Sally Cheshire Peter Thompson Karen Conyers Stevan Cirkovic Joanne Anton	
Invited speaker	Present	Alistair Sutcliffe (UCLH) Sue Montgomery (CARE Fertility)	
Observers	Present	Dafni Moschidou (DHSC)	

1. Welcome, apologies, declarations of interest

- 1.1. The Chair welcomed the committee members to the meeting. Apologies had been received by Joyce Harper, Sheena Lewis, Daniel Brison and Ermal Kirby, and from Richard Scott who will be arriving late to the meeting at around 12 o'clock.
- 1.2. Declaration of interest was received from Raj Mathur due to having a private practice in fertility.

2. Matters arising

- 2.1. Minutes of the meeting held in October 2019 were agreed remotely prior to the meeting.
- 2.2. The Scientific Policy Officer updated the committee on matters arising. Three outstanding actions from the October 2019 meeting were for the HFEA to determine how often the treatment add-ons webpage is visited, to create a priority list of work around treatment add-ons and to review the stroke national database to see what resources are required to maintain this kind of database.
- 2.3. The Scientific Policy Officer informed the committee that the HFEA plans to carry out some of this work as part of the treatment add-ons project for which the plan is currently being finalised. The Committee will be updated on the project plan at the Committee meeting in June 2020. Any work that requires scientific and clinical input will be brought to the attention of the Committee.

3. Chair's Business

- 3.1. The HFEA add-ons webpage had recently been updated, pre-implantation genetic screening (PGS) on day 5 embryos being changed from an amber to a red traffic light rating. The HFEA received feedback on this decision from the sector and will prepare a response.
- 3.2. The Chair informed members that the treatment add-ons working group, formally known as the consensus statement working group, will be meeting on the 17th March 2020. The group will consider the next steps that will build on the principles agreed in the [consensus statement](#) to move towards a more consistent and transparent approach to the use of treatment add-ons in fertility services.
- 3.3. One member spoke on the Fertility 2020 conference which was very successful with over 1000 delegates. There were sessions on social and demographic elements, as well as basic science and clinical dedicated sessions.

4. Prioritisation of issues identified through the horizon scanning process and the Committee workplan

- 4.1. The Head of Policy presented a summary of the high priority issues for consideration by the Committee in 2020/21. These topics were identified through consultation with experts, journal articles and conferences, as well as thought discussion at the horizon scanning meeting.
- 4.2. A recap was given on the agreed criteria implemented to help prioritise topics into high, medium and low. The criteria are:
 - whether the topic is within the HFEA's remit,

- if it has an imminent timescale for likely introduction to clinic (2-3 years),
- if it seems likely to have a high patient demand and/or clinical use,
- if it is technically feasible, and
- if it raises ethical issues or public interest issues.

To be listed as high priority, a topic must be within the HFEA's remit and meet at least two others of these criteria.

- 4.3.** Based on this criteria, nine topics have been scored high priority for SCAAC for the next business year. No new topics have been added to this list. There are papers on two of these issues coming later on the agenda.
- 4.4.** A workplan was presented on how SCAAC should consider the remaining seven topics, with a timescale for now until June 2021 for when these topics will be addressed. The committee was asked to consider the workplan and approve it and to give thoughts as to whether any changes should be made regarding the prioritisation of the topics. For some priority topics (synthetic embryo-like entities, genome editing and AI) external speakers will be invited, and the committee was asked to suggest speakers.
- 4.5.** The Chair asked the committee about the Academies [International Commission](#) meeting on genome editing of the human germline that was held in Nov 2019, but members felt there was no new published policy position or recommendations to report from this.
- 4.6.** One member mentioned that the [WHO expert panel on genome editing](#) is publishing a report at the end of May or early summer 2020 and it was agreed for the SCAAC discussion on genome editing (as part of assisted reproduction) to come in October. One member mentioned that other work is also currently underway to review the appropriateness of reproductive genome editing in humans. One member pointed out that the WHO has already put out one survey to gather responses.
- 4.7.** One member mentioned a Jan 2020 [debate](#) in the House of Lords on gene editing brought by Baroness Bakewell and while nothing specific was decided, there were some calls for a Lords select committee on human genomics. The committee discussed how attitudes to pre-implantation genetic diagnosis (PGD) and genome editing are linked despite there being differences, and while we have many policies, other countries do not. There is some debate about whether PGD might require assistance in some cases from genome editing.
- 4.8.** The Chair highlighted that for the topic of mitochondrial donation, the committee would need an update and feedback from Newcastle Fertility Centre at Life as the only centre currently offering this treatment in the UK.
- 4.9.** One member commented on the topic of embryo culture media, which is the only high priority area that is in current practice and may be worth discussing earlier. The Head of Policy explained that this timescale was decided based on when this issue was last discussed (2019 in the case of culture media). The Chair mentioned that the scientific committee are often not forthcoming with information on this topic. One member discussed how this overlaps with the health outcomes in children topic.
- 4.10.** The Chair suggested an order to the list of topics, with add-ons being first as a hot topic, followed by health outcomes in children and embryo culture medium, then new technologies in embryo testing, genome editing, mitochondrial donation, synthetic embryo-like entities, and finally in vitro

derived gametes. One member suggested that in vitro derived gametes should come before synthetic embryo-like entities. One member mentioned that synthetic embryo-like entities will be discussed at a forthcoming international meeting, and they will feed back any recommendations to the committee.

- 4.11.** One member mentioned that we should stop saying PGD and PGS and refer to them instead as preimplantation genetic testing for monogenic diseases (PGT-M) and preimplantation genetic testing for aneuploidy (PGT-A). One member pointed out that patients do not use the terms PGT-A and M, although some clinics have started to adopt this.
- 4.12.** The Chair discussed in vitro derived gametes and mentioned that the pace in this is not as fast as in other topics such as genome editing, and milestones are happening slowly, but the committee still need to be aware. The committee agreed that this topic is less urgent.

Action

- 4.13.** HFEA will revise the workplan and prioritisation list as agreed in this discussion and circulate by email to committee members.

5. New technologies in embryo testing (focus on non-invasive methods)

- 5.1.** The policy officer introduced the topic of new technologies in embryo testing, focusing on non-invasive methods. The topic was last discussed by the committee in [February 2017](#) and covered next generation sequencing (NGS), karyomapping, SNP arrays and array CGH. The topic was also discussed at an HFEA Horizon scanning meeting in 2019. There, concerns were raised regarding whole genome sequencing and the possibility of incidental findings when embryos are screened for both genetic and chromosomal abnormalities without the need to develop any disease-specific test, and also around testing for polygenic traits where the result is a risk of a trait rather than a diagnosis.
- 5.2.** The literature review analysed studies published in the last three years. There has been growing interest in the use of non-invasive preimplantation genetic testing, specifically in analysing DNA in the spent culture medium of embryos, but conclusions have been inconsistent regarding the specificity and efficacy of these methods, showing a need to increased research. Embryo testing for polygenic traits is still new, and we need to consider ethical implications of this and of whole genome sequencing.
- 5.3.** The Chair discussed with the committee that the results of non-invasive testing were initially promising, however there are two problems to consider. The first being that the DNA within the spent culture media may be derived cells that had undergone apoptosis involved in the spontaneous correction of aneuploidy. This would bring into question whether the results would be truly reflective of the embryo genetic make-up. The second being that the results could be contaminated by maternal granulosa cells.
- 5.4.** The Chair highlighted that the study by [Huang et al. \(2019\)](#), mentioned in the literature review, removed all granulosa cells which led to the false negative rate being zero; this highlighted the role that granulosa cells can play in discordant results. The Chair summarised that this study suggests that, compared to trophectoderm biopsy, culture media had an advantage. However, the Chair questioned whether the same result would have been achieved if the embryos had not been

previously biopsied or whether the biopsy had created leakage of genetic material into the culture media that was then available for testing. He concluded that this practice was not easily extrapolated to clinical practice and that these non-invasive techniques should be approached with the same caution and scrutiny as an invasive technique.

- 5.5.** The Chair suggested that these techniques should not be used to identify embryos to be discarded but instead should be used to rank embryos, with the highest ranked embryos being used in that treatment cycle and the remaining embryos being frozen for potential future use.
- 5.6.** A committee member highlighted the technique of aspirating blastocoel fluid alongside analysing spent culture media to increase the accuracy of the results. The committee member argued that the removal of blastocoel fluid is invasive, and we do not know the function of blastocoel fluid so can't be sure of its impact. The Chair commented that the removal of blastocoel fluid before vitrification increases the survival rate of embryos. The member questioned whether we knew the long-term impacts on the health of the child born after using this technique. Another member pointed out that this removal of blastocoel fluid for vitrification is only for those that are meant to be frozen and is not a standard practice for all embryos.
- 5.7.** The chair discussed that if non-invasive methods of embryo testing were to be introduced then all embryos undergoing this technique would need to be frozen because of the time taken to get the results of any testing. This would influence the cost, the safety and the effectiveness of the patient's treatment.
- 5.8.** A member raised a concern that testing for polygenic traits is not in line with the licensing of conditions that meet the requirements set out in the HFE Act. It was clarified that this testing is not currently taking place in the UK, it is predominantly taking place in the USA. It was highlighted by the Chair that some of the conditions that polygenic scores test for are treatable in adult life, e.g. diabetes and hypothyroidism so would not meet the 'seriousness' condition in the HFE Act. There is also concern that fertile couples might seek out this treatment outside of the UK to create so-called 'super babies' that are supposedly at a reduced risk of many common health problems such as heart disease. One member suggested that this type of technology is unlikely to be possible except in rare cases. It is unlikely that any embryo will have a reduced risk of more than a few common health problems and may have an increased chance of others.
- 5.9.** One member highlighted that not all diseases are caused exclusively by genetic mutations and that embryos could be ranked on metabolic phenotypes. The member argued that although previous studies have suggested that metabolomics do not add much value to the selection of embryos, it does not mean the technique did not have potential value. One member wanted to highlight that one of the studies included in the review did suggest that there are factors involved in the inheritance of complex traits other than genes.
- 5.10.** The committee discussed the issue of incidental findings alongside genetic testing. A member questioned whether clinicians should inform patients if genetic diseases, outside of those that were being tested for, were identified. The committee felt that that it could be negligent to not share information with patients that could cause harm. The committee felt that if genetic counselling were provided, patients could be informed, although counselling after the finding is not ideal. One member highlighted that next generation sequencing (NGS) had the potential to identify hundreds of abnormalities, a large proportion of which would not be disease causing. The committee were not aware of aneuploidy screening that looks at single genes, rather that the test identifies chromosome copy number.

- 5.11.** The committee discussed that the uptake of embryo testing is reduced because of the risks involved with biopsy, including a reduction in implantation rate. If it became possible to remove this risk by using non-invasive techniques that had tests with a rapid turnaround time, avoiding the need for embryo freezing, and allowing the embryos to be ranked rather than deselected; then embryo testing could become clinically more widespread, although the timescale is not clear. A member raised that cost would still be a factor in patients choosing embryo testing unless it could be used to prevent wasted embryo transfers. However, there would need to be high level of confidence that what was discarded was worthy of discarding.
- 5.12.** One member highlighted that, currently, the cumulative live birth after a cycle of IVF without testing when compared with testing is higher because there is inevitably damage caused to the embryos or exclusion of healthy embryos due to false positives. Another member felt that this might not always be the case and that if non-invasive techniques allowed for the testing of embryos on day two or day three of development then culture conditions could be personalised for those embryos, optimising their potential. Members acknowledged that this is far-fetched but could be possible.
- 5.13.** A member highlighted that the rating of PGT-A by the [HFEA traffic light system](#) is fair when you consider the outcome of live birth. However, when other outcomes are considered, such as miscarriage rate or time to pregnancy, then red might not be the best rating. However, as the current outcome assessed is live birth rate then the red rating for that metric is correct. The member highlighted that there are potential issues with focusing on only one outcome when there are other valid outcomes that patients and clinics may be concerned with and which may not be rated as red.
- 5.14.** The Committee discussed that although the Huang et al. (2019) study was promising it was on a small number of embryos and the technology was still at an early stage. They did not feel that the time taken for tests to be completed would stop the update of non-invasive testing, the committee believe that tests can be achieved an appropriate speed. A potential problem would be whether spent culture medium is representative of the embryo without too much 'background noise'.
- 5.15.** The HFEA Chair raised that the impact of incidental findings on patients was discussed by the Authority in [January 2016](#) and a decision was made that there would need to be either genetic counselling or a conversation with the patient of the potential risks before the test took place. Clinics need to be clear at the start with patients to determine whether they want to know about potential incidental findings, or whether they only want to know about the specific genetic condition(s) being tested for. A member raised concerns about the quality and accessibility of genetic counselling for patients at fertility clinics and questioned whether it should be compulsory when genetic tests are taking place. The member suggested that the technology has moved on since previous discussions around genetic counselling and the HFEA's regulation may need to be reviewed.

Action.

- 5.16.** HFEA will clarify with the Committee the exact wording in the [Code of Practice](#) for genetic counselling and incidental findings
- 5.17.** The Chair discussed that when preimplantation genetic testing for structural re-arrangements (PGT-SR) is performed they do not look at the whole set of chromosomes but rather focus on the targeted ones, due to the potential risk of discarding an embryo for an incidental finding that may

or may not be pathogenic. This means that other genetic conditions, such as trisomy 13, could be missed. The Chair acknowledged that this decision could be debated.

- 5.18.** One member raised concerns that the current license to test embryos for chromosomal re-arrangements (various) is leading to confusion in the sector about what would fall under this category and be classed as a serious condition under the Act. The sector may appreciate some guidance of conditions that fall within this category.
 - 5.19.** The HFEA Chief Executive asked the committee how they saw this technology being used if it was proven that non-invasive testing was effective. The committee suggested that if high quality whole genome sequencing that avoiding biopsy was possible, you could find the genetic make-up of the embryo without the risk of potential damage. However, there is not enough known about human genomics to say where this will lead. The committee suggested that the next big step would likely be to use this non-invasive testing to rank embryos for transfer according to their quality.
 - 5.20.** The committee suggested potential speakers for future committee meetings on this topic. Dr Alan Thornhill, a previous Authority member, to discuss the potential positives around PGT-A and Prof Lyn Chitty at UCL to discuss non-invasive prenatal testing and the common challenges faced, especially in terms of incidental findings.
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6. Health outcomes in children born following ART

- 6.1.** The Scientific Policy Officer introduced the topic of health outcomes in children following ART. The last time this was discussed was in June 2017, where it was highlighted that there was a lack of information available on the HFEA website about the link between ART and birthweight. A literature review had been carried out of 56 studies, which indicated an increase in the amount of research investigating the effects of fresh and frozen embryo transfer on perinatal outcomes. However, studies looking at longer term developmental outcomes still appeared to generally have small sample sizes compared to studies that focused on birth outcomes.
- 6.2.** The committee was joined by Professor Alastair Sutcliffe, consultant paediatrician at University College Hospital with research interest in studies of IVF children and their mothers to speak more on this subject and to present his views on recent findings on health outcomes in children born following ART.
- 6.3.** Professor Sutcliff discussed the fact that there is a lot of variation in terms of how good the science is in the papers that were included in the literature review, and some studies needed larger numbers to reach conclusions. The idea of wanting children conceived by ART to be the same as naturally conceived children is false, as there is a reason why infertile couples need help to conceive, and it is normal that there would be some differences in outcomes. Regarding outcomes of fresh versus frozen transfers, the overall message of all the papers was that freezing is not quite as safe as we may once have thought. Children born through frozen transfer are larger, which should be of concern to the scientific community, especially since larger babies and children can have other health issues. One member asked whether it should be reassuring that babies are being born larger rather than too small. Professor Sutcliffe responded that any abnormal growth pattern should be worrying, and it is not quite as simple as large babies being good.
- 6.4.** One member asked if there was an overall effect on the majority of babies rather than there being a subset who have a large effect, which skews the average. Professor Sutcliffe responded that he

thought the former, otherwise this would be more concerning. One member asked whether there is an age at which the differences in weight disappear, Professor Sutcliff said this was around the age of ten, although this is not very clear.

- 6.5.** One member mentioned that he expected sub-fertile women to have smaller babies as a general predisposition, which Professor Sutcliff agreed with. One member mentioned that the differences in weight were small at 160g, although Professor Sutcliff said that in fact this was still a change in one direction throughout the literature. As the population of children born using ART is getting older, an area to focus on in the future will be how this change in weight continues through life, and there is a plan to do this study in the UK.
- 6.6.** Regarding neuro-developmental outcome, Professor Sutcliff explained that it is extremely rare, in fact there has only ever been one study, that a difference is seen between ART and naturally conceived children. One member mentioned that one paper by Aoki had found that children born after ART had higher development of receptive language than naturally conceived, although Professor Sutcliff explained that these advances stopped by the age of 10. However, the member pointed out that the first 10 years may be the most formative and important. Professor Sutcliff explained that often the socioeconomic status of ART conceived children is higher, which is a factor in why they do well, and added that spontaneous abortion and miscarriage rates are higher in ART pregnancies.
- 6.7.** Professor Sutcliff discussed how studies on congenital malformations have been consistent over the last three years, showing an increased risk from ART, but it is hard to know if this is due to IVF or to the nature of the couple, since some work in Denmark has shown that sub-fertile couples who conceive also have a higher risk of having children with congenital malformations. The only syndrome that has been shown without a doubt to be increased after ART is Beckwith-Wiedemann syndrome.
- 6.8.** Regarding the risk of cancer, Professor Sutcliff explained that large studies have generally concluded that there is not a difference in cancer rate after ART conception versus natural conception, although more work needs to be done on long-term cancer risk.
- 6.9.** Professor Sutcliff then discussed where things are going regarding research in the UK. His research will be looking at the concerns over women undergoing ART, as there is an increased risk of ovarian cancer and invasive breast cancer. The research will therefore be looking at other potential health issues in women, as well as long-term health issues of sub-fertile males.
- 6.10.** The Chair discussed how in these types of studies, there are many cofounders which are hard to account for. Traditionally, frozen embryos were surplus and were only produced by good prognosis patients. Their profile may therefore have had an impact on the children born. Additionally, it is hard to establish association from causation.
- 6.11.** One member asked about what the message on birth weight should be if patients are asking, and Professor Sutcliff explained that with 'standard' IVF there may be a risk of a smaller baby, and with frozen IVF there may be a risk of children being larger than average. The Chair pointed out that nobody knows if this is good or bad, however this is important to know. The committee discussed how the control group for research in this area is potentially sub-standard, since families who have babies through IVF are often very different from families who have babies naturally, and the environment is very difficult to control. Additionally, a bigger study is not necessarily better if the wrong control group is used.

- 6.12.** A member raised a concern over using the term ‘macrosomia’ since an increase in 160g is very little and Professor Sutcliff agreed that this was an exaggeration. Birthweight can be an indicator of what is to come later in terms of metabolic syndromes when the child reaches 50 or 60. A member pointed out that babies have been getting heavier in the last few years, so this is a general trend. Another member brought up the point that there may be a selective advantage for embryos who have survived freezing and thawing.
- 6.13.** The committee discussed how to summarise what to tell patients, and how this should be mentioned by the HFEA because of other risks like pre-eclampsia. The committee concluded that the research shows nothing major to worry about in terms of health outcomes is reassuring, and the overall trajectory of IVF is getting better, not worse.
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7. Treatment add-ons data that CARE Fertility collect

- 7.1.** The Scientific Policy Officer introduced Dr Sue Montgomery, CARE Manchester’s Laboratory Manager and the PR for the clinic’s licence to provide fertility treatment to discuss what data clinics currently collect on treatment add-ons.
- 7.2.** Dr Montgomery began by discussing the HFEA’s traffic light system and explained that the way add-ons are used in clinics is different to how the HFEA approaches them. For instance, for time lapse imaging, CARE fertility has their own algorithms based on assessment of large data sets, and patients can only get specific information related to this if they come to CARE. Secondly, the HFEA traffic light system does not take into account the different categories of patients who are treated with add-ons, for instance PGT-A, which may be beneficial to certain age groups or for patients suffering from recurrent miscarriages. Thirdly, results from clinic to clinic can be quite variable, and the HFEA traffic light system doesn’t account for this. For instance, for EmbryoGlue, an internal trial was carried out at CARE where no evidence or benefit for its use was found, therefore CARE currently do not recommend this add-on to patients.
- 7.3.** In terms of data collected on add-ons, Dr Montgomery explained that CARE has a system in which all patient details and add-on use are entered, and data can be analysed across their clinics. This enables them to constantly review results and benchmark the clinics within the group against each other. This constant results monitoring allows them to compare clinics within the group and get advice from clinics that are doing well.
- 7.4.** To answer the question of how data sets are assessed and fed back into practice, Dr Montgomery introduced the example of time lapse, which CARE calls CAREmaps. This was first introduced in 2011 without charge, and subsequently a retrospective analysis was done of KID (‘known implantation data’) embryos. An algorithm was then developed to show predictability of a successful outcome.
- 7.5.** To develop the algorithm, morphokinetics was used to time stamp when a particular development event has taken place (e.g. cleavage) and to record differences in timings in development (e.g. time taken to for the embryo to go from 2 cells to 3 cells). There has been an association made between the length of time an embryo spends in the morula stage and live birth rate. Additionally, a short difference between t2 and t3 (2 cells to 3 cells) is strongly associated with poor implantation rates.
- 7.6.** Dr Montgomery discussed a publication which came out of CARE data, which showed a significant difference between euploid and aneuploid blastocysts, with euploid embryos being

associated with early blastulation. This pattern was seen throughout all the CARE algorithms across 10,000 blastocysts.

- 7.7.** The way CAREmaps works was explained, by looking for key timings in the development of embryos for instance the time of pronuclei fading. Each embryo is then given a score, and ranked A, B or C. Other data analysis is also done, for instance whether or not all cells are included in a morula.
- 7.8.** Dr Montgomery discussed how, while a randomised control trial is the gold standard in research, this is not able to account for the embryo cohort. Therefore, this would not necessarily benefit the patients as they know that some embryos should be excluded from transfer, and it would not be fair for patients in the control group to not benefit from this. CARE's retrospective data is in very large numbers, has been peer-reviewed and published, and should be considered when decisions are made. Studies showed significant improvement in live birth rate compared with no time lapse, and a recent study showed strong evidence of superiority of the algorithm compared to grading alone.
- 7.9.** Dr Montgomery said that CARE are constantly reviewing and improving their data, looking at results and striving to improve their system and improving their algorithm. New technologies are only introduced into clinical practice if CARE believes in them improving patient outcomes. When patients were asked about their thoughts on CAREmaps, most patients (80%) found that it helped with their understanding of what happens in the lab.
- 7.10.** In terms of what the HFEA can do to help clinics, Dr Montgomery believes that more data should be collected on add-ons, which would allow comparisons to be made between age groups and between clinics. This could be used to drive improvements, which has been shown to be effective before in the HFEA's campaign to reduce multiple births.
- 7.11.** Dr Montgomery concluded her presentation by saying that there is a lot of evidence for add-ons that are not from RCTs, there is a possibility of there being a lot of clinic to clinic variation, and some patients may be being misled by the current HFEA traffic light system as it is too generalised.
- 7.12.** Dr Montgomery explained that although CAREmaps makes a difference to patient outcomes, it is very expensive, and a lot of effort goes into data analysis. Currently the charge is £800, but it is included in some packages. A member mentioned that the sector is moving towards time lapse incubators being the standard in clinics, and that this may save clinics money as time lapse imaging saves embryologists' time. A member asked what the difference in pregnancy rates was for the patients using CAREmaps, to which the answer was around a 10% increase, although this depends on age range and it is usually more successful in the older population, potentially because they have more aneuploid embryos that the algorithm can pick up. Around 80% of CARE patients use CAREmaps.
- 7.13.** A member asked if patients can use the time lapse incubators without the analytics, to which Dr Montgomery responded yes, if there is space, and they are currently trialling Geri incubators without the algorithm.
- 7.14.** A member asked whether machines have been trained with the data sets, and Dr Montgomery explained that AI technology is being developed for the embryoscope machinery.

- 7.15.** A member asked whether any data had been collected after birth, for instance birth weight and sex, and whether any correlation had been seen. Dr Montgomery was not aware of any analysis of this data.
- 7.16.** A member thanked Dr Montgomery for the presentation, as this was a new area for the committee. It was pointed out that the committee treats each add-on as a separate issue, and they are not all the same. Being able to compare clinics does not answer the question of whether or not a patient should be offered the treatment, and we still need to answer this question.
- 7.17.** A member asked at what point time lapse could become green under the HFEA's traffic lights criteria, to which Dr Montgomery replied that in terms of ranking embryos for transfer, according to data collected by CARE she would consider the algorithm to be green because it does its job and is able to select the best embryo.
- 7.18.** The HFEA Chief Executive asked whether CARE laboratories over time may have changed practices or culture media or whether it was the time lapse which was making the difference, but Dr Montgomery explained that media had only been changed once, and embryo outcomes were kept separate according to the media change.
- 7.19.** A member asked how CARE justifies other more controversial add-ons such as artificial oocyte activation (AOA). Dr Montgomery explained that CARE have processes in place to mitigate against risks, and this procedure is only used in rare cases and in specific patient groups for instance those who previously had no fertilisation or no blastocysts. This is usually a last resort before egg donation. Regarding RCTs, these are not always practical in a clinical setting as if a patient could benefit from AOA, it is hard to justify them being in a control group. A member mentioned that this would depend on how the RCT is explained, and if patients are told about the trial, they would respect this, but Dr Montgomery disagreed. She said that CARE provides patients with a lot of information about how AOA is still experimental and hasn't been proven to be beneficial, but some patients still choose to try it. A member asked Dr Montgomery how CARE chooses which RCTs to participate in, to which she answered that this depends on where they can collect enough meaningful data for an RCT to be useful; regarding AOA, this is so rare that a trial would take a very long time and would be unfair to some patients who were allocated to the control group.
- 7.20.** A member of the Executive asked what data points could CARE provide to the HFEA in terms of add-ons, and how easy this would be. Dr Montgomery replied that (in terms of time lapse) it would be useful to know which type of incubator was used and which algorithm was used, as well as patient characteristics like age and previous cycles. Submitting this data to the HFEA would be simple, as this is already recorded electronically by CARE.
- 7.21.** A member asked what proportion of patients using CAREmaps were NHS versus private. Dr Montgomery estimated this to be around 20% NHS and 80% private. In terms of take-up, about 80% of private patients chose CAREmaps. For the NHS patients this depends on whether their CCG allows add-ons, and it was around 50%.
- 7.22.** A member asked whether the CAREmaps algorithm was getting better. Dr Montgomery said that comparing to the original data set, there have been improvements in clinical pregnancy and live birth rates, but the difference in algorithm is hard to assess because of different sets of data.
- 7.23.** A member asked whether the [CAREmaps algorithms](#) are published, to which the answer was yes.

7.24. A member asked how many other add-ons CARE offer based on their own data rather than published RCTs. Dr Montgomery said that they offer Embryo Glue and endometrial scratching if a patient requests it, PGT-A and AOA. About 5% of CARE Manchester patients choose PGT-A, and the cost of CAREmaps is included in the cost.

7.25. The Chair thanked Dr Montgomery for her interesting presentation and insights.

8. Any other business

8.1. A member mentioned that it is important to make a distinction between ethics and science and that interventions can only be objectively assessed by randomising patients in a trial.

8.2. The Chair brought forward a paper entitled '[Is Research from Databases Reliable](#)', which highlighted that this type of research is good for generating hypotheses and to support RCTs, but that it could not be used to determine whether an intervention is effective or not.

8.3. The chair congratulated committee member Raj Mathur on his announced position of Chair-Elect of the British Fertility Society (BFS).

8.4. The Chair summarized the meeting and thanked the Committee and the guest speakers.

9. Chair's signature

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

Signature



Chair: Yacoub Khalaf

Date: 14/05/2020