

Scientific and Clinical Advances Advisory Committee - minutes

06 February 2017

Evolve Suite, Etc. Venues One Drummond Gate, Victoria, London
SW1V 2QQ

Committee members	Present	Yacoub Khalaf (Chair) Kate Brian Andy Greenfield Anne Lampe	
	Apologies	Tony Rutherford	
External advisors		Daniel Brison Robin Lovell-Badge Gudrun Moore Melanie Davies Joyce Harper	Raj Mathur Jane Blower Sheena Lewis
Members of executive		Anna Quinn (secretary) Juliet Tizzard Joanne Anton Peter Thompson Lesley Brown	Anna Coundley
Invited Speakers		Andy Vail Sjoerd Repping	Dagan Wells
Observers	Present	Margaret Gilmore	
	Apologies	Steve Pugh (DH)	

1. Welcome, apologies and declarations of interest

- 1.1. The Chair welcomed committee members to the meeting and conveyed apologies on behalf of Tony Rutherford and Steve Pugh.
- 1.2. In relation to the meeting agenda, interests were declared by Daniel Brison, who is an IVF unit Scientific Director with research interests in human embryo development, follow up studies and

sperm DNA damage. Interests were also declared by Sheena Lewis who is Director of a company working on development of treatment add ons.

2. Matters Arising

- 2.1.** Minutes of the meeting held on 17 October were agreed remotely prior to the meeting.
-

3. Chair's Business

- 3.1.** The Chair noted the 2017 meeting dates are 16 June and 19 October. Both meetings will be held at the HFEA offices at 10 Spring Gardens, London SW1A 2BU.
-

4. Developing a traffic light system for treatment add ons

- 4.1.** The Chair welcomed Professor Andy Vail to the meeting and thanked him for his work assessing the quality of evidence for treatment add ons.
- 4.2.** The Scientific Policy Manager provided an overview on the progress of the HFEA's treatment add ons work to date and explained that the purpose of the discussion would be to finalise the traffic light system for treatment add ons.
- 4.3.** Prof Vail gave an overview of his methods for assessing quality of evidence and highlighted that as a statistician he assessed the methodological quality of studies without taking into account the biological or clinical plausibility of the treatment add ons. Quality was assessed by looking at PICO criteria (population, intervention, controls, outcomes) and factors including risk of bias, allocation concealment, selective outcome reporting and blinding. Prof Vail highlighted some common errors that are made when carrying out randomised trials in this area, such as randomising patients at the start of the cycle, before they meet the eligibility criteria, which leads to post randomisation drop out.
- 4.4.** The committee discussed the three category traffic light rating and whether it would be appropriate to use more categories. The committee agreed that in order to keep the patient information easy to understand, three categories would be most appropriate - but with the addition of accompanying text to provide further clarity and background that might be obscured by having only three categories. Members agreed that traffic lights will appear as a coloured circle with no symbol, and that:
- Red indicates no evidence of improved clinical outcomes
 - Amber indicates a small or growing body of evidence which shows promising results, but further research is needed
 - Green indicates that more than one high quality study has shown that the treatment add on improves clinical outcomes.
- 4.5.** The committee agreed that clinical outcomes would refer to pregnancy and live birth rates, rather than outcomes such as blastocyst development or implantation rate.
- 4.6.** Some committee members highlighted the importance of educating patients about the evidence for treatment add ons so that they can make an informed decision of whether or not they are willing to pay for these treatments.

4.7. The HFEA Director of Strategy explained to the committee the Executive's plans for dealing with treatment add ons, noting that the traffic light system is the starting point with further work to be carried out as part of the HFEA's 2017-2020 strategy. This includes an awareness campaign to educate patients, working with clinics to ensure that they are providing patients with accurate information and exploring the potential for using regulatory levers where possible, if clinics are found to be offering treatment add ons unnecessarily.

4.8. Prof Vail provided the committee with an overview of his analysis for each treatment add on, based on a literature search carried out by the Executive:

Artificial egg activation

4.9. Prof Vail and the committee noted that there are very few studies relating to artificial egg activation, however the results from the few existing studies are promising. The committee agreed that artificial egg activation would be categorised as amber. Due to amber being a broad category, the committee also agreed that a short tag line would sit next to the traffic light symbol on the HFEA website to give an indication of the level of evidence. In the case of artificial egg activation, the tag line will flag that there are only a small numbers of studies with promising results and further research is required.

Assisted hatching

4.10. The committee agreed that several studies have shown the assisted hatching does not improve clinical outcomes and should therefore be categorised as red.

Elective freeze-all

4.11. The committee agreed that elective freeze-all will be categorised as amber. Prof Vail explained that there is a small amount of promising research in this area and the tag line should match artificial egg activation. The committee agreed that it would be valuable to flag in the patient information that there is a large freeze all trial currently taking place and a link to the trial website should be provided.

Embryo glue

4.12. Prof Vail informed the committee that one large, good quality study on embryo glue dominates the research in this area. The other research into embryo glue is poorer quality and the positive results are not as strong. Some committee members suggested that embryo glue should be green as there is a good quality study indicating an improvement in clinical outcomes. However, other members preferred amber as the results of this study had yet to be replicated by other research groups. Due to the divide in opinion, the committee agreed to use the recommendation from the independent assessor that embryo glue will be amber with the tag line explaining that further research is required to replicate the existing findings before this treatment can be recommended for use in routine clinical practice.

Endometrial scratching

4.13. The committee agreed that endometrial scratching will be amber as there are consistent, moderate quality studies suggesting improved clinical outcomes. The committee also requested that the patient information links to the current clinical trial being carried out in this area.

Intrauterine culture

- 4.14.** Prof Vail noted that there have been no clinical studies using intrauterine culture and committee members agreed that this add on will be categorised as red.

Preimplantation genetic screening (PGS)

- 4.15.** Prof Vail explained that PGS can be divided into two categories: PGS carried out on day three embryos and PGS carried out on day five embryos. Prof Vail told the committee that there was strong evidence that PGS carried out on day three embryos has negative effects on clinical outcomes. There were a small number of studies carried out on day five embryos, which showed a promising effect on clinical outcomes; however, it was noted that whilst PGS might improve live birth rate per embryo transfer, it cannot increase cumulative live birth rate per treatment cycle started (including transfer of frozen embryos). The committee discussed how to present these findings in the patient information and agreed that two traffic lights should be published, red for PGS on day three embryos and amber for PGS on day five embryos.

Reproductive immunology

- 4.16.** The committee agreed that reproductive immunology will be categorised as red as there is no evidence that this treatment add on improves clinical outcomes.

Time-lapse imaging

- 4.17.** The committee agreed that time-lapse imaging will be categorised as amber with the tag line stating that early results on embryo selection are promising but further research is required.
- 4.18.** The committee thanked Prof Vail for his input into this work and requested that he be invited to input again when patient information is developed for new treatment add ons.

Actions

- 4.19.** The Scientific Policy Manager will work with the Communications Manager to incorporate the committee's decisions into the new HFEA patient information that will be launched in Spring 2017 as part of the new HFEA website.

5. New technologies in embryo testing

- 5.1.** The Chair welcomed Professor Sjoerd Repping from the University of Amsterdam and Dr Dagan Wells from Reprogenetics and thanked them for agreeing to present to the committee on the topic of new technologies in embryo testing.
- 5.2.** Dr Wells provided an introduction to embryo testing technologies with particular focus on karyomapping, a technique which looks at specific polymorphisms across the genome to identify the presence of a particular gene mutation. Dr Wells highlighted that this technology does not lead to incidental findings as it is not looking for specific gene mutations. This means that you can gather information only about the particular gene in question.
- 5.3.** Dr Wells went on to discuss the evidence base for preimplantation genetic screening (PGS), highlighting that it should be used as a tool for embryo selection to reduce the time to pregnancy. Dr Wells informed the committee that next generation sequencing (NGS) is more commonly being used for PGS, as this technique only requires sequencing of 0.1% of the genome and therefore produces very few incidental findings. The use of NGS also means that mosaic embryos can be identified in which some cells may have the correct number of chromosomes and some cells do not. Dr Wells explained that mosaic embryos may have a lower chance of generating a viable

pregnancy. He highlighted that the Preimplantation Genetic Diagnosis International Society (PGDIS) has recently published a position statement stating that mosaic embryos should only be transferred where there is no other alternative and preferably only after the patient has received appropriate genetic counselling. Dr Wells concluded by stating that whilst he thought the initial evidence around PGS on day five embryos is promising, further research is needed in poor prognosis patients and looking at clinical outcomes such as pregnancy or live birth rate rather than implantation rate.

- 5.4.** Prof Repping began his presentation by highlighting the need for responsible innovation and the importance of introducing new procedures into clinical practice in the context of a clinical trial. Prof Repping gave an overview of the use of PGS over time, explaining that use of this technique decreased after publication of a trial which showed it decreased implantation rate. Since the publication of this trial, PGS has been further developed and refined, leading to publication of research showing that PGS on embryos at day 5 could improve implantation rates. Prof Repping explained to the committee that currently there is insufficient data to support the clinical and cost effectiveness of screening embryos for aneuploidy using PGS. It is important to note that some PGS cycles will result in no embryo being transferred, as no euploid embryos are identified. Prof Repping pointed out that these no-transfer cycles are often not reported in clinical trials.
- 5.5.** Prof Repping spoke about the possibility that transfer of an aneuploid embryo could still result in a live birth, meaning that PGS could lead to discarding embryos which could have resulted in a live birth. Prof Repping then went on to discuss mosaicism and the potential for mosaic embryos to lead to live births. He explained how sampling a small number of cells in a mosaic embryo could lead to misdiagnosing an embryo as euploid or aneuploidy depending on the chromosomes present in the biopsied cells. One recent paper in which mosaic embryos were transferred showed that transfer of mosaic embryos can lead to live births. Prof Repping explained that there is insufficient evidence to show that PGS can reduce the time to pregnancy, but including the technology can greatly increase the cost of a treatment cycle.
- 5.6.** Prof Repping noted the importance of providing evidence-based, objective information for patients so that they can make informed decisions about their treatment options. Prof Repping explained that in the Netherlands PGS is not carried out, however, in one centre information about chromosome number is gathered as part of PGD and the data regarding chromosome number is used to rank embryos for transfer.
- 5.7.** The Chair thanked both speakers for their presentations and opened the floor for questions from committee members. One member asked the speakers about how common mosaicism is and how frequently mosaic embryos might be being discarded. Dr Wells explained that mosaicism is a common phenomenon, however, it is less common for mosaicism to impact on the decision of whether to transfer an embryo as it usually occurs alongside a more significant chromosomal abnormality. Prof Repping added that in many cases, mosaicism observed in a day three embryo is no longer present by day five, suggesting that mosaicism can be reduced or eliminated during embryo development.
- 5.8.** One committee member asked the speakers whether the use of PGS could reduce miscarriage rates. Prof Repping explained that whilst PGS could reduce miscarriage rates, it cannot improve live birth rates per cycle and should therefore be used only as a selection tool to rank embryos. It was noted that PGS also has the potential to increase time to pregnancy by putting women through multiple cycles and possibly discarding viable embryos. Dr Wells highlighted that

embryos are frequently discarded by clinics who, for example, may have high eligibility criteria for freezing embryos.

- 5.9.** The committee considered that one positive aspect of PGS could be to provide patients with information about why previous embryos have failed to implant and discussed whether PGS could provide some closure by identifying a chromosomal abnormality in a patient's embryos.
- 5.10.** The committee discussed egg banking, where a patient goes through multiple cycles of egg collection before having any treatment. Dr Wells explained that some clinics may offer this service for specific patients, for example, older patients who may benefit from generating a number of embryos quickly.
- 5.11.** Members discussed the difficulties in providing genetic counselling for patients when technologies in this area are advancing rapidly. Dr Wells reassured members that counselling does not necessarily have to become more complicated when it is possible to use technologies that will only provide information on the gene in question and will not present incidental findings.
- 5.12.** One committee member noted that for older women, using PGS might increase the number of cycles required. For women over 40 years old, approximately five blastocysts would be required in order to have a good chance of having one euploid embryo for transfer. Accumulating this number of blastocysts would require several rounds of ovarian stimulation and egg collection.
- 5.13.** The committee asked the speakers how they would rate PGS in a traffic light system where red means 'do not use', amber means 'there is some evidence to support the use of this technique' and green means 'there is good quality evidence supporting the use of this technique'. Prof Repping rated PGS as red as it cannot increase cumulative live birth rates per treatment cycle started. Dr Wells rated PGS as amber as there is some evidence suggesting that it could increase the chance of transferring a viable embryo; however, further research is still required.
- 5.14.** The committee noted that patients may be attracted to PGS for different reasons. For example, patients may want PGS to improve implantation per embryo transfer, or they may want to reduce the miscarriage rate per pregnancy. These reasons may be sufficient for a person to choose to have PGS as part of their treatment, despite the knowledge that it will not improve cumulative live birth rate per treatment cycle started.
- 5.15.** When asked about the future of PGS, Dr Wells highlighted that further research is needed to provide a better understanding of the causes of mosaicism as well as research into non-invasive methods for embryo testing. Prof Repping noted that more data is needed in order to determine the benefits of PGS and information provided to patients must be impartial and evidence-based.

6. Prioritisation of issues identified through the horizon scanning process

- 6.1.** The horizon scanning process is an annual cycle that feeds into the business planning of the Executive, SCAAC and the Authority's consideration of ethical issues and standards. Issues that could have an impact on the field of assisted production or embryo research are identified from journal articles, conferences and contact with experts such as members of the Authority's Horizon Scanning panel. The issues identified in this cycle of the horizon scanning process were presented to the committee in the horizon scanning spreadsheet.

Horizon scanning spreadsheet

- 6.2.** The Scientific Policy Manager presented the horizon scanning spreadsheet to the committee and asked members if they had any additional papers which they felt should be included. The committee noted that the spreadsheet was a fairly comprehensive collection of the research published in 2016 which is relevant to the Authority's work. Members agreed that it would be useful to consider altering the format of the spreadsheet for 2017, with all studies being presented in one tab that can be sorted by subject. This would allow simpler cross referencing of studies that fall under more than one topic.
- 6.3.** The Scientific Policy manager explained that a number of issues have been identified as high priority for 2017. Briefings were presented for some high priority issues; briefings were not presented for high priority issues which are standing items considered by the committee every year. The committee's standing items are embryo culture media, health outcomes in children conceived from assisted reproduction, alternative methods to derive embryonic and embryonic-like stem cells and new technologies in embryo testing.

Use of ICSI

- 6.4.** The Scientific Policy Manager presented a briefing to the committee on the use of ICSI. It was noted that ICSI is being used in around 66% of IVF cycles and it is unclear why it is being used so frequently in cases where there is no male factor infertility. The Scientific Policy Manager informed the committee that the Executive will be embarking on a piece of work in 2017 to explore the reasons for the popularity of ICSI and consider what the HFEA can do to educate the sector about unnecessary use of ICSI.
- 6.5.** The committee were in agreement that ICSI is being overused. One member informed the committee that development of professional body guidance relating to the use of ICSI has been delayed and is unlikely to be published in the next year. The committee agreed to consider a literature review on the use of ICSI in 2017.

Mitochondrial donation

- 6.6.** The Scientific Policy Manager presented a briefing on the topic of mitochondrial donation, highlighting developments in research over the last year and the decision by the Authority to permit the clinical use of mitochondrial donation techniques as a risk reduction strategy in selected patients. The committee agreed that it would be too soon to consider a full literature review or invite a speaker on this topic in 2017 and agreed to review this topic in detail in 2018.

Genome editing

- 6.7.** The Scientific Policy Manager presented a briefing on genome editing, highlighting that in 2016 the Authority approved the first research licence using genome editing in human embryos. The committee agreed to consider genome editing in 2017 and suggested some speakers who may be able to present on this topic.

Fertility preservation

- 6.8.** The Scientific Policy Manager presented a briefing on fertility preservation, outlining key research published in the last year, particularly in relation to ovarian and testicular tissue freezing and transplantation. It was also noted that there has been increased media attention in the last year on social egg freezing.
- 6.9.** Members agreed that it is important to monitor developments in fertility preservation and noted that the HFEA could record the reasons for freezing eggs, sperm and embryos more clearly. One

member also noted an increase in recent years in the number of transgender patients enquiring about preserving their fertility before transitioning. The Head of Regulatory Policy told the committee that the Executive is currently undertaking a body of work involving providing patient information for transgender patients and developing a suite of gender-neutral consent forms. The committee agreed to consider a broad literature review on fertility preservation in 2017.

Actions

- 6.10.** The Scientific Policy Manager will develop a work plan for the committee for 2017 based on discussions outlined above. This work plan may be altered to some extent over the year if further issues arise which are relevant to the Authority's work.

7. Committee work plan

- 7.1.** The Scientific Policy Manager presented a draft work plan for 2017 to the committee which was broadly agreed by members.
- 7.2.** Some committee members noted that a review of culture media is due in 2017 after relevant research in this area was published in 2016. One member highlighted the importance of recording the culture media used during IVF cycles and using these data when following up children in order to find out if particular culture media are associated with different health outcomes in children. The committee suggested some speakers who may be able to present on the topic of culture media and the Scientific Policy Manager noted that a representative from the MHRA will also be invited to observe when the committee consider this topic.

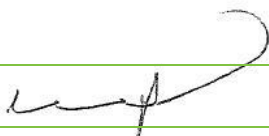
8. Any other business

- 8.1.** One committee member noted that the Nuffield Council on Bioethics held a meeting on the 14-day limit in December 2016 and the findings from that meeting will be published soon. It was also noted that this issue is currently being looked at in Australia.

9. Next meeting:

- 9.1.** Monday 19 June 2017, 10 Spring Gardens, London SW1A 2BU.

Signature



Name Yacoub Khalaf

Committee chair

Date 03/04/17
