

Prioritisation of issues identified through the horizon scanning process

Strategic delivery:	<input checked="" type="checkbox"/> Safe, ethical, effective treatment	<input type="checkbox"/> Consistent outcomes and support	<input type="checkbox"/> Improving standards through intelligence
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)		
Agenda item	6		
Paper number	SCAAC(05/02/2018)03		
Meeting date	05 February 2018		
Author	Anna Quinn, Scientific Policy Manager		
Output:			
For information or decision?	For decision		
Recommendation	<p>Members are asked to:</p> <ul style="list-style-type: none"> note the issues identified as high priority through the horizon scanning process, including progress of research (since February 2017); consider the high priority issues and work recommendations; and consider whether advice from additional external advisors would help in achieving the work recommendations. 		
Resource implications	Depends on the number of issues the Committee agrees to be high priority		
Implementation date	The Committee work plan for 2018		
Communication(s)	Work priorities (as defined by the Committee) will be communicated to the Head of Planning and Governance		
Organisational risk	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Medium	<input type="checkbox"/> High
Annexes	<p>Annex 1: Briefing on issues that have been identified as high priority through the horizon scanning process</p> <p>Annex 2: Issues identified through the horizon scanning process (see spreadsheet)</p>		

1. Background

- 1.1. The Authority established a horizon scanning function in 2004, the purpose of which is to identify issues that could have an impact on the field of assisted reproduction or embryo research. By identifying these issues, the Authority can be aware of potential licence applications and prepare, if necessary, a policy of position, or relevant patient information.
- 1.2. Issues are identified from journal articles, conferences and contact with experts such as members of the Authority's Horizon Scanning Panel. The Horizon Scanning Panel is an international panel of experts who meet annually and are contacted via email throughout the year.
- 1.3. The horizon scanning process is an annual cycle that feeds into the business planning of the Executive, the Scientific and Clinical Advances Advisory Committee (SCAAC) and the Authority's consideration of ethical issues and standards. The issues identified in this cycle of the horizon scanning process will be incorporated into the 2018/19 business plan and workplan for the Executive, SCAAC and the Authority.

2. Prioritisation process

- 2.1. A full list of issues identified since February 2017 can be found in Annex 2 to this paper.
- 2.2. To help with the business planning process, it is important for the Executive to be fully aware of which issues members consider to be high priority. New techniques which have been identified this year have been categorised as low, medium or high priority using the following criteria:
 - Within the HFEA's remit
 - Timescale for likely introduction (2-3 years)
 - High patient demand/clinical use if it were to be introduced
 - Technically feasible
 - Ethical issues raised or public interest
- 2.3. New techniques are considered to be high priority if they meet at least three of these criteria and medium if they meet at least two. Whilst low priority issues are unlikely to impact on research or treatment in the near future, published studies in these areas will continue to be collected and considered as part of the horizon scanning process.
- 2.4. High priority is also given to established techniques or issues which fall within the HFEA's remit and require ongoing monitoring or provision of patient information.

3. High priority issues

- 3.1.** The Executive considers the following topics to be high priority for consideration in 2018/19. Briefings about these issues, based on horizon scanning findings, can be found at Annex 1.
- a) Mitochondrial donation
 - b) Synthetic human entities with embryo like features, “SHEEFs”
 - c) The impact of stress on fertility treatment outcomes
 - d) The impact of the microbiome on fertility and fertility treatment outcomes
 - e) Genome editing
 - f) Embryo culture media
 - g) Health outcomes in children conceived by ART
 - h) Alternative methods to derive embryonic and embryonic-like stem cells
 - i) New technologies in embryo testing (including embryo biopsy and non-invasive methods for PGD)
 - j) Treatment add ons
- 3.2.** Briefings have been written about issues a) to d), based on horizon scanning findings, these can be found at Annex 1. Briefings have not been written for the remaining high priority areas, as these topics are either standing items that are considered by the committee every year, or they have already been considered by the Committee recently.
- 3.3.** Following discussions on the briefings, and their priority status, the Executive asks the Committee to consider whether any of the priorities should be amended.

Annual review of treatment add ons

- 3.4.** As part of the annual horizon scanning process, the Executive will collate published research relating to treatment add ons and ask the Committee to assess whether the current patient information or traffic light rating for any treatment add on needs to be reviewed. The Executive will then seek an independent assessment of the quality of evidence for the treatment add on and consider whether any amendments are required.
- 3.5.** Based on the research collated through the horizon scanning process, the Committee will also be asked if any new treatment add ons need to be added to the HFEA patient information. If a need for new patient information is identified, the Executive will seek an independent assessment of the quality of evidence for the particular add on and assign a traffic light rating to it in consultation with SCAAC.

Annex 1: Briefings on issues that have been identified as high priority through the horizon scanning process

1. Mitochondrial donation

Background

- 1.1.** In February 2015 the UK Parliament approved the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, making maternal spindle transfer (MST) and pronuclear transfer (PNT) to avoid serious mitochondrial diseases lawful treatments. The Regulations came into force in October 2015, along with the HFEA's system for licensing clinics to use mitochondrial donation and for approving individual applications. However, the Authority agreed it would only accept applications once an independent panel of experts were satisfied that MST and PNT were sufficiently safe and efficacious to move from research to clinical treatment.
- 1.2.** In 2016 significant progress was made in addressing recommendations that had previously been set out by the expert panel in their 2014 report. In response to these developments, the expert panel was reconvened to assess the current state of the research. In November 2016 the panel recommended that it was now appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment in carefully selected patients.
- 1.3.** In December 2016 the Authority met to consider the findings of the expert panel. The Authority made the decision to approve the use of mitochondrial donation in certain, specific cases where PGD is inappropriate or likely to be unsuccessful. This decision means that, for the first time, clinics are able to apply to vary their licence to permit the use of MST or PNT in clinical treatment, once a clinic has varied their licence they can then apply on a patient by patient basis for permission to treat individual patients.

Summary of developments

- 1.4.** In early 2017 the Executive received the first application from a clinic to vary their licence to permit the use of PNT in treatment. The application was considered by the HFEA's Licence Committee and the Newcastle Fertility Centre was granted permission to vary their licence.
- 1.5.** In Summer 2017 the HFEA's Statutory Approvals Committee considered the first patient specific application for PNT to be used in treatment. This application was approved, meaning that for the first time mitochondrial donation can be used in treatment in the UK.
- 1.6.** Following the 2016 reports of the first mitochondrial donation baby born after treatment which took place in Mexico, Palacios-Gonzalez and Medina-Arellano published a report exploring Mexico's laws in relation to mitochondrial donation techniques. The authors challenge the impression that Mexico presents an environment where there are no rules and instead show that certain instances

of mitochondrial donation are prohibited at federal level and others are prohibited at state level.

- 1.7.** The first live birth following mitochondrial donation carried out for fertility reasons was reported in 2017. The treatment was carried out in Ukraine and the doctors involved reported that the child appears to be ‘completely normal’ following genetic testing (Dockrill (2017)).

Impact

- 1.8.** The process of making MST and PNT lawful treatments in the UK for the avoidance of serious mitochondrial disease has been closely followed by scientists, clinicians and patients across the world. As with any new treatment it will be important to follow up patients, closely monitor the progress of any children born, and keep the scientific and clinical literature under review. SCAAC will play a key role in this work by advising the Authority on any developments in the literature and commenting on the analysis of any follow up data received by the HFEA.

Level of work recommendation

- 1.9.** The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to mitochondrial donation techniques. In order to aid discussions on this topic, the Committee is asked if they would like to invite any specialist speakers to present at the relevant meeting and take part in discussions with the Committee. The Executive will update the Committee on the analysis of any follow up data they receive on children born following MST and PNT. These discussions will help the Executive in their monitoring of mitochondrial donation and highlight any possible issues with the techniques which may impact on their clinical use.

References

Dockrill (2017). World-First in Ukraine as ‘Three-Parent’ Baby Born to an Infertile Couple. Available at: <https://www.sciencealert.com/world-first-in-ukraine-as-three-parent-baby-born-to-an-infertile-couple>

Greenfield A, Braude P, Flinter F, Lovell-Badge R, Ogilvie C, Perry T. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 Update. November 2016. Available at: <http://www.hfea.gov.uk/10557.html>

Palacios-González C, Medina-Arellano MD. Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case. *Journal of Law and the Biosciences*. 2017 Apr 1;4(1):50-69.

2. Synthetic human entities with embryo-like features (SHEEFs)

Background

- 2.1. In recent years research has demonstrated that human pluripotent stem cells, when cultured in the right conditions, have the ability to self-organise into a structure which closely resembles a post-implantation embryo. These structures have been commonly termed ‘synthetic human entities with embryo-like features’, or ‘SHEEFs’.
- 2.2. Developments in this area have generated questions about whether a real synthetic human embryo would fall under the definition of an embryo according to UK legislation. If SHEEFs were considered to be embryos they would be subject to the same close regulation as human embryos generated through IVF or ICSI and could only legally be cultured in the laboratory for 14 days.
- 2.3. Whilst researchers tend to be in agreement that it is not yet possible to create a ‘real’ synthetic human embryo, the prospect of this being possible in future raises several important questions. This includes what features of an embryo are sufficient for SHEEFs to be treated as embryos under UK legislation, and should there be specific rules about how long SHEEFs can be kept in culture if the 14-day rule is deemed not to apply?
- 2.4. SCAAC discussed emerging technologies in embryo research at its June 2017 meeting. At this meeting the committee commented on the poor efficiency of techniques and the need for research to be reproduced. Committee members were in agreement that this will be an important area of research to monitor in future.

Summary of developments

- 2.5. In 2014, Warmflash et al. treated human embryonic stem cells with bone growth factor (BMP4) and confined them to a circular micropattern. Under these conditions the embryonic stem cells self-organised into three germ layers: an outer trophectoderm-like ring, and inner ectodermal circle and a ring of mesendoderm expressing primitive streak markers in between. These layers mirrored (in two dimensions) the organisation of post-implantation embryos.
- 2.6. A review published in by Pera et al. in 2015 summarised recent studies which demonstrated that pluripotent stem cells can undergo self-organised development *in vitro* into structures that mimic the body plan of a post-implantation embryo. The authors also highlighted the need to consider the ethical issues raised by the prospect of modelling embryogenesis *in vitro* and urge widespread discussion to consider the potential of these techniques and any policy implications.

- 2.7.** A further review by Aach et al. (2017) explored the ethical issues raised by SHEEFs. The authors note that while the entities produced by Warmflash et al. replicated certain embryonic features covered in current guidelines, they remain very far removed from actual human embryos. They proposed that research limits associated with SHEEFs should be based on the appearance of features or capacities that are associated with the emergence of moral status.
- 2.8.** Harrison et al. (2017) combined mouse embryonic stem cells and extraembryonic trophoblast stem cells in a three-dimensional scaffold to produce entities whose structure and constituent cell types closely resemble that of natural embryos. This study demonstrates that cross talk between embryonic and extraembryonic stem cells in a three-dimensional scaffold is sufficient to trigger self-organisation leading to construction of embryo architecture and patterning.

Impact

- 2.9.** Scientific research generating entities which closely resemble natural human embryos is developing at a rapid pace. This research raises questions about the definition of an embryo and how research using SHEEFs should be regulated. There has already been some discussion of these questions within the scientific community, however, engagement by regulators and the public may also be required to develop an acceptable regulatory framework for SHEEFs.

Level of work recommendation

- 2.10.** The Committee is asked if they would like to see a wider literature review on SHEEFs. In order to aid discussions on this topic, the Committee is asked if they would like to invite any specialist speakers to present at one of the 2018 meetings and to take part in discussions. These discussions would help the Executive to better understand potential issues raised by SHEEFs and highlight any issues which require further consideration by the Authority.

References

- Aach J, Lunshof J, Iyer E, Church GM. Addressing the ethical issues raised by synthetic human entities with embryo-like features. *Elife*. 2017 Mar 21;6:e20674.
- Harrison SE, Sozen B, Christodoulou N, Kyprianou C, Zernicka-Goetz M. Assembly of embryonic and extraembryonic stem cells to mimic embryogenesis in vitro. *Science*. 2017 Apr 14;356(6334):eaal1810.
- Pera MF, de Wert G, Dondorp W, Lovell-Badge R, Mummery CL, Munsie M, Tam PP. What if stem cells turn into embryos in a dish? *Nature methods*. 2015 Oct 1;12(10):917-9.
- Warmflash A, Sorre B, Etoc F, Siggia ED, Brivanlou AH. A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. *Nature methods*. 2014 Aug 1;11(8):847-54.

3. The impact of stress on fertility treatment outcomes

Background

- 3.1. Patients undergoing fertility treatment often report feeling stressed. In recent years researchers have become increasingly interested in stress and its relationship with fertility and fertility treatment outcomes.
- 3.2. Previous work by Fertility Network UK has identified that patients often do not receive adequate emotional support before, during and after their treatment and the impact of this can be significant. However, it is unclear how stress may impact upon a couple's chance of having a successful treatment cycle.
- 3.3. If stress is found to be related to fertility treatment outcomes, the HFEA may be able to help by providing information and advice both to clinics and patients.

Summary of developments

- 3.4. In 2014, Massey et al. published a systematic review exploring the association of physiological cortisol (a hormone released in response to stress) and IVF treatment outcomes. The authors interrogated seven electronic databases to identify eligible studies. Overall they found that the evidence for the role of cortisol in relation to IVF outcomes was mixed, with three studies finding that higher levels were associated with more favourable outcomes and five studies finding lower levels of cortisol were related to favourable outcomes. The authors also noted that many of the studies identified were assessed as low quality.
- 3.5. Massey et al. published a further study in 2016 investigating the associations between hair and salivary cortisol and pregnancy in women undergoing IVF. Hair sampling provided a longer term measure of stress by allowing the authors to analyse systemic cortisol levels over the preceding three to six months. 135 women were included in the study with a subgroup of 88 women providing hair samples for analysis. Salivary cortisol levels were found to be unrelated to clinical pregnancy. However, lower levels of hair cortisol were found to be predictive of clinical pregnancy. Whilst this was a very small observational study, it does provide some evidence in favour of interventions aimed at reducing cortisol in the months leading up to IVF treatment.
- 3.6. Cesta et al. (2017) carried out a prospective cohort study of 485 women receiving fertility treatment. The authors set out to determine if there is any impact from perceived stress, infertility-related stress (both measured by online questionnaire) and cortisol levels on embryo quality and clinical pregnancy rate. The study reported that perceived stress, infertility-related stress, and cortisol levels were not associated with IVF cycle outcomes which the authors suggested could be reassuring for women undergoing fertility treatment.

Impact

- 3.7.** If stress (either long or short term) was found to be relating to fertility treatment outcomes, there would be potential for interventions aimed at reducing stress levels to improve fertility treatment outcomes. As this is a relatively unexplored area of research there may not be a significant amount of literature to review. However, with the potential for positive impacts on patients it may be worth considering the evidence in more detail.

Level of work recommendation

- 3.8.** The Committee is asked if it would like to consider a more detailed literature review on the impact of stress on fertility treatment outcomes. To aid discussions in this area the Committee is also asked if it would like to invite any specialist speakers to present at the relevant meeting and take part in discussions on this topic. These discussions would help the Executive to determine whether it would be helpful to publish information about stress on the HFEA website, and whether any literature review should feed into a project the HFEA Executive has just started with the aim of improving emotional support to patients throughout their treatment pathway.

References

Cesta CE, Johansson AL, Hreinsson J, Rodriguez-Wallberg KA, Olofsson JI, Holte J, Wramsby H, Wramsby M, Cnattingius S, Skalkidou A, Nyman Iliadou A. A prospective investigation of perceived stress, infertility-related stress, and cortisol levels in women undergoing in vitro fertilization: influence on embryo quality and clinical pregnancy rate. *Acta obstetrica et gynecologica Scandinavica*. 2017 Dec 18.

Massey AJ, Campbell B, Raine-Fenning N, Aujla N, Vedhara K. The association of physiological cortisol and IVF treatment outcomes: a systematic review. *Reproductive Medicine and Biology*. 2014 Oct 1;13(4):161-76.

Massey AJ, Campbell BK, Raine-Fenning N, Pincott-Allen C, Perry J, Vedhara K. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. *Psychoneuroendocrinology*. 2016 Dec 31;74:397-405.

4. The impact of the microbiome on fertility and fertility treatment outcomes

Background

- 4.1.** The microbiome refers to the microorganisms which inhabit a particular environment, for example, the body or part of the body. Our understanding of the microbiome has developed rapidly in recent years, along with our understanding of its role in human health and disease.

- 4.2.** Researchers have long been interested in the possible interactions between the reproductive tract and its microbiome. If the composition of the microbiome is shown to be related to fertility, or indeed, fertility treatment outcomes, there may be potential for development of interventions aimed at altering the microbiome to improve outcomes for patients.

Summary of developments

- 4.3.** In 2015, Franasiak and Scott published a review exploring what was known about the microbiome of the reproductive tract and how it relates to assisted reproductive technologies. The authors summarised the literature looking at vaginal, uterine and ovarian follicle microbiome, as well as the male reproductive tract microbiome. Overall the literature showed that areas which were previously thought to have been sterile actually host a complex microbiome which may change according to the hormonal environment. Future research should seek to better understand the microbiome of the male and female reproductive tracts with the potential for development of interventions aimed at manipulating this microenvironment to improve outcomes.
- 4.4.** A further review published by Mor et al. (2015) also explored the microbiome of the female reproductive tract and highlighted that accurately characterising the healthy microbiome and an unbalanced one has the potential to improve ART outcomes by allowing clinicians to ensure that different treatments can take place within the most appropriate environment.
- 4.5.** A prospective study was carried out in 2016 by Haahr et al. to determine if characterisation of the vaginal microbiota could predict clinical pregnancy during IVF. This was a small study including 130 infertile patients. Abnormal vaginal microbiota appeared to negatively impact on clinical pregnancy rate, however the authors noted that the study should be repeated with larger sample size to confirm any association.
- 4.6.** In 2017 Garlia-Velasco et al. published a review outlining what fertility specialists should know about the vaginal microbiome. The authors concluded that the vaginal microbiome may be manipulated in order to improve pregnancy outcomes. However, much more research is required to determine the optimal balance of bacterial species which would lead to the optimal reproductive outcomes for individual women.

Impact

- 4.7.** The microbiome clearly has an important role to play in human health and disease and there is some evidence to suggest that the composition of the reproductive tract microbiome is related to fertility and fertility treatment outcomes. As research in this area develops, there is the potential for the development of interventions aimed at altering the composition of the microbiome in order to improve fertility or fertility treatment outcomes. However, it appears that much more research is required before these interventions could become a reality.

Level of work recommendation

- 4.8.** The Committee is asked if it would like to consider a more detailed literature review on the impact of the microbiome on fertility and fertility treatment outcomes. To aid discussions in this area the Committee is also asked if it would like to invite any specialist speakers to present at the relevant meeting and take part in discussions on the topic. These discussions will help the Executive to better understand the level of research in this area and how likely it is that interventions may be developed in future.

References

- Franasiak JM, Scott RT. Reproductive tract microbiome in assisted reproductive technologies. *Fertility and sterility*. 2015 Dec 31;104(6):1364-71.
- García-Velasco JA, Menabrito M, Catalán IB. What fertility specialists should know about the vaginal microbiome: a review. *Reproductive BioMedicine Online*. 2017 Apr 19.
- Haahr T, Jensen JS, Thomsen L, Duus L, Rygaard K, Humaidan P. Abnormal vaginal microbiota may be associated with poor reproductive outcomes: A prospective study in IVF patients. *Human Reproduction*. 2016 Feb 23;31(4):795-803.
- Mor A, Driggers PH, Segars JH. Molecular characterization of the human microbiome from a reproductive perspective. *Fertility and sterility*. 2015 Dec 31;104(6):1344-50.