Scientific and Clinical Advances Advisory Committee (SCAAC) - agenda

Monday 31 January 2022, 10:30am – 2:30pm
Teleconference meeting via Zoom

Agenda item	Time
1. Welcome, apologies, declarations of interest	10:30am (5')
2. Matters arising Ana Hallgarten (HFEA)	10:35am (5')
3. Chair's business	10:40am (5')
4. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy	10:45am (15')
5. Prioritisation of issues identified through the horizon scanning process and the Committee work plan Amber Haywood (HFEA)	11:00am (40')
Break	*11:40pm (10')*
6. Mitochondrial donation update Dr Jane Stewart, Consultant in Reproductive Medicine and Gynaecology, Newcastle Fertility Centre at Life Prof Mary Herbert, Professor of Reproductive Biology and Scientific Director, Newcastle University	11:50pm (40')
7. Alternative methods to derive embryonic and embryonic like stem cells literature review Ana Hallgarten (HFEA)	12:30pm (30')
Lunch break	*13:00pm (40')*
8. Traffic light system review Georgina Allen (HFEA)	13:40pm (40')
9. Any other business	14:20pm (5')
10. Meeting summary and close	14:25pm (5')

Scientific and Clinical Advances Advisory Committee (SCAAC) – Matters arising

Monday 31 January 2022

Date	Action	Responsibility	Due date	Progress to date
06/06/2020	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.	All SCAAC members	Ongoing	The Committee were reminded to highlight relevant papers ahead of the meeting. An agenda item will be scheduled at SCAAC meetings for this discussion.
31/10/2021	The Committee agreed that there should be increased promotion of the HFEA webpage regarding the effects of COVID-19 on fertility, assisted conception, and early pregnancy.	Victoria Askew, Policy Manager	Ongoing	The HFEA patient and professional information on COVID-19 is assessed and promoted on an ongoing basis by the HFEA regulatory policy and communications teams. This includes patient and clinic FAQs which are updated frequently as and when COVID-19 guidance changes.
31/10/2021	Consider androgen supplementation as a separate treatment add-on from immunological tests and treatments.	Victoria Askew, Policy Manager	Ongoing	A treatment add-on application form for androgen supplementation is to be completed prior to the June SCAAC meeting for further discussion.
31/10/2021	The Committee agreed to several changes to the treatment add-ons webpage information including: **Elective freeze all cycles** Increased messaging about elective freeze-all cycles reducing the risk of OHSS	Victoria Askew, Policy Manager	Complete	Updates to the website, in line with the committee's recommendations, have been completed. This information was reviewed by an expert and the chair of SCAAC and is now live.

	and not reducing patient chances of success.	
	Endometrial scratching Increased information about risks associated with endometrial scratching, and a link to the Cochrane review.	
	ERA Create a webpage for this new treatment add-on.	
	Immunological tests and treatments Split out traffic light ratings for different treatments and remove androgen treatments from this treatment add-on.	

Horizon scanning prioritisation of issues.

Details about this paper

Area of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (31/01/2022) 005
Meeting date:	31 January 2022
Author:	Amber Haywood, Policy Manager
Annexes	Annex A: Briefing on key issues identified during horizon scanning Annex B: Horizon scanning reference list Annex C: Committee workplan

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • note the issues identified as high and medium priority through the horizon scanning process; • consider the high and medium priority issues and work recommendations; • consider whether advice from additional external advisors would help in achieving the work recommendations; and • recommend whether any additional consideration needs to be given to the use of immature sperm in the form of round headed spermatid injection.
Resource implications:	Subject to committee recommendations
Implementation date:	As per Committee workplan for 2022/23 (Annex C)
Communication(s):	NA
Organisational risk:	Low

1. Background

1.1. The Authority established a horizon scanning function in 2004 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 license applications and prepare, if necessary, a policy position or relevant patient information.

1.2. Issues are identified from journal articles, conferences, and contact with experts who are invited to the Authority's Horizon Scanning meetings (an international panel of experts who meet annually to discuss developing and future technologies within the fertility sector).

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 scientific and ethical issues and standards.

1.4. The proposed workplan, found in Annex C, may be liable to change due to uncertainties caused by the pandemic. The Authority understand that the ever-developing situation could impact capacity of SCAAC members or the HFEA's priorities.

2. Prioritisation process

2.1. A full list of papers identified during the 2022 horizon scanning process can be found in Annex B 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 issues which have been identified this year have been categorised as high, medium, or low priority using the following criteria:

a) Within the HFEA's remit
b) Timescale for likely introduction (2-3 years)
c) High patient demand/clinical use if it were to be introduced
d) Technically feasible
e) Ethical issues raised or public interest

2.3. New issues are high priority if they are within the HFEA's remit and meet at least two other criteria. New issues are medium priority if they are within the HFEA's remit and meet one other criterion, or are outside of HFEA remit but meet at least two other criteria. Low priority issues are those outside of HFEA's remit and 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 categorisation is also given to established techniques or issues which fall within the HFEA's remit that 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 2022/23.

a) Treatment add-ons

b) Health outcomes in children conceived by ART (including the impact of culture media)
c) New technologies in embryo and gamete testing
d) In vitro derived gametes
e) Genome editing
f) Mitochondrial donation
g) Alternative methods to derive embryonic and embryonic-like stem cells
h) Synthetic embryo like entities
i) Artificial intelligence (AI)
j) Extension to the '14-day rule'

3.2. Based on this year's horizon scanning findings, key developments on some of these high priority issues can be found in Annex A. Briefings have not been written for all prioritised issues, as these topics are either standing items that are considered by the Committee every year, or they have been considered by the Committee recently.

3.3. One new topic has been included in the high priority list, the extension to the '14-day rule'.

3.4. The Executive has recommended some changes to existing priority topics. This includes the addition of gamete testing to the topic 'new technologies in embryo testing'. Also, as the regulation of culture media falls outside of the HFEA remit and is evaluated in the context of its safety for the embryo and the health of any child born as a result of fertility treatment, the Executive suggests that the monitoring of culture media is incorporated into the 'Health outcomes in children conceived by ART' topic.

3.5. It was also noted during the horizon scanning process that treatment using immature sperm, in the form of round spermatid injection, was identified as a current research topic. However, the HFEA lists the use of immature sperm as a **prohibited process**. For this reason, the Executive has highlighted this research for review by the Committee in Annex A and asks whether, in light of these findings, any further consideration of this technique is required.

Annual review of treatment add-ons

3.6. The Authority currently undertakes an annual evidence review for treatment add-ons. Evidence, in the form of randomised control trials, for treatment add-ons that the HFEA provides information on is reviewed annually by an expert in systematic reviews and evidence assessment. They carry out an independent assessment of the quality of evidence using the GRADE methodology[1] for each treatment add-on. The SCAAC consider the quality of new evidence for each treatment add-on at their October meeting, based on the findings from the independent assessor and recommend updates to the HFEA's **treatment add-ons information**.

3.7. As part of this horizon scanning process, the Executive have identified wider research investigating treatments that claim to increase live birth rate that are not currently part of the HFEA's **treatment add-ons information**. A briefing on these can be found at Annex A.

[1] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

4. Medium priority issue

4.1. The Executive considers the following topics to be medium priority for consideration in 2022/23.

a) The impact of the microbiome on fertility and fertility treatment outcomes
b) The impact of stress on fertility treatment outcomes
c) COVID-19
d) Artificial wombs for early or whole gestation (ectogenesis)

4.2. During the horizon scanning process the Executive identified artificial wombs for early or whole gestation (ectogenesis) as a medium priority topic. Whilst, the timescale for introduction is not within 2-3 years and is likely to have low patient demand, it has the potential to fall within the HFEA's remit and would raise ethical issues.

Review of COVID-19 research

4.3. SCAAC's role is to consider advances in science and clinical practices which are relevant to the Authority's work. At the June 2020 SCAAC meeting the Committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research as a standing agenda item. However, the Executive identified several papers during horizon scanning that had not been highlighted by the committee.

4.4. A summary of the relevant research that has been highlighted since June 2020 by SCAAC members and through horizon scanning by the Executive can be found in Annex A of this paper.

5. Recommendations

5.1. Members are asked to:

- note the issues identified as high and medium priority through the horizon scanning process;
- consider the high and medium priority issues and work recommendations;
- consider whether advice from additional external advisors would help in achieving the work recommendations; and
- recommend whether any additional consideration needs to be given to the use of immature sperm in the form of round headed spermatid injection.

Annex A Briefing on key issues identified during horizon scanning

6. Treatment add-ons

Background

6.1. Since the introduction of the HFEA's traffic light rated list of **treatment add-ons**, other organisations and research groups have published their own lists of what they would classify as treatment add-ons. These lists contain some treatments that the HFEA does not currently provide information on. Some of these potential treatment add-ons are summarised below.

Summary of developments

6.2. Treatment adds-on that featured on Australian and New Zealand clinic website (Lensen S et al., 2021) that do not feature on the HFEA list were:

- GM-CSF (embryogen) or growth factors in culture media
- Platelet-rich plasma (PRP)
- Adjuncts during ovarian stimulation e.g. GH, androgens/ androgen modulators, aspirin, sildenafil, Heparin/LMWH
- Non-invasive genetic testing (NIPGT-A)
- Flushing of uterus with Lipiodol, hCG, culture medium, growth factors or platelet rich plasma
- Meiotic spindle visualisation
- Melatonin

6.3. Of note ESHRE is currently developing **good practice recommendations** for the use of treatment add-ons in fertility treatment.

Level of work recommendation

6.4. Committee members, medical professionals, academics or patient organisations are encouraged to **apply** for any treatments to be considered for inclusion in the HFEA's traffic light rated list of treatment add-ons. If accepted, the evidence base for that treatment would then be reviewed in line with the annual review of treatment add-ons conducted by the Executive and the Committee

7. Genome editing

Background

7.1. Genome editing was last discussed at the October 2020 meeting, where regulatory changes and the development of CRISPR/Cas9 were discussed. Genome editing is a helpful tool within research, and the HFEA approved the first license for the use of the CRISPR/Cas9 in human embryos in 2016. Genome editing can either be applied in somatic cells for non-heritable changes, or in germline cells for heritable and permanent changes. The latter has raised many legal and ethical questions over the past years, given the interest in using the technology within

assisted reproduction to aid prospective parents in having genetically related children without heritable conditions.

Summary of developments

7.2. Since the last meeting, significant regulatory work has been published on the use of genome editing technologies in human gametes and embryos. The Parliamentary Office of Science and Technology **published a UK Research Briefing** by Kaur and Border, 2020, discusses the UK regulations surrounding genome editing.

7.3. Two significant publications were also published by the World Health Organisation in 2021. The first was **a piece of governance framework** on human genome editing, and the second was **a set of recommendations** of the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The framework for governance considers the important ethical values and principles that should form part of good governance.

7.4. Genome editing has significant potential within laboratory research, clinical applications, and disease modelling. However, significant work needs to be done to improve the specificity of the systems, their delivery, and to reduce the number of off-target effects as examined in Jacinto et al., 2020. A review by Yip, 2020, discusses different Cas9 delivery strategies that could be applied to ensure cost-effective and efficient delivery in vivo to improve gene editing.

7.5. A recent study by Papathanasious et al., 2021, examined the spontaneous and Cas9-induced karyotype aberrations created in the first three divisions of embryonic development following genome editing. CRISPR/Cas9 is known to create significant off-target effects, including the major chromosome structural alterations investigated by this study.

7.6. A review by Naeem et al., 2020, examined a number of approaches to reduce the off-target effects caused by CRISPR/Cas9 in order to improve its basic and clinical applications. Averina et al., 2021 looked to increase the precision of genome alteration by applying different systems for genome editing and observing whether error-prone non-homologous end joining was less prevalent than homologous recombination. A study by Zuccaro et al., 2020, evaluated the repair outcomes following the use of CRISPR/Cas9 to examine the issues in correcting mutations in human embryos using the system.

7.7. Genome editing has been useful in animal and plant models and research. In Ai et al., 2021, CRISPR/Cas9 was used to complete a gene knockout in cotton bollworms to study in-vivo gene functions and interactions. The use of prime editing in Drosophila melanogaster is examined in Bosch et al., 2021, for research in gene function. Mizuno-Iijima et al., 2021, used the CRISPR/Cas9 system to genetically engineer mice and highlighted its use as a tool for producing mouse models with specific mutations. A publication by Zhan et al., 2021, describes the use of different gene systems with CRISPR technologies for plant research and crop improvement. Further work by Banan, 2020, reviews the application of CRISPR/Cas9 in mammalian cells and strategies used to increase CRISPR/Cas9 efficiency.

7.8. The possible application of genome editing and CRISPR/Cas9 in assisted human reproduction and embryo research has been a large source of debate due to the significant ethical, social, and legal questions and issues that it raises. A publication by Greenfield, 2021, discusses the themes that are most present in international discussions and debates regarding the application of the technology.

Level of work recommendation

7.9. Committee members who are attending the Royal Society Genome Editing Roundtables in March 2022 and the **Third International Summit on Genome Editing** in 2023 are encouraged to inform us of any further developments in scientific, ethical, and regulatory developments relating to genome editing. The Authority will continue to monitor any developments as part of the annual horizon scanning.

8. COVID-19

Background

8.1. At the **June 2020 SCAAC meeting** the Committee agreed to monitor research into the effects of COVID-19 on fertility, conception and early pregnancy. To date, SCAAC has identified 14 papers for discussion. During the horizon scanning process, the Executive identified a further 45 papers that had been published on this topic since 2020.

Summary of developments

Fertility

8.2. 12 studies were identified that explored the relationship between SARS-CoV-2 infection and semen parameters. Although researchers reported alterations in different semen parameters, all studies reported a significant short-term change in at least one of the semen parameter.

8.3. Analysis of semen samples from men who had recovered from COVID-19 (n=70, n=24, n=41) found total sperm count and total motility were commonly reported as reduced compared to control groups (Ruan et al., 2021, Pazir et al., 2021, Guo T et al., 2021).

8.4. Ruan et al., 2021, found that total sperm count and total motility measurements associated with infection severity and recovery time, but remained within the WHO reference range. Sperm concentration (Guo et al., 2021), sperm morphology (Hamarat et al., 2021) and all semen parameters (Erbay et al., 2021) have also been reported to be impacted.

8.5. Falahieh et al., 2021, reported that any altered semen parameters at day 14 after moderate infection were improved by day 120 (n=20) and that the raised seminar reactive oxygen species and malondialdehyde (MDA) levels in day 14 were resolved by day 120. Gul et al., 2021, also found no long-term impact of infection or its treatment (n=29) on spermatogenesis.

8.6. Ma et al., 2020, reported degenerated germ cells from the seminiferous tubules and degenerated germ cells after comparing testis tissue of 5 patients who died of COVID-19 compared to uninfected age-matched controls. Peirouvi et al., 2021, also reported a reduction in Sertoli cell numbers and downregulation of junctional proteins at the blood-testis barrier (n=10), important in spermatogenesis, compared to control tissue. Achua et al., 2021, found an inverse relationship between ACE-2 receptor count and spermatogenesis in testes tissue with fatal infection (n=6). SARS- CoV-2 was isolated from testis tissue following fatal infection (n=2) but has not been detected in urine, prostatic secretions or semen in patients who have recovered (n=74) (Ma et al., 2020, Ruan et al., 2021).

8.7. None of the included studies reported infection in the female reproductive system but there have been some contradictory fertility findings. Herrero et al., 2021, found an association

between increased antibody levels against SARS-CoV-2 and reduced oocyte retrieval number in assisted reproduction (n=46). However, Kolanska et al., 2021, and Wang et al., 2021, observed similar results in ovarian reserves and responses between case (n=65, n=65) and control groups. Herrero et al., 2021, also reported disruption to the follicular microenvironment despite previous research indicating no altered follicular function post infection (n=9) (Bentov et al., 2021). A large-scale study is needed to fully understand the altered fertility parameters.

Pregnancy outcomes

8.8. Some studies have reported a small decrease in live birth rates over the course of the pandemic (Corda et al., 2021), but the difference could be attributed to change in pregnancy planning behaviors or the closure of fertility services (Bhattacharya et al., 2021, Smith et al., 2021). In a UK pregnancy planning questionnaire on 267 women January-June 2020, over half of the women planning a pregnancy reported that SARS-CoV-2 had impacted their plans, with 72% of them deliberately postponing pregnancy (Flynn et al., 2021).

8.9. Multiple small scale observational studies have compared the pregnancy outcomes between women who have had SARS-CoV-2 and control groups. Findings suggest that pregnant women reported more severe disease than age-matched non-pregnant women, with a greater risk of pre-eclampsia. Preterm delivery and caesarean delivery were reported more frequently in the SARS-CoV-2 infected group, but no impact on live birth rate was seen. No differential impact of SARS-CoV-2 infection was seen between natural pregnancies and ART. However, the odds of admission to intensive care units were found to be significantly higher in neonates born to mothers who had a SARS-CoV-2 infection (n=13) (Allotey et al., 2021, Cribiù et al., 2021). A small-scale observational study (n=56) also found an association between maternal infection in week 5 and 6 with severe fetal eye malformations (Mohart et al., 2021). Further large-scale studies are needed to understand whether these findings are representative.

8.10. Vertical transmission of SARS-CoV-2 to neonates has been rare. The placenta has been regarded as an effective barrier to transmission, in spite of SARS-CoV-2 RNA being isolated from half of the placental tissues (n=21) sampled by Cribui et al.,2021. Atyeo et al.,2021, found poor placental antibody transfer, although the altered placental antibody biochemistry was predicted as a mitigation.

Vaccination

8.11. No fertility or adverse pregnancy outcomes have been associated with the SARS-CoV-2 vaccines (Wesselink et al., 2022). The **British Fertility Society** states that there is “absolutely no evidence” that COVID-19 vaccines can affect the fertility of women or men.

Level of work recommendation

8.12. The Committee will be asked to continue to monitor and inform us of any further developments in scientific and clinical literature relating to the effects of COVID-19 on fertility, reproduction and early pregnancy. These developments will be discussed as part of the standing agenda item at SCAAC meetings.

9. Artificial wombs for early or whole gestation

Background

9.1. Artificial wombs (AW) offer the possibility of creating an environment where a fetus can be sustained and developed until birth outside of a 'natural' womb. There are two possible forms of AW. First, AWs for short-term late support, for example to support premature babies instead of the use of an incubator. Second, the use of an AW for the entirety of the pregnancy from implantation to 'birth'. The gestation of a human fetus outside of a human womb is also known as ectogenesis.

Summary of developments

9.2. Partridge et al., 2017, published a ground-breaking study on the use of an extra-uterine system to physiologically support a fetal lamb for up to four weeks. An extra-uterine 'Biobag' maintained a closed system that replicated the environment of a sheep's womb. The lambs 'gestated' in these biobags showed normal growth and maturation. Usuda et al., 2019, published a similar study on their 'EVE platform' which replicated the conditions of a uterus in order to sustain sheep fetuses. Further work on the use of extra-uterine developmental technologies has included work from Ozawa et al., 2021, who examined umbilical venous flow volume in fetal sheep when using the Environment for Neonatal Development (EXTEND) system. These studies demonstrate a possibility for future applications to support premature human babies.

9.3. Significant scientific research would be required before considering the use of AWs. De Bie et al., 2021, published a review on the history of artificial placenta and womb technology and their possible use for assisting in cases of extreme prematurity. The review highlights recent models of AWs, and discusses the current challenges for future clinical translation of the technology. A paper by Segers, 2021, summarises the benefits and concerns regarding human ectogenesis and the need for translational and clinical research of AW technology. Additionally Romanis, 2020, examines the need of clinical trials with AW for clinical translation.

9.4. The use of AW for premature babies, and for the whole of pregnancies raises a myriad of ethical and legal questions. Romanis, 2020, examines whether AW technologies should be considered innovative treatment or medical research and the ethico-legal questions raised by its experimental use. In Segers et al., 2020, the balancing of fetal interests against the interests of the pregnant mother when considering new fetal interventions is discussed. Davis, 2019, questions the status of a fetus on AW technology and how at present a human is either 'born' or 'not born' whereas this technology may create an 'intermediate stage'. In Segers, 2021, the classification of possible uses of AW technology is discussed. Although the technology may be initially used for premature fetuses, there may be a social demand for non-medical uses for example to avoid the 'burdens' of pregnancy.

9.5. The role of the HFEA within research that would require human embryos in ectogenesis is unclear, as is the regulatory remit when using AW technology either for whole or partial gestation.

Level of work recommendation

9.6. There will be no action for the committee on AW technology. The Executive will continue to monitor any developments as part of the annual horizon scanning.

10. Artificial Intelligence

Background

10.1. Within reproductive medicine current applications of Artificial Intelligence (AI) and data driven technologies include assisting embryologists in the ranking and selection of embryos, automating semen analysis, predicting treatment success rates, aiding in clinical decision making and robotic surgery.

10.2. There are issues that need to be taken into consideration with the introduction of AI-driven processes into clinical practice. It is not always possible to explain how decisions are made by machine learning models. This lack of transparent decision-making creates both legal and ethical concerns and could risk creating unintentional biased decisions. Training AI systems requires large amounts of data in order to create high quality and reliable outputs. Considerations also need to be made for obtaining informed consent for the sharing of data and considering the implications of data passing between countries. Further issues arise for the accountability of each element of a model's output.

Summary of developments

10.3. In 2021 the European Commission released a draft proposal for the regulation of AI, the Cyberspace Administration of China passed a set of draft regulations for algorithmic systems and the US Congress introduce several pieces of federal AI governance and data-protection legislation, such as the Information Transparency and Personal Data Control Act.

10.4. The World Health Organisation (WHO) produced a report into the **ethics and governance of AI for health**. This report identifies ethical challenges and risks with the use of AI for health and contains six consensus principles to ensure AI works to the public benefit of all countries.

10.5. The UK AI Council is an independent non-statutory expert committee that advises the government on AI. In January 2021 they produced a report called the **'AI Council AI Roadmap'** which gave 16 recommendations to the government to help them develop the UK National AI Strategy.

10.6. The Office for AI is responsible for overseeing the implementation of the **National AI Strategy**, which was publish in September 2021. The Strategy is split into three pillars. Investing in the long-term needs of the AI ecosystem, ensuring AI benefits all sectors and regions, and governing AI effectively. For each pillar it lays out the short-, medium- and long-term actions, which for the third pillar includes publishing a white paper on the national position for governance and regulating AI by March 2022.

10.7. The Centre for Data Ethics and Innovation (CDEI) recently published a **roadmap to an effective AI assurance ecosystem**, as outlined in the National AI Strategy. As with the Office for AI they have other important publications such as a review into bias in algorithmic decision making.

10.8. The MHRA recently undertook a **consultation into the future regulation of medical devices in the UK**. This consultation included considerations for regulating software and AI as a medical device. MHRA have also recently published 10 guiding principles for good machine

learning practice for medical device development, in collaboration with the US Food and Drug Administration (FDA) and Health Canada.

10.9. NHS AI lab, which sits under NHSx, aims to accelerate the safe, ethical and effective development and use of AI tech to tackle the challenges in health and social care. They have a number of key pieces of working including producing a National Strategy for AI in Health and Social Care, in line with the National AI Strategy, to be launched in early 2022.

10.10. The Information Commissioners Office (ICO) is an independent authority set up to uphold information rights in the public interest, promoting openness by public bodies and data privacy for individuals. They have produced guidance on AI including, in collaboration with the Alan Turing Institute, three sets of guidance on **explaining decisions made by AI**.

10.11. The Alan Turing Institute, have produced guidance into **understanding AI ethics and safety**, and the Ada Lovelace Institute have recently published the report '**regulate to innovate'** which provides evidence for how the UK might develop its approach to AI regulation and offers recommendations for the Office for AI's forthcoming White Paper on the regulation and governance of AI

Level of work recommendation

10.12. Executive will monitor the progress in the use of, and research around, AI within the fertility sector. This will include determining the HFEA's role in the regulation of AI, considering both existing guidance and the publication of the whitepaper on the national position for governance and regulating AI, and the National Strategy for AI in Health and Social Care, early this year. The Committee is, therefore, asked to consider whether there are any further studies or developments in the area and identify particular concerns or issues that should be highlighted.

11. New technologies in embryo and gamete testing

Background

11.1. An in-depth literature review of the new technologies in embryo testing was covered at the October SCAAC meeting and can be found in the **meeting papers.** However, the Executive has made a recommendation that gamete testing be incorporated into the topic of 'new technologies in embryo testing' and a summary of the relevant findings are below.

Summary of developments

Sperm selection

11.2. A variety of techniques have been developed to optimise gamete selection or predict the success of ART cycles. Researched biomarkers that lacked sufficient evidence to support their predictive ability were: sperm DNA fragmentation testing, testis-specific actin capping proteins, and sperm morphology in inseminated sample (Inagaki et al., 2021, Le et al., 2021, Stanhiser et al., 2021, Fuentes et al., 2021).

11.3. Conversely, evidence has been found to support the use of sperm motility before preparation as a predictor for ART success (Jeong et al., 2021). Dearing et al., 2021, found the computer-assisted sperm analyser (CASA- Mot) system reduced, but did not eliminate, sperm motility

measurement uncertainty compared to the WHO manual method. The researchers reasoned that this technique could optimise IVF fertilization success predictions.

11.4. Using AI, Ito et al., 2021, developed the first tool to use automated machine learning to determine spermatogenesis activity of testis samples based on Johnsen scores. The two datasets, with positive predictive values of 82.6% and 99.5% (n=275), were deemed to be helpful to support pathologists' evaluations. Similarly, Li et al., 2021, developed an intelligent nomogram to predict the success of different methods of fertilisation of men with borderline semen. The model was deemed to be clinically useful to select optimal fertilisation methods.

11.5. As an alternative method to hyaluronic acid for physiological selection of spermatozoa in ICSI (PICSI), the microfluidic sperm sorting (MSS) technique has been tested. Anbari et al., 2021, found MSS to successfully utilise channels that mimic the female reproductive environment, such that higher quality spermatozoa were selected. An increasing in quality embryo formation, implantation and pregnancy (n=95) were reported.

11.6. However, sperm sorting techniques have been criticised for their trade-off between quantity and quality of sperm, both of which embryologists need. Therefore, Simchi et al., 2021, have developed a 3D device to be inserted above semen samples in a test tube that densely packs thousands of channels to optimise the isolation of sperm. Results found that the technique outperformed current clinical methods by improving DNA integrity of the selected sperm subpopulation up to 95%, whilst reducing the sperm preparation time 3-fold.

Male infertility

11.7. Multiple methods have been evaluated for assisting in the diagnosis of male infertility. A meta-analysis by Liu L et al., 2021, found the use of multiple miRNAs and seminar plasma-derived miRNAs gave high sensitivity for male infertility diagnosis. Similarly, Dutta, Henkel and Agarwal, 2020, compared the accuracy of assays for diagnosing infertility using sperm chromatin integrity and Da Costa, Redmann and Schlatt, 2021, saw promise with simultaneous detection of sperm membrane along with DNA fragmentation with flow cytometry.

11.8. Another technique that has shown early promise is Karabulut et al., 2021, MiOXSYS system for measuring the overall oxidation-reduction potential (ORP) in semen samples. ORP was found to reliably distinguish between normal and impaired semen parameters. However, further study is needed before this is used to predict ART success or diagnose infertility clinically (Panner et al., 2021).

Oocyte testing

11.9. Two novel methods for oocyte testing have been developed. Liu C et al., 2021, assessed the ability to use RNA sequencing of granulosa cells as a method to assess oocyte quality. Further study is needed to assess whether the genes that were found to associate with developmental outcomes could be used to predict oocyte quality and embryo development. Similarly, Daei-Farshbaf et al., 2021, found calcineurin levels to predict oocyte fertilisation potential, but further study is required before it is considered as an oocyte selection method.

Level of work recommendation

11.10. The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to gamete testing techniques or uses. Committee members should more

closely monitor any techniques which are being used in clinics, whether this be trailing the technique, using routinely, or being offered as a treatment add-on.

12. Synthetic embryo-like entities

Background

12.1. Pharmaceuticals intended for use in patients with childbearing potential must be tested for teratogenicity to ensure that the agent does not disrupt embryo or fetal development. Restrictions on embryo use and the 3R principles (replace, reduce and refine) have prompted the use of in vitro models. However, in vitro models currently available lack the spatiotemporal and morphological characteristics of a developing embryo, so researchers are developing synthetic embryo-like models.

Summary of developments

12.2. Synthetic embryo-like entities have been developed to mimic different stages of development. Pre-implantation 'iblastoid' models have been created through the induction of pluripotent stem cells. The models mimic early stages of implantation to further our knowledge of embryogenesis and aid in the development of therapies associated with ART (Liu et al., 2021).

12.3. Post-implantation models, termed 'embryoids', have been in use for years but historically lacked the morphology and signaling interactions needed for accurate modelling. However, the recent addition of bioengineered extracellular matrix like structures and growth factors to induced pluripotent step cells (iPSCs) have enabled the creation of embryo-like entities with defined germ layers (Han et al., 2021, Naticchia et al., 2021, Glykofrydis et al., 2021).These 'embryoid bodies' currently serve as research tools to further developmental understanding and assist in embryotoxicity screening (Konala et al., 2021).

12.4. To model later development, researchers have also induced embryoid bodies to differentiate into specific cell types or aggregated 'organoids'. Girgin et al., 2021, co-cultured stem cells to create a model that is capable of undergoing gastrulation-like events and axial morphogenesis. The resultant entity, termed 'EpiTS embryoid', included structures with anterior development and brain-like regions. Mantziou et al., 2021, assessed a similar embryoid and observed morphological impacts and aberrant gene expression after the application of reference compounds. Some species-specific susceptibilities were also observed suggesting that the model could outperform existing animal models for teratogenicity testing. Such models have also been used to test substance toxicity to organ specific perinatal progenitor cells experimentally (Rebuzzini et al., 2021, Guerra-Crespo et al., 2021) or to better understand organ formation (Radojevic, Conley and Bennett., 2021,Garcia-Alegria et al., 2021).

Level of work recommendation

12.5. The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to synthetic embryo-like entities. The Authority will continue to monitor any developments as part of the annual horizon scanning.

13. Round Spermatid Injection

Background

13.1. Round spermatid injection (ROSI) is an alternative method for oocyte fertilisation in men with severe infertility. The technique involves using immature round spermatids, in the absence of mature tail-bearing spermatozoa, for intracytoplasmic sperm injection (ICSI). Non-obstructive azoospermia accounts for up to 15% of male infertility so the method presents an opportunity for these patients to access fertility treatment (Tekayey and Vuruskan, 2021). Although the technique first successfully resulted in a live birth in 1993, there has been limited progress due to low success rates and safety concerns. The use of immature round head spermatids for ICSI is a **prohibited process** in the UK in due to genetic abnormality risk and low success rates.

Summary of developments

13.2. The St. Mother Clinic in Japan has successfully assisted the birth of 90 babies from 2657 ROSI cycles between 2011 to 2014. Follow up revealed that the ROSI group had a significantly shorter gestation period and lower body mass index at birth compared to natural babies. Three of the ROSI group were born with congenital abnormalities which were all corrected by 1 year. Follow up at 12 and 18 months also showed a significantly lower body weight than naturally conceived infants. No other physical or mental differences were observed but follow up will continue until the age of six years (Tanaka et al., 2018).

13.3. Concerns remain about long-term imprinting abnormalities. Mouse studies by Kurotaki et al., 2015, and Zhu et al., 2021, have shown inconsistent DNA methylation and chromosome segregation in ROSI-derived zygotes, which may explain the high abortion rate. Technological developments for selecting suitable round spermatids and our understanding of developmental DNA methylation could increase the efficiency of ROSI to clinical levels in future. The papers identified during horizon Scanning support that further study is needed to determine the long-term health outcomes of ROSI, as well as improving the efficiency.

Level of work recommendation

13.4. The Executive has highlighted the research for review by the Committee and asks whether, in light of these findings, any further consideration of this **prohibited process** is required.

14. Extension to the '14-day' rule

Background

14.1. The legislation in the UK (HFE Act 1990) states that a license cannot authorise keeping or using an embryo after the appearance of the primitive streak. For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with [the day on which the process of creating the embryo began], not counting any time during which the embryo is stored.

14.2. This legal limitation of not culturing embryos in vitro beyond 14 days originated from recommendations in the Warnock committee report in the UK (1984), with other commissions with similar recommendations being published around this time (Ethics Advisory Board of the US Department of Health, Education, and Welfare (1979) and US National Institutes of Health's

Human Embryo Research Panel (1994)). The '14-day rule' has since been legally implemented in at least 12 countries (Hyun et al., 2016).

14.3. In 2021 the International Society for Stem Cell Research (ISSCR) published updated guidance for stem cell research and clinical translation. This included the culture of human embryos. Their recommendation 2.2.2.1 is, "given advancements in human embryo culture, and the potential for such research to yield beneficial knowledge that promotes human health and well-being, the ISSCR calls for national academies of science, academic societies, funders, and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research. Should broad public support be achieved within a jurisdiction, and if local policies and regulations permit, a specialized scientific and ethical oversight process could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives."

14.4. It would be for the Department of Health to decide if and when to review the HFE Act and would be for the UK Parliament to make any changes to the legislation. However, it continues to be important for the HFEA to understand the scientific, legal and ethical implications of extending the 14-day limit of in vitro embryo culture, in the event that the HFEA is required to give advice or take a position on this topic.

Summary of developments

14.5. Rather than providing a definitive moral boundary, the '14-day rule' is a practical policy tool that balances the moral status of the embryo whilst allowing for scientific developments and research to take place. This limit has so far been seen as effective at achieving these objectives, but arguments advocating for the potential to culture embryos for longer periods of time in vitro within the law and regulation, have begun to increase.

14.6. When the '14-day rule' was proposed it was not possible to culture embryos in vitro beyond day five or six of development. However, advances over the last 40 years have shown that it could be technically feasible for scientists to culture embryos up or beyond to this 14-day limit. In 2016 Deglincerti et al., 2016, and Shahbazi et al., 2016, both reported culturing embryos in vitro past day seven, when implantation would usually occur, and had to terminate their experiments on day 13 due the '14-day rule'.

14.7. Another scientific development which has brought the '14-day rule' into question is the creation of synthetic embryo-like entities. These models include embryonic or induced pluripotent stems cells that can self organise into complex structures that mimic early post implantation embryos. However, there are concerns about the ethical status of these models. Their characteristics and development potential mean that they don't fall under current regulatory requirements for the culture of embryos. It is unclear what their moral status should be, although it is argued that they could allow for the less ethically contentious study of early human development and disease. However, it is likely that human embryos will always be needed as a research tool. Also, whilst these models share features with human embryos, due to both ethical and safety concerns, they currently cannot (and should not) be implanted or used in clinical treatment (McCully 2021, Hengstschlager et al., 2021, Williams et al., 2020).

14.8. There have been many benefits proposed to increasing the limits on embryo research, for example to day 28 of culture. It would allow scientists a valuable insight into development between days 14 and 28, when tissues begin to be established. It could also allow for the study of disease processes, such as miscarriage and the development of congenital abnormalities, of which we currently have limited understanding. Further benefits include the validation of synthetic embryo-like entities discussed in point 14.7 against actual human development beyond 14 days, and the investigation of new therapeutic interventions (Lovell-Badge, 2021, McCully, 2021).

14.9. However, the use of human embryos in research and the suggestion of increasing the current limits remains contested by some. One argument, termed 'the slippery slope', has been present since the '14-day rule' was originally proposed. It suggests that allowing research on embryos to take place would be the first step towards limits of research being pushed beyond what is ethically acceptable. Any change to the 14-day limit could risk undermining public trust and increase opposition (Chan, 2017, Chan, 2018, Warnock, 2017).

14.10. There is no clear consensus on any threshold by which embryos take on a moral status. In a commentary article, Blackshaw et al., 2021, discuss the moral status of the embryo, including the timing of an embryo splitting to create twins (which does not normally occur beyond day 14) and the implications this has for individual identity. They argue that, as it has only recently become technically feasible to culture embryos to the current limit, it is premature for it to be extended. Scientists should first exhaust the discoveries possible from recent developments in culturing embryos.

14.11. Our position is that if the '14-day rule' were to be reconsidered by the government in future, there is a need for public engagement and discussion of the implications of this, as the ISSCR guidelines, and many others previously recommend.

Level of work recommendation

14.12. There will be no action for the Committee to consider an extension to the '14-day rule'. However, the Authority will continue to monitor any developments as part of the horizon scanning work to be prepared to make recommendations or a position if required.

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Alternative methods to derive embryonic and embryonic-like stem cells.

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (31/01/2022) 007
Meeting date:	31 January 2022
Author:	Ana Hallgarten, Scientific Policy Officer

Output from this paper

For information or recommendation	For information
Recommendation:	Members are asked to: • consider the progress of research into alternative methods to derive embryonic or embryonic-like stem cells; • advise the Executive if they are aware of any other recent developments; and • review whether any outputs from the HFEA are required.
Resource implications:	NA
Implementation date:	NA
Communication(s):	NA
Organisational risk:	Low

1. Introduction

1.2. Human embryonic stem cells (hES cells) have the potential to form every other type of cell in the body. They are important for research into cell biology, drug testing, and disease modelling, and could potentially be used in therapies for patients.

1.3. hES cells are derived from the cells of human embryos. Currently the only way to derive hES cells involves using viable embryos. However, researchers are investigating alternative methods of deriving hES cells, or hES-like cells, that do not involve the use of viable embryos, which for some, may raise fewer ethical concerns because they don't involve viable embryo destruction.

1.4. Section 3A(1)(c) of Schedule 2 of the HFE Act 1990 (as amended) requires embryo research to be "necessary or desirable" for defined purposes. If in future alternative methods of deriving hES or hES-like cells become fully developed, a question may be raised whether it may become less 'necessary' for licensed research groups to use viable embryos in all of the research purposes in which they are currently used now. Therefore, it is important for the Authority to keep up to date with developments regarding these alternative methods so that the HFEA Licence Committee can bear them in mind when considering research licence applications in line with the Act.

1.5. Alternative methods to derive hES-like cells has been brought to SCAAC as a standing high priority item for several years. The last update was discussed at the October 2018 meeting.

2. Induced pluripotent stem cells

2.1. One alternative way to derive hES-like cells is by producing induced pluripotent stem cells (iPS cells). iPS cells are adult somatic cells which have been reprogrammed to an embryonic stem cell-like state. This process is controlled by mediators including transcription factors which bind to DNA and alter gene expression, and also by epigenetic changes which involve changes to the information in the genome over and above that contained in the DNA sequence.

2.2. The International Society for Stem Cell Research (ICSSR) published 2021 updates to their **Guidelines for the Field of Stem Cell Research and Regenerative Medicine**. These guidelines state that research using iPS cells can be exempt from science and ethics oversight processes if the research is assessed by "the appropriate existing mandates and committees for laboratory research". This could allow researchers to conduct research with increased ease and increase their research outputs. The exemption from ethics oversight processes suggests that ICSSR may consider the use of iPS cells to be less ethically concerning than the use of hES cells.

Recent developments in iPS cells

2.3. A recent article by Liu et al., 2020, provides an overview of experimental advances in pluripotent stem cells, the creation of iPS cells, and the maintenance of iPS cell pluripotency. The article considers different protocols for inducing pluripotency and methods for delivering reprogramming factors including integrating viral transfection (e.g., a retrovirus), non-integrating viral transfection (e.g., using a Sendai virus), self-excising vectors, and non-integrating non-viral

methods. The ethical benefits of using iPS cells in comparison to human embryonic stem cells are discussed, as well as the possible clinical potential of the iPS cells with benefits including reduced immune rejection.

2.4. An article by Deyle, 2021, provides a discussion of the creation of iPS cells and different methods to create iPS cells from mitotically arrested mouse embryonic fibroblasts. The article serves as an overview of methods to create iPS cells using viral vectors, and iPS cell preservation.

2.5. A study by Lee C et al., 2020, investigated the use of elastin like polypeptides as a non-viral gene delivery system to generate iPS cells from mouse fibroblasts. Viral vectors have been found to cause genome-integration of the viral DNA into the iPS cells, which is a significant limitation in the creation of iPS cells. The iPS cells created showed embryonic stem cell-like characteristics.

2.6. In a study by Lee S et al., 2020, a conditioned medium was used to stimulate specific chemokine receptors in human somatic cells with specific pluripotency-associated transcription factors. This led to an increased reprogramming efficiency of somatic cells into iPS cells.

2.7. In a study by Han et al., 2021, the generation of human iPS cells was investigated for the regeneration of cardiomyocytes. The study reprogrammed human dermal fibroblasts and blood cells into iPS cells using the Sendai virus. Following this, chemically defined media were used to differentiate the iPS cells into cardiomyocytes.

2.8. In a study by Ahmed et al., 2020, episomal vectors were used to create iPS cells. The study used pericytes in the experiment to harness their multipotency. The iPS cells created from the pericytes expressed pluripotency markers. Given the abundancy and accessibility of pericytes, the study considered them to be a promising source for the creation of iPS cells.

2.9. Protocols for deriving iPS cells, and for cell reprogramming for laboratories to create iPS cells for research, are available online. These include the Draper et al., 2019, protocol to create iPS cells from primary human fibroblasts using the Sendai virus, and the Olender et al., 2021 protocol on the critical steps to reprogram blood cells into induced hematopoietic stem cells.

iPS cells in drug and disease modelling

2.10. iPS cells have been used for modelling conditions, drug discovery, and investigated for their possibility for clinical applications.

2.11. A review by Paik D et al., 2020 emphasized the benefits of using iPS cells for drug discovery, therapy, and research in cardiovascular disease. They noted the limitations presented by animal models and the poor efficiency of clinical trials which are unable to reflect the genetic and epigenomic variations between patients. This review discussed the use of patient-specific iPS cells to tailor treatments specifically to each patient. A review by Aboul-Soud et al., 2021, examined the potential of iPS cells in research including in drug screening, disease modelling, and considers the ethical benefits of using iPS cells. A paper by Beghini et al., 2020, provides a summary of methods to create iPS cells and their applications. It examines application of iPS cells in drug and disease modelling and discusses current clinical trials in phase I and II.

2.12. In a study by Pang et al., 2020 iPS cells were used to model Li-Fraumeni syndrome. This syndrome is associated with a high osteosarcoma incidence. These iPS cells were used experimentally for cancer modelling.

2.13. A review by Martínez-Larrosa et al., 2020 highlights the use of iPS cells for disease modelling of multiple sclerosis, drug screening, and cell therapy. As multiple sclerosis is a highly complex disease, iPS research was noted as an efficient tool for further research.

2.14. In a recent study by Bellák et al., 2020, undifferentiated iPS cells were grafted in rats with spinal cord contusion injuries. The rats with grafted iPS cells showed better recovery and functional improvement, suggesting that the use of the iPS cells could be beneficial for patients with spinal cord contusion injuries.

2.15. Work by Chen et al., 2020, has theorised that iPS cells could be beneficial when creating bio-artificial liver systems to assist patients with acute liver failure. Using iPS cells would be beneficial due to their ability to self-renew in vitro. The publication presents a method of efficiently differentiating iPS cells to hepatic spheroids to assist pigs with acute liver failure.

2.16. A recent study by Hwang et al., 2020, used iPS cells to create an organoid model mimicking the complex features of glioblastoma cancer. This serves as a research tool for glioblastoma research and demonstrates the use of iPS cells to create organoid models for disease.

2.17. Additional uses of iPS cells within research and treatment include that for diabetes mellitus in Arroyave et al., 2020, Parkinson's Disease in Kouroupi et al., 2020, epilepsy in Hirose et al., 2020, leukemia in Wehbe et al., 2021, mitochondrial conditions in Liang et al., 2020, and congenital heart disease in Lin, et al., 2021. Work has also taken place within neurodegenerative diseases in Chang et al., 2020, neurodevelopmental and neuropsychiatric disease in Ren et al., 2021 and Chen et al., 2019, and in Central Nervous System Diseases in Cherashova E et al., 2020. These studies present methods and discussions regard the use of iPS cells in the study, modelling, and treatment of such conditions, as well as within drug research.

2.18. Nonetheless, the use of iPS cells as gene therapy is still limited by issues such as the need to ensure that patient's immune systems will not reject the transplanted stem cells. iPS cells must be stable, in order to ensure that genomic mutations and insertions in clinical applications are minimized, as discussed in Fus-Kujama et al., 2021. This paper examines the need to make the reprogramming process more efficient and safer by properly selecting reprogramming factors.

2.19. Additional issues are discussed in Colter et al., 2021, which examined the small number of clinical trials that are currently taking place with iPS cells. iPS cells must meet high levels of regulatory safety criteria, be generated in high volumes, and be of high quality for clinical research, which is currently challenging. This paper focused on the use of continual assessments of molecular and cellular characteristics of iPS cells and using large analytics datasets to improve iPS cell development for clinical applications.

3. Naïve state pluripotent stem cells

3.1. Two states of pluripotency are present in mammals: naïve and primed. iPS cells resemble primed pluripotent state found in post-implantation epiblast. Naïve pluripotency occurs in the

pre-implantation stage when there is more differential capacity and is therefore a more beneficial state for research and clinical applications.

Inducing and maintaining naïve pluripotency

3.2. In a study by Martinez-Val et al., 2021, the effects of inhibiting Mek1/2 and Gsk3 on embryonic stem cells were investigated. The study used mass spectrometry to investigate the effects of inhibiting these enzymes. It was concluded that the inhibition of Gsk3 stabilized embryonic stem cells in a naïve state.

3.3. A review of sequencing datasets of human and monkey embryos by Bourillot et al., 2020, investigated the role of specific signaling pathways for creating naïve pluripotent stem cells. The review found that the GP130/JAK/STAT3 pathway is expressed in pluripotent cells of human, monkey, and pig preimplantation embryos. It was established that the pathway is essential to reprogram pluripotent stem cells to naïve-like pluripotency. However, it was noted that the efficiency of creating naïve cells from primed cells was low.

3.4. The use of chemical agonists was used by Taei et al., 2020, to induce naïve-like pluripotency. This was achieved in pre-established human pluripotent stem cells and during the reprogramming of fibroblasts.

3.5. A study by Bredenkamp et al., 2018, found that inhibiting Wnt signaling promoted naïve pluripotency in human pluripotent stem cells. The induced naïve pluripotent stem cells that were created were observed and had similar gene expression to naïve epiblast cells.

3.6. An additional study by Osnato et al., 2021, investigated the role of TGFβ in maintaining human pluripotent stem cells in a naïve state. The study highlighted the benefits of maintaining human pluripotent stem cells in a naïve state for signaling pathway models in early human development.

3.7. A study by Lynch et al., 2020, used chemical inhibitors in order to stabilize human PS cells in their naïve state. In inhibiting CDK8/19 the study found that the equilibrium of naïve and prime pluripotent cells were shifted towards naïve features, allowing a stable population of cells in the naïve state.

3.8. A protocol by Rugg-Gunn, 2022, used chemical resetting to induce naïve pluripotency in primed cells. The method was beneficial due to its simplicity and efficiency at creating a stable culture of naïve pluripotent stem cells.

Inducing naïve pluripotency in iPS cells

3.9. In order to enhance the pluripotency of iPS cells Shi et al., 2020, investigated the effects of interferon regulatory factor 1(IRF-1) on iPS cell pluripotency in pigs. The results found that expressing higher levels of IRF-1 within the inner cell mass of the cells enhanced the pluripotency of the iPS cells derived from the pig blastocysts.

3.10. A study by Zorzan et al,. 2022, aimed to address the issues with scalability in creating naïve iPS cells as well as limitations including the need for viral vectors or stable genetic manipulations. The study delivered messenger RNAs using a microfluidic system in order to increase primed and naïve iPS cells, to develop a method that was easy to reproduce and was less time consuming.

3.11. In a study by Onfray et al., 2022, a protocol was developed to reprogram human fibroblasts into naïve iPS cells. This was done by overexpressing transcription factors using Sendai viruses. The resultant naïve iPS cells corresponded to pre-implantation epiblast cells.

4. Conclusions

4.1. SCAAC last considered research in this area in October 2018. At the meeting a member noted that as human embryonic stem cells are the gold standard of pluripotent cells, that such cells will always need to be derived from embryos. It was also noted that viable embryos are not the only source for ES cells, parthenogenetic embryos and androgenetic embryos can also be used. There are also more types of pluripotency than primed and naïve, suggesting a spectrum of differentiation potentials.

4.2. Researchers and clinicians continue to investigate the clinical application of iPS cells. Using iPS cells may also carry fewer ethical concerns for some, as somatic cell nuclear transfer (SCNT) still requires creation of an embryo to derive stem cells whereas iPS cells can be derived from adult cells. Although there are issues of genomic instability of iPS cells, this could be overcome by screening via sequencing for mutations, though there needs to be more research into the feasibility of such screening. Additionally, new protocols are being researched to use different methods to deliver reprogramming factors to reduce genomic instability.

4.3. There is increasing understanding of naïve PS cells, which have more potential than primed PS cells as they have similarities to early-stage embryonic cells. Significant work has been conducted in the pursuit of creating and maintaining naïve pluripotency SCNT.

5. Recommendations

5.1. Members are asked to:

- consider the progress of research into alternative methods to derive embryonic or embryonic-like stem cells;
- advise the Executive if they are aware of any other recent developments; and
- review whether any outputs from the HFEA are required.

5.2. Information updates summarised in this paper and SCAAC's view will be used to update the paper 'Alternative methods to derive stem cells' used by the HFEA Licence Committee when considering research licence applications which involve the use of viable embryos for research purposes.

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Treatment add-ons rating system review – an update

Details about this paper

Area(s) of strategy this paper relates to:	The best care/The right information
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	8
Paper number:	HFEA (31/01/2022) 008
Meeting date:	31 January 2022
Author:	Georgina Allen, Policy Manager Sonia Macleod, Scientific Policy Manager
Annexes	Annex A: 10 Options presented to Licenced Clinic Panel (LCP), Patient Organisation Stakeholder Group (POSG) & Treatment Add-ons Working Group (TAG) Annex B: Key findings from scoping work. Annex C: LCP and POSG's preferred options

Output from this paper

For information or recommendation?	The SCAAC is asked: • to note the progress made in relation to scoping the add-ons rating system, • for their views on the 10 options for presenting add-ons information and/or their alternative suggestions, and, • for their views on the proposals for engagement for evolving the rating scheme for add-ons.
Recommendation:	NA
Resource implications:	NA
Implementation date:	NA
Communication(s):	A full communications plan to engage patients and clinics in this work will be developed in due course.
Organisational risk:	Medium

1. Introduction

1.1. Treatment add-ons are optional additional treatments, which are also referred to as 'supplementary', 'adjuvants' or 'embryology treatments'; they often claim to be effective at improving the chances of having a baby (live birth rate) but the evidence to support this for most fertility patients is usually missing or not very reliable; and are likely to involve an additional cost on top of the cost of a routine cycle of proven fertility treatment. Some treatment add-ons can cost hundreds or thousands of pounds each.

1.2. Addressing how treatment add-ons are offered by clinics and information given to patients is a key feature of the HFEA strategy for 2020-24.

1.3. A key element of our work on add-ons is the use of a traffic light system for rating some treatment add-ons. The rating system first went onto the HFEA website in 2017 and has been subject to minor revisions since.

1.4. The current traffic-light rating system consists of three colours (red, amber and green (RAG)), that indicate whether the evidence, in the form of high-quality Randomised Control Trials (RCTs), shows that a treatment add-on is effective at improving the chances of having a baby for someone undergoing fertility treatment.

1.5. Our work on treatment add-ons so far means that patients can access clear information on our website which may enable them to better understand the evidence, risks and potential benefits for each add-on. Information on each add-on is framed within a reminder that for most patients, routine IVF is an effective treatment.

1.6. At the Authority meeting in September 2021it was agreed that we would undertake work to further **evolve the presentation of the rating system for treatment add-ons**, specifically that we would:-

- Carry out scoping work on the extent to which the current rating system could evolve and improve (e.g. do we stick with RAG or move to a different rating scale) and/or introduce multiple ratings per add-on (e.g. for various outcomes for each add-on).
- Come back to a future Authority meeting to report the outcome of that scoping work and set out a proposed engagement strategy.
- Come back to an Authority meeting in 2022 with a recommendation on how best to evolve/change the rating system based on engagement findings.
- Aim to agree any changes to the rating system by July 2022 so that the required work to inform the October 2022 SCAAC meeting (at which ratings will be allocated to our list of add-ons as part of their annual review) can be undertaken.

1.7. The Authority also agreed to consider broadening the range of data that the HFEA consider when assigning ratings to include other evidence types in addition to RCTs and to recommend whether

any should be included in the HFEA's annual review (currently using the GRADE methodology1) of evidence for treatments add-ons. This will be brought back to SCAAC later in 2022 to make a recommendation to the Authority.

1.8. This paper outlines the work we have carried out to date to review the presentation of the add-ons ratings. Section 2 looks at the scoping work we have done with researchers and feedback from stakeholders. Sections 3 and 4 outline engagement work we plan to undertake; section 5 sets out the next steps in terms of our engagement with SCAAC; and section 6 asks SCAAC to discuss the progress made to date.

2. Scoping work

2.1. We have met with:

- Researchers:- Professor Brian Zikmund-Fisher[2], from the University of Michigan, and Dr. Claudia Schneider[3], Dr. Alexandra Freeman[4] and Dr Gabriel Recchia[5] from the Winton Centre for Risk and Evidence Communication, University of Cambridge, to gain their views and insights on the current RAG rating system and into how best to present health data to patients in a simple yet informative and clear way.
- The VALUE study lead (Dr Sarah Lensen)[6] to discuss their progress and insight into how we could evolve our traffic light rating system.
- Our Licensed Clinics' Panel (LCP)[7] to gain the views from licenced clinics.
- Our Patient Organisation Stakeholder Group (POSG)[8] to gain the views from patients and patient organisations.

[1]GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

[2] **Professor Brian Zikmund-Fisher** is a professor of Health Behaviour and Health Education at the University of Michigan. He uses his background in decision psychology and behavioural economics to design and evaluate methods of making health data more intuitively meaningful and clear.

[3] **Dr. Claudia R. Schneider** is a researcher at the Winton Centre for Risk and Evidence Communication at the University of Cambridge. Her focus is on how the quality of the evidence underlying scientific claims and numbers can be best communicated to support comprehension, transparent information sharing, and information decision making.

[4] **Dr. Alexandra Freeman** is the Executive Director of the Winton Centre. She has a particular interest in helping professionals communicate numbers and uncertainty in a clear way to inform but not persuade.

[5] **Dr. Gabe Recchia** is a researcher at the Winton Centre. His current research concerns the communication of information in ways that support comprehension and information decision-making taking into account the audience's needs and preferences.

[6] The **VALUE Study** is a research project between Melbourne University in Australia and Sheffield University in the UK interested in understanding the decisions making processes that occur when patients, doctors and embryologist think about, or opt to use add-ons in an IVF or ICSI cycle. The study aims to improve the care of future IVF patients, by better understanding how information and add-ons should be shared.

[7] LCP members are drawn from a number of HFEA licensed clinics.

[8] The membership of the POSG is made up of organisations which represent different patient groups to raise the views of patients and highlight how decisions may affect certain patients.

- The Treatment Add-ons Group (TAG) to gain the views of signatories to the consensus statement

Researchers' Opinions

2.2. When we discussed evolving the treatment add-ons information with researchers, they suggested:

- **Rating the effectiveness of an add-on and the strength of the evidence for that add-on separately**.[9]
- Using **layered information** (information on another page when you click on a link) because it balances the need for simplicity and clarity with providing detail for those who want or need it.
- **Colour choice** is important because some colours, particularly red and green, intuitively convey certain messages, such as 'stop' and 'go'.
- RAG may not be the most effective way to communicate information[10], and that other evidence-based approaches (e.g. using + and – symbols) should be considered.

2.3. Other key findings from our engagement with researchers can be found in **Annex B**.

2.4. Based on input from researchers we developed 10 different presentation options, which we tested with LCP and PSOG (see below). These options are listed at **Annex A**. A feasibility check with the HFEA communications team indicated it would be possible to implement any of these options on the HFEA website.

LCP Opinions

2.5. The discussion with the LCP gave rise to 3 preferred options:

- To **keep the current rating system** (i.e. option 1 in Annex A) because it communicates clear and easy to understand information, and patients and clinics were used to using it.
- To **change the red rating to demonstrating 'evidence of potential negative effects' and adding another rating (e.g. grey) to demonstrate 'no evidence'** (i.e. option 2 in Annex A). LCP members suggested that we should consider **changing the grey to a yellow** and that we should also review the **ordering of the ratings** (i.e. moving the red to the bottom so that the ratings go in order from the best to the worst).
- To include **additional outcomes** (i.e. option 9 in Annex A) because it would provide patients with more information about the add-ons. Members also suggested we should consider **changing from additional outcomes to additional patient groups** (e.g. those at risk of OHSS) rather than only looking at 'most fertility patients'. **We will need to look into the feasibility of rating add-ons for additional patient groups.**

2.6. More information on the views of LCP members can be found in **Annex B**.

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[9] Examples of the Education Endowment Foundation, and the College of Policing Quality scale and their Effect Scale were provided.

[10] 'Communicating evidence in icons and summary formats for policymakers: what works?'

POSG Opinions

2.7. The discussion with the POSG gave rise to 3 preferred options:

- To **keep the current rating system** (i.e. option 1 in Annex A) because it works well for patients as it can be easily understood quickly. However, they were of the view that some patients want **more information and suggested adding this through drop downs or layered information.** They felt this would be useful for patients because it would allow access to more information when and if wanted/needed whilst also ensuring that the simple, clear and easy to understand ratings are not lost.
- To **change the red rating to demonstrating 'evidence of potential negative effects' and adding another rating (e.g. grey) to demonstrate 'no evidence'** (i.e. option 2 in Annex A). They suggested that this provides more information (particularly about when there is potential negative effects) and may be clearer for patients to understand, although some members thought it could potentially add more confusion.
- To include **additional outcomes** (i.e. option 9 in Annex A) because it would provide patients with more information about the add-ons. Members also suggested we should consider **changing from additional outcomes to additional patient groups** (e.g. those at risk of OHSS) rather than only looking at 'most fertility patients'. **We will need to look into the feasibility of rating add-ons for additional patient groups.**

2.8. More information about views of POSG members can be found in **Annex B**.

TAG Opinions

2.9. The discussion with the TAG gave rise to the following suggestions:

- To **change the red rating to demonstrating 'evidence of potential negative effects' and adding another rating (e.g. grey) to demonstrate 'no evidence'** (i.e. option 2 in Annex A). This was because members believed that patients want more information and are also interested in knowing if there is any harm associated with an add-on which this option would provide.
- To **improve accessibility issues for those with red/green colour blindness**. Two options were suggested. Firstly, that this could be achieved by **changing the colours of the rating system from RAG to a gradient of colours** (i.e. option 3 in Annex A) as it overcomes accessibility issues particularly and was not too dissimilar from the current rating system. Secondly, modifying the RAG or GRAG system by **writing the name of the colour or putting a letter in the middle of the coloured circle** were also raised as ways to resolve this issue (i.e. modifications of options 1 & 2 in Annex A).
- To include **additional outcomes** (i.e. option 9 in Annex A) because it would provide patients with more information about the add-ons. However, it was mentioned by members that this level of information (i.e. information about additional outcomes) may not be necessary for all add-ons (e.g. add-ons which target one particular outcome). Equally, for some add-ons it may be more useful to provide information about patient groups rather than additional outcomes and some add-ons may require both information on additional outcomes and additional patient groups. **We will need to look into the feasibility of providing different**

levels of information for each add-on and look into the feasibility of providing ratings for patient groups.

2.10. More information about the views of TAG members can be found in **Annex B**.

3. Future scoping work planned (until February 2022)

3.1. In thinking about evolving the rating system we need to take account of the differing circumstances in which the information on our website is read. While some patients may do so in the presence of a clinician, others may not and so we need to ensure that the rating system is capable of being understood without expert input. It is, therefore, essential that patients are involved in any evolution of the RAG rating.

3.2. We already have some information about patient views from the survey on add-ons carried out in 2020. In addition, we plan to carry out some in-depth one-to-one interviews with patients in early 2022. Findings from these interviews will be used to establish their:

- Understanding of the current RAG rating system.
- Understanding of the alternative options.
- Top three preferences for evolving the current rating system.

3.3. Based on feedback and views from researchers, stakeholders, patients and TAG, we will develop options for evolving the current RAG rating system for treatment add-ons which will be presented in a public engagement. The current RAG system will be one of the options presented in the engagement. We intend to present a maximum of two other options, but this will be contingent on the results of the scoping work which has currently not been completed.

3.4. It should be noted that some of the ten options we have used in the scoping phase will have cost implications. For example, if outcomes other than live births are included then the evidence base for these outcomes will need to be externally reviewed. This would involve a one-off retrospective review of eligible papers reporting the selected outcome(s) as well as an annual review of any new papers reporting that outcome. There may be some limitations to this depending on the resource priorities of the wider organisation. Until we have greater clarity on the outcomes of interest it is not possible to determine the scale of the cost implications.

4. Public and clinic engagement

4.1. The results of the scoping work will be analysed and we will create both patient and clinic surveys on evolving the RAG rating.

4.2. An online targeted patient survey, planned to start in Spring 2022, will present a maximum of three options for evolving the RAG rating system. We will use the findings from this targeted survey and the national patient survey to assess patient views on the three options. The targeted patient survey will be promoted as part of a wider communication plan to ensure we maximise our reach. We will monitor respondent demographics so we can check we have a broadly representative sample.

4.3. At the same time we will conduct an online clinic survey on the same three options. This will mean we have both the patient and clinic perspectives on the potential evolutions of the rating.

4.4. We also plan to conduct focus groups from members of the HFEA Patient Engagement Forum. These will take place after the targeted surveys so we can gain a deeper understanding of patient views.

4.5. The results from this engagement work and the information gained during the scoping phase will be used to develop a recommendation for the evolution of the RAG rating system.

5. Next Steps

5.1. **Presentation of add-ons ratings and outcomes rated.** We will go to a future Authority meeting with a recommendation on how best to evolve/change the rating system based on the scoping work outlined above.

5.2. **The evidence base used to generate add-ons ratings.** Along with the work on the presentational aspects of the rating system is the work on expanding the evidence base. At the June SCAAC meeting we will hold a workshop style session for SCAAC members on evidence bases, including looking at the types of evidence used by other ALBs, etc and the positive and negatives of different evidence types. SCAAC will then discuss the evidence base and formulate a recommendation on what the evidence base for rating add-ons should consist of.

5.3. We will take both our recommendation on presentational format and SCAAC's recommendation on the evidence base to the Authority at the same time. Recommendations made by the Authority at their July meeting might enable SCAAC to undertake their annual review at the October SCAAC meeting based on the modified rating system/evidence base. This is with the caveat that if *either* the rating system or the evidence base changes substantially then more time may be required for external reviewing before SCAAC can be asked to review each add-on, most likely at the February 2023 meeting.

5.4. In the longer term substantially expanding the evidence base could lead to longer intervals between ratings and/or to reviewing the rating for different add-ons at different times of the year rather than the current system where all add-ons are reviewed together once a year. These options can be discussed at the October SCAAC meeting once there is clarity on the size of any changes to the evidence base.

5.5. Any changes to the RAG rating system will be subjected to user-acceptance testing, and published as part of a wider communications plan, including infographics for use on social media, social media posts and in Clinic Focus.

6. Recommendations

6.1. SCAAC is asked:

- to note the activities undertaken in relation to scoping the add-ons rating system,
- for member's views on the 10 options for presenting add-ons information and/or alternative suggestions, and,

- for their views on the proposals for engagement for evolving the rating scheme for add-ons.

Annex A – 10 options presented to LCP and POSG

- Below are the options presented to LCP and POSG.
- Please note that the options below cannot be taken as fact and do not reflect the true current situation on add-ons.

1. Option 1 - The current rating system

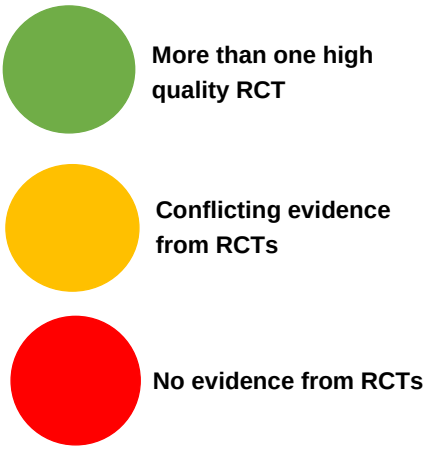
1.1. This would mean that there is no change to the current RAG (red, amber, green) rating system on our website.

1.2. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

1.3. Uses RCTs.

1.4. Currently, no add-on is rated as green because any add-on which would have been rated as green becomes part of the standard fertility treatment.

1.5. Additional outcomes could be rated in this way as shown in Option 9.



2. Option 2 – An additional rating (grey)

2.1. This would mean that there are four colours (grey, red, amber, green) GRAG.

2.3. Red would change to mean that there is potential detriment (or negative effects).

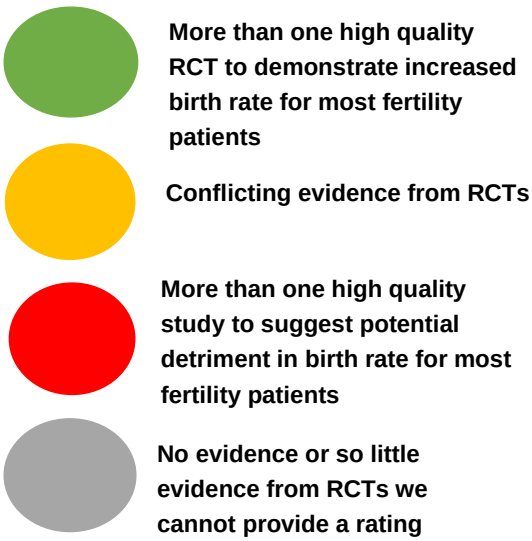
2.4. Grey would mean that there is no evidence (i.e. what red currently means).

2.5. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

2.6. Uses RCTs.

2.7. There would be no green ratings as any add-ons which would be rated as green would be part of the standard fertility treatment.

2.8. Additional outcomes could be rated in this way as shown in Option 9.



3. Option 3 - Colour gradient

3.1. Does not use red, amber green.

3.2. Uses a gradient of one colour where the darker the colour the more evidence there is that the add-on is effective at increasing birth rates for most fertility patients.

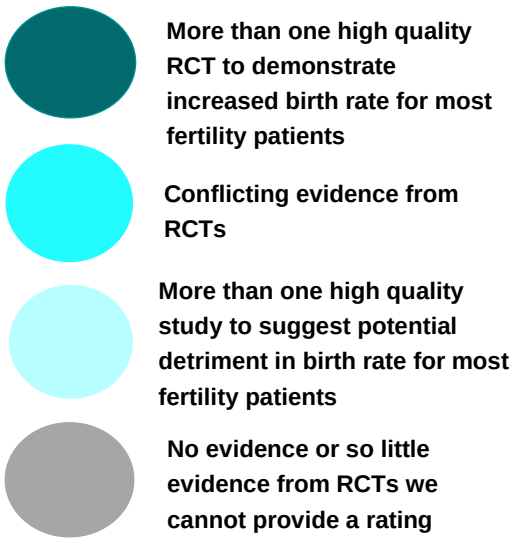
3.3. The grey would demonstrate that we have no evidence and so are unable to rate the add-on.

3.4. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

3.5. Uses RCTs.

3.6. There would be no dark turquoise colour as any add-ons which would be rated as dark turquoise would be part of the standard fertility treatment.

3.7. Additional outcomes could be rated in this way as shown in Option 9.



4. Option 4. - STAR ratings

4.1. The stars demonstrate how much evidence there is for each add-on.

4.2. There is no colour distinction to demonstrate how much evidence each add-on has.

4.3. It is not possible to demonstrate through a star rating system whether there is evidence of negative effects.

4.4. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

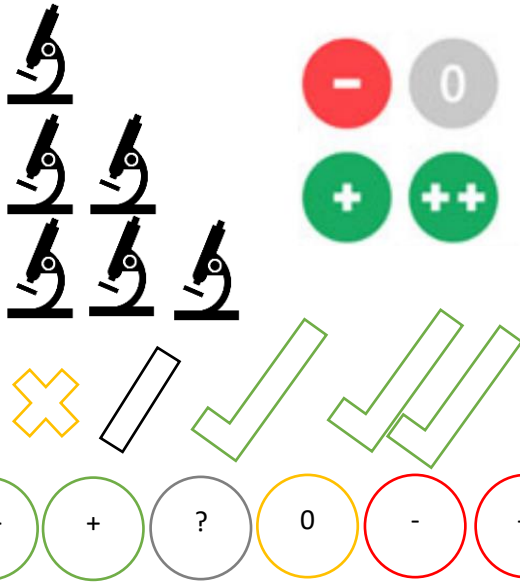
4.5. Uses RCTs.

4.6. There is likely to be no 3 star rated add-on (similarly to how there is no green rated add-on) because any add-on which would be rated three stars would be part of the standard fertility treatment.

4.7. Additional outcomes could be rated in this way as shown in Option 9.

5. Option 5. – Symbols

5.1. Any kind of symbols can be used. These are a few examples.



5.2. Different symbols could convey both positive and negative impacts, for example the ticks and crosses.

5.3. Symbols can provide nuance such as showing the difference between 'no evidence' and 'evidence of no impact'.

5.4. Symbols can also be used to distinguish between substantial positive impact and moderate positive impact and vice a versa for negative impacts.

5.5. Some symbols create a better intuitive understanding than others, so care is needed when matching the symbol to the outcome it represents.

5.6. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

5.7. Uses RCTs.

5.8. Additional outcomes could be rated in this way as shown in Option 9.

6. Option 6 – Wording

6.1. This would be where there are only words to describe how much evidence there is and what the evidence shows for each add-on.

6.2. It could reduce the intuitive understanding/misunderstanding of symbols and colours.

6.3. However, the choice of words could influence a person's choice.

6.4. This option may have accessibility issues for people where English is their second language, for those with low literacy and those with disabilities (e.g. dyslexia).

More than one high quality RCT to demonstrate increased birth rates for most fertility patients.

Conflicting evidence from RCTs.

No evidence.

More than one high quality study to suggest potential detriment in birth rates for most fertility patients

6.5. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients

6.6. Uses RCTs.

6.7. Other outcomes could be rated in this way as shown in Option 9.

7. Option 7 – Letter Grading

7.1. The letter/grade would be what rates the add-on.

7.2. A demonstrates good evidence and a positive effect and D is good evidence with a negative effect.

7.3. It could reduce the intuitive understanding/misunderstanding of symbols and colours.

7.4. This option may have accessibility issues for people where English is their second language, for those with low literacy and those with disabilities (e.g. dyslexia).

A. **More than one high quality RCT to demonstrate increased birth rates for most fertility patients**

B. **Conflicting evidence from RCTs**

C. **No evidence**

D. **More than one high quality study to suggest potential detriment in birth rates for most fertility patients**

7.5. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

7.6. Uses RCTs.

7.7. Additional outcomes could be rated in this way as shown in Option 9

8. Option 8 – Number Rating

8.1. The numbers would be what rates the add-on.

8.2. The lower the number the more evidence there is.

8.3. It could reduce the intuitive understanding/misunderstanding of symbols and colours.

8.4. This option may have accessibility issues for people where English is their second language, for those with low literacy and those with disabilities (e.g. dyslexia).

8.5. Some people may get confused with the rating as they may think that the higher number is better. Therefore, if this is preferred, we will need to assess what is best.

1. **More than one high quality RCT to demonstrate increased birth rates for most fertility patients**
2. **Conflicting evidence from RCTs**
3. **No evidence**
4. **More than one high quality study to suggest potential detriment in birth rates for most fertility patients**

8.6. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

8.7. Uses RCTs.

8.8. Additional outcomes could be rated in this way as shown in Option 9.

9. Option 9 – Additional Outcomes

9.1. We could use any of the rating systems suggested above (Options 1-7 in Annex A) or any other rating system if it is preferable. **This is an illustrative example.**

Treatment add-on	Outcome			
	Successful birth	Reduction in miscarriage	Reducing the time to a positive pregnancy test	Ovarian Hyperstimulation Syndrome
Artificial egg activation calcium ionophore	●	●	●	●
Assisted hatching	●	●	●	●
Elective freeze all cycles	●	●	●	●

9.2. Rates other outcomes rather than only rating whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

9.3. We have included in our example reduction in miscarriage, time to conception and OHSS risk (already looked at by SCAAC), however, any outcome could be considered.

9.4. The add-on itself would not have an overall rating for increasing birth rates, but each outcome would be individually rated for each individual add-on.

9.5. Each additional outcome could be rated green (or equivalent) but it is unlikely that there would be green ratings (or equivalent) for successful birth rates.

9.6. Uses RCTs.

10. Option 10 – Split evidence and effectiveness

10.1. Currently, the evidence and the effectiveness are merged together in one rating (e.g. green would currently demonstrate that there is more than one high quality RCT which demonstrates the add-on is effective at increasing birth rates for most fertility patients).

Treatment Add on (Please click on the add on for more information)	Impact	Evidence
Artificial egg activation calcium ionophore	-	🔬🔬🔬
Assisted hatching	0	🔬🔬🔬
Elective freeze all cycles	+	🔬🔬🔬

10.2. This option would split evidence and effectiveness so that they are rated distinct from each other to show how much evidence there is and what this evidence shows the effect is. This could potentially allow for nuances where there is a small amount of evidence all showing a positive effect or occasions where there is a lot of evidence showing no effect etc.

10.3. There are suggestions from researchers that doing this could reduce confusion about how much evidence there is and what this evidence indicates to help patients make a more informed choice as they know how much evidence there is and what this evidence suggests.

10.4. We have used symbols in this example, however, any of the rating systems suggested above (options 1-7 in Annex A) or any other rating system if it is preferable. This is only an example of what it could look like if we split the evidence and effect (impact).

10.5. Only looks at whether the add-on is effective at increasing the chances of successful birth in most fertility patients.

10.6. Uses RCTs.

10.7. Additional outcomes could be rated in this way as shown in Option 9.

Annex B – Key findings from scoping work

- Please see below further information from our discussions with researchers, LCP, POSG and TAG.

1. Further key findings from researchers:

1.1. Other key suggestions and information provided by our conversations with researchers include:

- **Symbols** can be more effective at communicating information to people than text alone.
- **Tables communicate information in a simple and comprehensive way**[11] even to those with lower literacy skills as they are a good way to recognise patterns and trends at a glance.
- **A scale of effect** (e.g. ++, +, 0, -, --, ?) should be considered. This will allow nuanced communication. For example, the difference between 'no evidence to show any impact' and 'evidence of no impact'.
- When patients are offered add-ons they are faced with a choice of taking the add-on (i.e. a positive action) or not taking it (i.e. no action). **Our add-ons webpage should include information on what standard IVF treatment entails as it indicates to patients that they are already acting positively.**
- As green rated add-ons are not possible in our current rating system, this can cause confusion and misunderstanding. Therefore, it was suggested that **each rating should be at least possible to achieve** otherwise we are setting unachievable standards.

2. Key information for LCP discussion:

2.1. When we met with LCP members we went through each of the 10 options which we had developed to gain their opinions on each option. LCP members thought:

- **Option 1 (i.e. the current rating system) is useful for patients** to see clear messages and is straightforward for clinics to explain to patients.
- **Option 2 (i.e. the addition of a grey rating) would be an improvement from the current rating system** because it would ensure that red means 'stop'. They suggested that the **red rating should be at the bottom** rather than the grey so that the ratings flowed from the best to the worst and that we should **consider changing the grey to another colour such as yellow**.
- **Options 3 (i.e. colour gradient) would not be an improvement from the current rating system** as it would be difficult to know intuitively what each colour meant and so would be difficult for patients to understand and for clinics to describe the rating to patients.
- **Option 4 (i.e. stars), would not be an improvement from the current rating system** and was potentially confusing as stars are already used for rating clinics. Also, stars denote good

[11] 'Risk communication in tables versus text: a registered report randomized trial on 'fact boxes'

practice and even one star would be a reward or praise when that would not necessarily be what the star is showing (e.g. conflicting evidence).

- **Option 5 (i.e. symbols) could potentially be confusing for patients** particularly those who are neurodiverse. LCP members agreed this option may provide nuance and provide patients with more information, but they argued this potential benefit of symbols was outweighed by the risk of misunderstanding and confusions as symbols would be more difficult for patients to quickly understand. They felt it would be **difficult for clinics to explain the symbols**.
- **Option 6 (i.e. wording), option 7 (i.e. letter grading) and option 8 (i.e. number rating) were not an improvement from the current rating system** as they are all too texted based and the lack of colour makes it difficult to see trends quickly potentially leading to accessibility issues.
- **Option 9 (i.e. additional outcomes) was seen as a useful improvement from the current rating system** as it would provide more information to patients. Members suggested that **instead of additional outcomes we should consider additional patient groups** such as those who are at risk of OHSS and those who have had multiple miscarriage and at risk of further miscarriages etc. This would ensure that patients receive more information and information about their specific group.
- **Option 10 (i.e. splitting the impact and evidence and rating them separately) was seen as too confusing for patients and so was not seen as a useful improvement from the current rating system**. Members explained that patients often want a 'yes' or 'no' answer and splitting impact and evidence would not provided them with this. It was suggested, however, that **this information could be useful to provide to clinics** to help them explain the ratings to patients.
- **Tables seemed to be useful** at communicating information.

3. Key information from POSG discussion:

3.1. When we met with POSG members we went through each of the 10 options which we had developed to gain their opinions on each option. POSG members thought:

- **Option 1 (i.e. the current rating system) is useful for patients** to see clear messages and is straightforward for clinics to explain to patients. Although the current rating system is useful to provide simple information they suggested that where patients want more information we should include more detailed information about each add-on (e.g. a link to the RCTs themselves) on our website through drop downs or layered information. They felt it would be particularly helpful to include information about how many people have had a baby after using that add-on. It was noted that the current system may be difficult for patients with colour blindness and that adding 'red', 'amber' and 'green' inside the dots would resolve this.
- **Option 2 (i.e. the addition of a grey rating) is likely to be more useful to patients than the current rating system.** It was suggested that some patients may see the red rating and think it is dangerous meaning they may not want to use it and may cause them to worry about their clinic if their clinic is suggesting they use an add-on which is rated red. Therefore, changing the definition of the red rating to show potential harm or negative effects could be useful to patients. There was some debate about whether a grey rating would be useful, but

in general members agreed that the grey rating would be useful to show where there is no evidence at all and for the red rating to demonstrate potential negative effects or harm as this is something patients often want to know. It was noted that the current system may be difficult for patients with colour blindness and that adding 'red', 'amber' and 'green' inside the dots would resolve this.

- **Options 3 (i.e. colour gradient) would not be an improvement from the current rating system** as it would be difficult to know intuitively what each colour meant and so would be difficult for patients to understand.
- **Option 4 (i.e. stars) would not be an improvement from the current rating system** as it would be too much of a change from the current rating system which is already useful to patients and could cause confusion.
- **Option 5 (i.e. symbols) would not be an improvement from the current rating system** as it would be a change from the current rating system and could provide too much information in one go which could cause confusion or misunderstanding if patients are looking at the rating system quickly.
- **Option 6 (i.e. wording), option 7 (i.e. letter grading) and option 8 (i.e. number rating) were not an improvement from the current rating system** as they are all too texted based and the lack of colour makes it difficult to see trends quickly potentially leading to accessibility issues.
- **Option 9 (i.e. additional outcomes) was seen as a useful improvement from the current rating system** as it would provide more information and detail about the add-ons to patients. They suggested that **additional patient groups may also be useful but should be included in addition to the information on additional outcomes**.
- **Option 10 (i.e. splitting the impact and evidence and rating them separately) was not seen as a useful improvement from the current rating system** because it would be too confusing for patients and not simple for them to understand quickly.

4. Key information from the TAG discussion:

- Members generally agreed with LCP and POSG stakeholder groups.
- We should not change the rating system drastically because patients would find it useful for there to be some continuity between the new rating system presentation and the current RAG rating system as it is easy and simple to understand.
- A **variation of the current rating system** (i.e. option 2 or 3) would be a useful change.
- The presentation of the rating system should be provided as high-level detail and **more information** (e.g. through layered information) should be included on the website for the sector and for patients who want or need it. Members believed this would balance the need for simplicity and detail.
- **Summaries with key information from the RCT** may be more useful to include rather than the RCTs themselves as RCTs themselves can be complex.

- Members agreed that **text-based ratings (i.e. options 6, 7 and 8) should be avoided** due to accessibility issue which may arise and also because text based ratings may reduce simplicity.
- Members clearly stated that we **should ensure that the rating is accessible to everyone**. For example, ensuring that the rating system is accessible to those with red/green colour blindness. A suggestion was made to put a **symbol or the words 'red', 'green' inside the coloured dot**.
- Members suggested that **some add-ons may need more information than or different information to other add-ons**. For example, it was suggested that for some add-ons it may be useful to include ratings for different patient groups where as for other add-ons this may not be necessary information as the results are the same for all patient groups etc. This avoids the issue of 'lumping everyone in the same group' with one colour rating for everyone and also avoids the issue of uninformative or useless information.
- Although it is useful to tell patients whether there is a small, moderate or large positive/negative effect is useful information to include, splitting the effect/impact and evidence (i.e. option 10) may be too complex and it was felt that **this information could be explained in text**.

Annex C – LCP, POSG, and TAG's preferred options

- We have developed options based on the discussions from LCP an POSG. Some of these options may be hybrids or slightly different to our suggested options in Annex A which we presented to LCP and POSG members.
- Please note that the opinions given on the options below are those of the stakeholders consulted and do not necessarily reflect the current status of the HFEA's traffic light rated treatment add-ons.

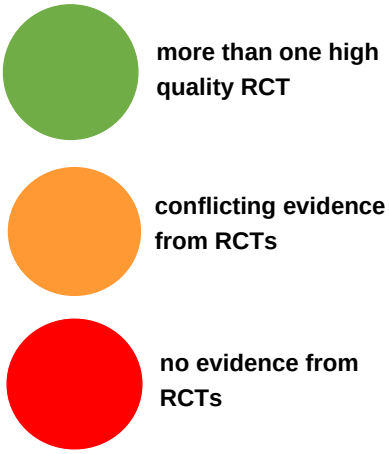
1. The Current rating system

1.1. Both LCP and POSG members suggested that the current rating system was useful for patients as it was easy for patients to understand quickly.

1.2. This would mean that there is no change to the current RAG (red, amber, green) rating system on our website.

1.3. POSG suggested that patients do want more information and that this should be provided through, for example, drop downs or layered/clickable information.

1.4. It was noted by POSG members that the current system may not be useful for patients with colour blindness and so potentially adding 'red', 'amber' and 'green' inside the dots to make it clear what the colour is could be useful. This should be considered further.



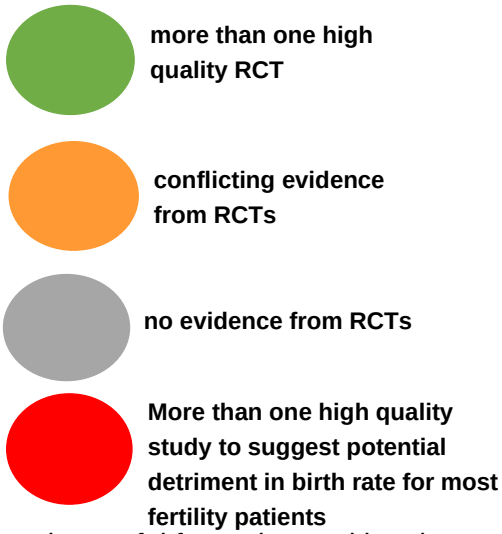
2. The GRAG rating system

2.1. Both the LCP and POSG members thought that the GRAG option, or something similar, could be an improvement to the current rating system.

2.2. Red would change to mean that there is potential detriment (or negative effects).

2.3. Grey would mean that there is no evidence (i.e. what red currently means).

2.4. Some LCP members felt that the grey should change to another colour such as yellow. **We will be able to review different variations of this option through our further scoping work.**



2.5. It was noted by POSG members that the use of colours may not be useful for patients with colour blindness and so potentially adding 'red', 'amber' and 'green' etc. inside the dots to make it clear what the colour is could be useful. This should be considered further. **We will be able to**

consider this and develop the best way to ensure that the ratings are accessible through our scoping work.

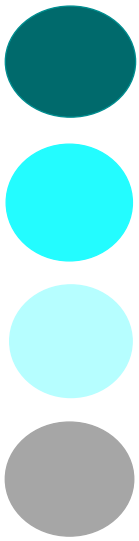
2.6. Based on the suggestions from the LCP members, the colours would go in order from best (i.e. green) to worst (i.e. red).

3. Option 3 - Colour gradient

3.1. TAG members suggested that a variation of the current rating system would be useful and, therefore, the colour gradient could be useful.

3.2. Rather than using RAG, the colour gradient rating system uses a gradient of one colour where the darker the colour the more evidence there is that the add-on is effective at increasing birth rates for most fertility patients.

3.3. An addition of a grey rating (or another colour) could be added to demonstrate that we have no evidence and so are unable to rate the add-on.



More than one high quality RCT to demonstrate increased birth rate for most fertility patients

Conflicting evidence from RCTs

More than one high quality study to suggest potential detriment in birth rate for most fertility patients

No evidence or so little evidence from RCTs we cannot provide a rating

3.4. Stakeholders have suggested that the add-ons rating system should be accessible to patients and using colour gradient ensure accessibility for those with red/green colour blindness.

3.5. This was **not a preferred option mentioned by LCP or POSG**.

4. Additional outcomes

4.1. Both LCP and POSG members thought that including additional outcomes would be useful to patients.

4.2. The additional outcomes to live birth rates included in this example are: reduction in miscarriage, time to conception and OHSS risk, however, any outcome could be considered. **We need to continue our scoping work to know if this is option is preferred and which patient groups would be preferred.**

Treatment add-on	Outcome			
	Successful birth	Reduction in miscarriage	Reducing the time to a positive pregnancy test	Ovarian Hyperstimulation Syndrome
Artificial egg activation calcium ionophore				
Assisted hatching				
Elective freeze all cycles				

4.3. This example uses the GRAG rating system, also used in the example shown in option 9 of Annex A. **Any rating system could be used and we will need to continue our scoping work to know which rating system is preferred.**

4.4. It would be possible for some additional outcomes to have green ratings for increased live birth rate as this would not necessarily mean that the add-on itself would be used in standard IVF treatment.

4.5. It is unlikely that it would be possible for live birth rates to be rated green because if they were rated green then the add-on would be used in standard IVF treatment.

4.6. Although LCP liked the addition of additional outcomes, they suggested having **additional patient groups** rather than outcomes may be more useful to patients (see options 4 in Annex C below).

4.7. POSG members suggested that rating the add-ons for additional patient groups would be useful information, but this should be provided in addition to additional outcomes.

5. Additional patient groups

5.1. LCP members suggested that rating add-ons for additional patient groups rather than for additional outcomes may be more useful to patients.

5.2. POSG members suggested that rating the add-ons for additional patient groups would be useful information for patients but this **should be provided in addition** to additional outcomes.

Treatment add-on	Patient Group			
	For most fertility patients	Patients who have suffered from multiple miscarriages	Patients who are over the age of 35	Patients at risk of Ovarian Hyperstimulation Syndrome
Artificial egg activation calcium ionophore	●	●	●	●
Assisted hatching	●	●	●	●
Elective freeze all cycles	●	●	●	●

5.3. Similar to option 9 presented in Annex A but, based on the suggestions from LCP members, rather than rating additional outcomes other than live birth rates, we would rate live birth rates for additional patient groups rather than only for 'most fertility patients'.

5.4. The patient groups we have included here are patients who have suffered from multiple miscarriages, patients who are over the age of 35, patients who are at risk of Ovarian Hyperstimulation Syndrome (OHSS). **We need to continue our scoping work to know if this is option is preferred and which patient groups would be preferred.**

5.5. This example uses the GRAG rating system. **Any rating system could be used, and we will need to continue our scoping work to know which rating system is preferred.**

5.6. As this is a newly suggested option. **We will need to further look into the feasibility of rating add-ons for additional patient groups to ensure that it is possible.**

5.7. If this option is feasible, it would be possible for some patient groups to have green ratings for increased live birth rate as this would not necessarily mean that the add-on itself would be used in standard IVF treatment.

5.8. If this option is feasible, it is unlikely that it would be possible for live birth rates for 'most fertility patients' to be rated green because if they were rated green then the add-on would be used in standard IVF treatment.