Scientific and Clinical Advances Advisory Committee (SCAAC) - Agenda

Monday 07 June 2021, 11:00am – 2:00pm
Teleconference

Agenda item	Time
1. Welcome, apologies, declarations of interest	11:00am (5')
2. Matters arising Matthew Mudford (HFEA)	11:05am (10')
3. Chair's business	11:15am (5')
4. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy All	11:20am (15')
5. Add-ons application – endometrial receptivity array (ERA) Matthew Mudford (HFEA)	11:35am (30')
Lunch break	*12:05pm (45')*
6. Artificial intelligence (AI) and machine learning – literature review Victoria Askew (HFEA)	12:50pm (35')
7. Fertility trends report Jane Darragh (HFEA)	1:25pm (20')
8. Any other business	1:45pm (10')
9. Meeting summary and close	1:55pm (5')

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

Monday 7th June 2021

Date and item	Action	Responsibility	Due date	Progress to date
19/10/2020 3.3	The Committee will continue to monitor and share relevant literature on COVID-19.	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.
19/10/2020 6.34	The Executive to consider how information about safety is presented within the HFEA's treatment add-ons information on the HFEA website along with the survey findings.	Victoria Askew, Policy Manager	Complete	Treatment add-on traffic light ratings no longer reflect the safety considerations of each treatment. Safety will be commented on for each treatment but outside of the traffic light ratings. These updates have been live on the HFEA website since mid-March 2021.
08/02/2021 3.13	The Executive to check what was agreed at the November Authority meeting in relation to complementary therapies webpages	Matthew Mudford, Scientific Policy Officer	Complete	The minutes from the November Authority state: The Authority agreed that holistic/alternative therapies should be featured as additional treatments that were sometimes offered during fertility treatment, especially in light of the new CMA guidance which mentions complementary therapies.

08/02/2021 5.5	The Executive will update their website in line with the BFS and ARCS guidance on vaccines when it becomes available.	HFEA	Complete	This update went live on the HFEA website on 12th February
08/02/2021 5.7	The Executive will add a section to the clinic portal website which will include all papers related to COVID-19 that have been discussed at SCAAC meetings.	Matthew Mudford, Scientific Policy Officer	Complete	This update went live on the HFEA website on 5th March
08/02/2021 6.12	The Executive to inform the relevant team to consider amending what PRISM data is being asked to be recorded for testicular biopsies for sperm retrieval. The reason for retrieval should be listed, distinguishing between obstructive and non-obstructive causes.	Matthew Mudford, Scientific Policy Officer	Complete	The PRISM team has been informed and will consider this when future updates are made to PRISM.
08/02/2021 6.7	The Executive to update the committee's 2021/22 workplan as follows: • Discussion on Artificial Intelligence (AI) to take place in 2021 • Discussion on synthetic human entities with embryo-like features, "SHEEFs", pushed back to 2022 and replace 'SHEEFs' with terminology used in the ISSCR guidelines • Include a discussion on new technologies in embryo testing including PGT-M and PGT-A in the Committee workplan for 2021-22.	Matthew Mudford, Scientific Policy Officer	Complete	The workplan has been updated as per the recommendations of the Committee. See Annex A below.

Annex A

Committee work plan 2021/2022

Priority topic	Item	Possible speaker(s)	Meeting
Artificial Intelligence (AI) Machine Learning	Literature review	Internal	June 2021
Review treatment add-ons	Literature review and external speaker	Expert reviewer	October 2021
New technologies in embryo testing including PGT-M and PGT-A’	Literature review and external speaker	Academic	October 2021
Mitochondrial donation	Literature review and external speaker	Newcastle Fertility Centre	February 2022
Alternative methods to derive embryonic and embryonic-like stem cells	Literature review	Internal	February 2022
Stem cell-based embryo models	Literature review and an external speaker	Academic	June 2022
The impact of stress	Literature review	Internal	June 2022
The impact of the microbiome	Literature review	Internal	June 2022

Application to include a new add-on on the HFEA traffic list

1. Background

Treatment add-ons **are often non-essential treatments that are commonly offered in fertility clinics in addition to routine treatment with the claim that they can improve a patient's chance of having a baby**. As with all new treatments or technologies being introduced into reproductive medicine, we expect the introduction of treatment add-ons into clinics to be preceded by good quality scientific research into the effectiveness and safety of these interventions. However, some treatment add-ons are being offered to patients without this evidence base for effectiveness at increasing live birth rate and safety. They are frequently offered outside of a research setting and are charged for at an additional cost.

Medical professionals, academics or patient organisations can use this form to propose that we review the evidence for a treatment add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase the live birth rate
- without conclusive evidence of its effectiveness at improving the live birth rate;
- it is not already listed in our the HFEA's traffic-light rated list of add-ons
- there is evidence that an add-on treatment is ineffective.

We will use the information given on this form to help us consider whether to include the proposed add-on(s) as part of our traffic-light rated list of add-ons, which are reviewed annually for evidence of their effectiveness for increasing the live birth rate and safety.

Your submitted information could be used to inform other webpages, outside of the HFEA's traffic-light rated list of add-ons.

2. Guidance

The purpose of this guidance is to assist you in completing the treatment add-ons application form. Add-ons could include tests, drugs, equipment, and surgical interventions.

Do not use this form to send information about treatment add-ons that are already on the HFEA's traffic-light rated list of add-ons.

Please use plain unabbreviated language (understandable to non-specialists) in your application.

SCAAC review

The HFEA Scientific and Clinical Advances Advisory Committee (SCAAC) considers advances in science and clinical practice which are relevant to the Authority's work. The SCAAC will review the

current published evidence base for the treatment, alongside this application, and determine its suitability to be part of the HFEA's traffic-light rated list of add-ons. The SCAAC review will consider:

- whether the treatment is an additional, non-essential treatment
- if patients undergoing fertility treatment are currently being offered, or are requesting, the treatment on a regular basis and/or are being charged for its use in their treatment;
- the likelihood that the treatment is unable to increase pregnancy or live birth rates compared to using established ART techniques without the treatment;
- whether there is a lack of standardised procedure between different laboratories and the lack of potential for this treatment to be implemented by other centres; and
- whether patients need information about the risks or safety of the procedure, for both patients and children born as a result of treatment.

Your application should be completed comprehensively to enable the committee to assess all areas.

A decision tree for SCAAC to use to determine what does and does not classify as a treatment add-on can be found in Annex A of the application form.

Submitted applications will be reviewed at the next available SCAAC meeting, which take place three times a year in February, June and October. If an application for this treatment has already been received and is currently under consideration, then we will let you know. If, after submitting your application, you wish to withdraw it from consideration, then please contact us as soon as possible.

If SCAAC recommends that this treatment is not suitable for inclusion in **the HFEA's traffic-light rated list of add-ons**, then we will notify you of this outcome by email. If, in the future, more evidence is published that supports this treatment as an add-on, i.e. conflicting evidence to show it can increase live birth rate, then you will be able to re-apply.

Assignment of a 'traffic light' rating

If SCAAC gives a recommendation that the treatment you told us about is suitable for inclusion in the annually-updated **HFEA's traffic-light rated list of add-ons**, then the published randomised control trials investigating the treatment will be reviewed for the outcome of live birth or pregnancy rate to allow SCAAC to assign a traffic light rating.

Once a traffic light rating has been assigned **the HFEA's traffic-light rated list of add-ons** will be updated accordingly and reviewed annually.

Thank you for taking the time to submit the application form and sharing your information.

3. Applicant information

Name	
Occupation and institution	
Email address	
Declaration of any financial or personal interest in relation to this treatment	

4. Proposed treatment add-on

4.1 What is the name of the treatment?

Endometrial Receptivity Analysis (ERA)

Also known as Endometrial Receptivity Array or Endometrial Receptivity Assay

Trade names include ERA®, ERPeak^{SM} ER Map® and ER Grade®

4.2 Please provide some background about the treatment and include how the treatment is used and how it claims to improve live birth rate. (max. 600 words)

Endometrial Receptivity Analysis (ERA) is a diagnostic method that classifies the endometrium as receptive, pre-receptive, or post-receptive, enabling women to undergo a personalized embryo transfer (pET), where the exact timing of the transfer has been tailored to each woman's personal window of implantation (WOI).

The test requires a small biopsy of endometrial tissue taken during scheduled treatment at either 7 days after the luteinising hormone peak (LH+ 7) in a natural cycle, or at the end of 5 days of progesterone administration after oestrogen priming in a hormonal replacement therapy cycle (P + 5). RNA extracted from the tissue is applied to a microarray to determine the transcriptomic (gene expression) profile of 238 genes. During the receptive phase, there is a receptor awakening causing upregulation of gene expression.

This profile, when coupled to a computational predictor, objectively identifies whether this endometrium is receptive, pre-receptive or post-receptive by clustering analysis against sample training sets.

The result obtained by ERA is independent of the histological appearance of the endometrium and has been demonstrated to be more accurate than histological dating.

Based on these findings, the algorithm then recommends the timing of progesterone treatment for the individual patient to find her personalised WOI. The pET can then be performed at the optimal time within that WOI, maximising the chance of successful implantation.

It is hoped that pET will allow the treatment of a significant number of cases of infertility: those with adenomyosis, endometriosis and chronic endometritis (because of altered ER) (**Mahajan, 2015**), thin endometrium and recurrent implantation failure (RIF). Determining the individualised receptive window could prevent embryo wastage and the need for multiple IVF cycles, thus averting the considerable financial and psychological burden that comes along with it.

It has good sensitivity and specificity of 0.99758 and 0.8857, respectively (**Diaz-Gimeno et al., 2013**) It was also affirmed that it has less intraobserver variability and is highly reproducible i.e. does not change for 1–2 years.

The ERA necessitates a freeze-all cycle and repeated medicated cycles to enable the endometrial biopsy and subsequent personalized embryo transfer. Freeze-all cycles and medicated cycles will be performed by most clinics routinely so patient information should already be available and staff should be competent in providing this care. This makes the test highly reproducible between centres.

The endometrial biopsy required should be a straightforward procedure for an experienced clinician. Information on it may already be made available to patients and should include the

risks and how to manage any complications. No new clinical skills or equipment will be required apart from the specific containers provided by the laboratory performing the assay. The biopsy sample must be preserved properly in specific containers and packaging, then transferred to the laboratory under strict temperature-controlled conditions. This would not vary greatly from already established procedures for handling biopsy samples.

The ERA test is closely integrated with the centres' existing procedures and must be integrated into the centres' quality system. In particular, as per Section 24 of the **Code of Practice**, the test providers (Igenomix and Copper Surgical) must, as part of a third party agreement, commit to the following:

(a) allow the entire service to be audited, and samples to be fully traced

(b) minimise cross-contamination

(c) follow relevant professional guidelines, and

(d) ensure that adverse incidents are reported and that any affected gametes and embryos can be effectively recalled.

4.3 Please demonstrate that this treatment is being offered to or requested by patients in a UK fertility clinic with the claim that this treatment increases live birth rate or chances of success. This could be contained in patient information leaflets, website content or anonymised conversations between patients and fertility clinic staff. (max. 300 words)

Endometrial receptivity analysis is being offered on the websites of 19 UK clinics for the investigation of implantation failure in IVF, for improving the chances of pregnancy and to "improve success rates". Some explain the rationale but without making any claim about effectiveness.

Of those, 11 are from three large clinic groups.

ERA is frequently offered as part of a combination of tests used to look at endometrial health and status. That may comprise 3 or 4 tests, commonly offered alongside EMMA (Endometrial Microbiome Metagenomic Analysis) and ALICE (Analysis of Infectious Chorionic Endometritis), and maybe part of the investigations performed in a dedicated 'Implantation clinic'.

ERA is most often advertised as being for women who have had recurrent implantation failure or multiple failed cycles. Most clinics specify those patient groups or claim that it "may benefit some groups of women". There are a few who do not define or narrow down who the test is for.

For example, one clinic claims that having four tests of endometrial health, one of which is ERA, gives them "a better understanding of your endometrial status in order to improve your chance of pregnancy". It is worth noting that at the same time that clinic admits "there is inconclusive evidence regarding the aforementioned additional investigations"

Cooper Surgical (ERPeak Endometrial Receptivity Test) and Igenomix (ERA® Endometrial Receptivity Analysis) are two examples of laboratories that are named as providing these tests. Cooper Surgical claim their test "helps to increase the chances of successful implantation". Igenomix claims that their ERA "maximizes the chances of pregnancy without losing valuable embryos"

The HFEA have been receiving increasing numbers of enquiries about the ERA, often from patients who have been offered the test, asking for further information and in particular whether it is effective.

4.4 Please provide any recommendations made by professional bodies, eg NICE, ESHRE, RCOG, BFS or ASRM, for or against the use of this treatment in fertility patients. (max. 500 words)

No professional bodies (NICE, ESHRE, RCOG, BFS or ASRM) currently provide any recommendations or guidelines related to ERA

5. Current evidence base

Effectiveness

5.1 To be included in the HFEA add-on review list, a treatment needs to lack published evidence about its effectiveness. Please provide peer-reviewed published evidence that this treatment add-on **is or is not effective at increasing live birth rate**, i.e. the extent to which this treatment is or is not able to deliver the promised benefits. Please include references to any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include references to data from animal studies, large data studies, research on human embryos, or clinical trial data. Study outcomes should include live birth rate as a primary or secondary outcome. (max. 500 words)

Effectiveness of the test and its ability to deliver promises of increasing chances of pregnancy can only be considered when it is used to guide personalised embryo transfer (PET). There are several studies that demonstrate that PET guided by ERA does improve chances of pregnancy but only one published RCT looking at live birth rate as a primary or secondary outcome.

The only RCT (**Simon et al, 2020)** is a 5-year, multicentre, open-label randomised controlled trial involving 458 patients aged 37 years or younger undergoing IVF. Blastocyst transfer at first appointment were randomized to PET guided by ERA, FET or fresh embryo transfer in 16 reproductive clinics.

Despite a large drop out of 50% of patients (compared with 30% initially planned), per protocol analysis demonstrated statistically significant improvement in pregnancy, implantation and cumulative live birth rates in PET compared with FET and fresh embryo transfer arms.

Reistenburg et al, (2021) conducted a prospective cohort study to compare the live birth rates between patients who undergo personalized embryo transfer (pET) after endometrial receptivity array (ERA) versus frozen embryo transfer (FET) with standard timing in first single euploid FET cycles. The live birth rate did not differ between patients who underwent FET with standard timing and patients who underwent ERA/pET, 45/81 (56.6%) and 83/147 (56.5%), respectively.

Other published studies do not have live birth as a primary or secondary outcome and have mixed findings as to the effectiveness of the ERA on implantation rates and pregnancy rates:

Ruiz-Alonso et al (2013) conducted a small prospective interventional multicentre clinical trial in which patients with a receptive ERA-diagnosed endometrium, embryos were transferred in a subsequent HRT or natural cycle and observed that pregnancy rate in

patients with RIF were similar to those in our general IVF population (53% vs. 48%, respectively).

Additionally, the implantation rate and pregnancy rate were calculated on a monthly basis, demonstrating that embryo implantation and pregnancy was not related to the local injury induced by the endometrial biopsy

J Tan et al (2018) performed a retrospective review for 88 patients who underwent ERA testing between 2014 and 2017. Outcomes were compared for patients undergoing frozen embryo transfer (FET) using a standard progesterone protocol versus those with non-receptive results by ERA and subsequent FET according to a personalized embryo transfer (pET) protocol. They found no statistically significant difference in implantation rate or pregnancy rates.

Bassil et al (2018), conducted a single-centre retrospective cohort study, including 53 consecutive good prognosis patients, examined whether adjusting the embryo transfer day according to the proposed shift in the window of implantation improves the pregnancy rate compared to non-ERA-tested patients. Performing the ERA test in a mock cycle prior to a FET does not seem to improve the ongoing pregnancy rate in good prognosis patients.

Safety

5.2 If there is evidence that this treatment is **not** safe or there is risk of harm, for either the patients or the children born after the use of this treatment, please outline it here. Please include references to any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include references to data from animal studies, large data studies, research on human embryos, or clinical trials data. (max. 500 words)

The test necessitates a freeze-all cycle and repeated medicated cycles to enable ERA biopsy followed by personalized embryo transfer. Elective freeze all cycles do not carry any increased risk for the person undergoing fertility treatment but there is a risk to the embryo that it will lose cells or not survive at all.

An increase in the number of medicated cycles increases any risk associated with those medications - adverse drug reactions, side effects, interactions, drug errors etc

The greatest safety risks to the patient from ERA are related to the endometrial biopsy procedure; pain/cramping, bleeding, and infection **(Will et al, 2020).**.

The most common side effect of an endometrial biopsy is cramping. This can be significantly reduced with the administration of pre- procedure anti-inflammatories or topical anaesthesis onto the cervix.

Once the procedure is completed, women may report light vaginal bleeding or spotting for several days.

Uterine perforation is possible but very rare.

Infections are rare and usually minor and local but in severe cases they may lead to pelvic infections, bacteremia, sepsis and acute bacterial endocarditis. The infection risk may be reduced by the use of prophylactic antibiotics.

The more severe complications from infection or perforation are monitored for by instructing the patient with strict return precautions to include returning to the centre for fever, cramping

continuing for more than 48 hours, increasing pain, bleeding heavier than a normal menstrual period, or any foul-smelling discharge.

If the patient were to be pregnant there is a risk of miscarriage so a pregnancy test should be performed before the procedure.

In approximately <1% of cases there is a “non-informative” result. In those cases, a new endometrial biopsy could be required. There is a risk (<5%) that the biopsy procedure will fail to obtain a sufficient quantity and/or quality of tissue to be able to make a diagnosis. If this should occur, a new biopsy will be required (**Igenomix, 2019**).

We have found no evidence that the ERA in particular has or could carry any medical risk greater to the patient than that carried by the endometrial biopsy procedure and the medicated cycles. There is a slight risk to the chance of success given that the test will delay treatment. It is also important to consider the additional psychological and financial burden for the patient.

Simon et al (2020) found personalized embryo transfer (PET) guided by endometrial receptivity analysis (ERA) did not differ significantly from frozen embryo transfer (FET) or fresh embryo transfer in infertile patients undergoing IVF, in obstetrical outcomes, type of delivery and neonatal outcomes.

6. Declaration

The information provided on this form is to the best of my knowledge true and accurate

Check the box to confirm acceptance of the above statement ☐

Signature: Completed by the HFEA

Date: _____

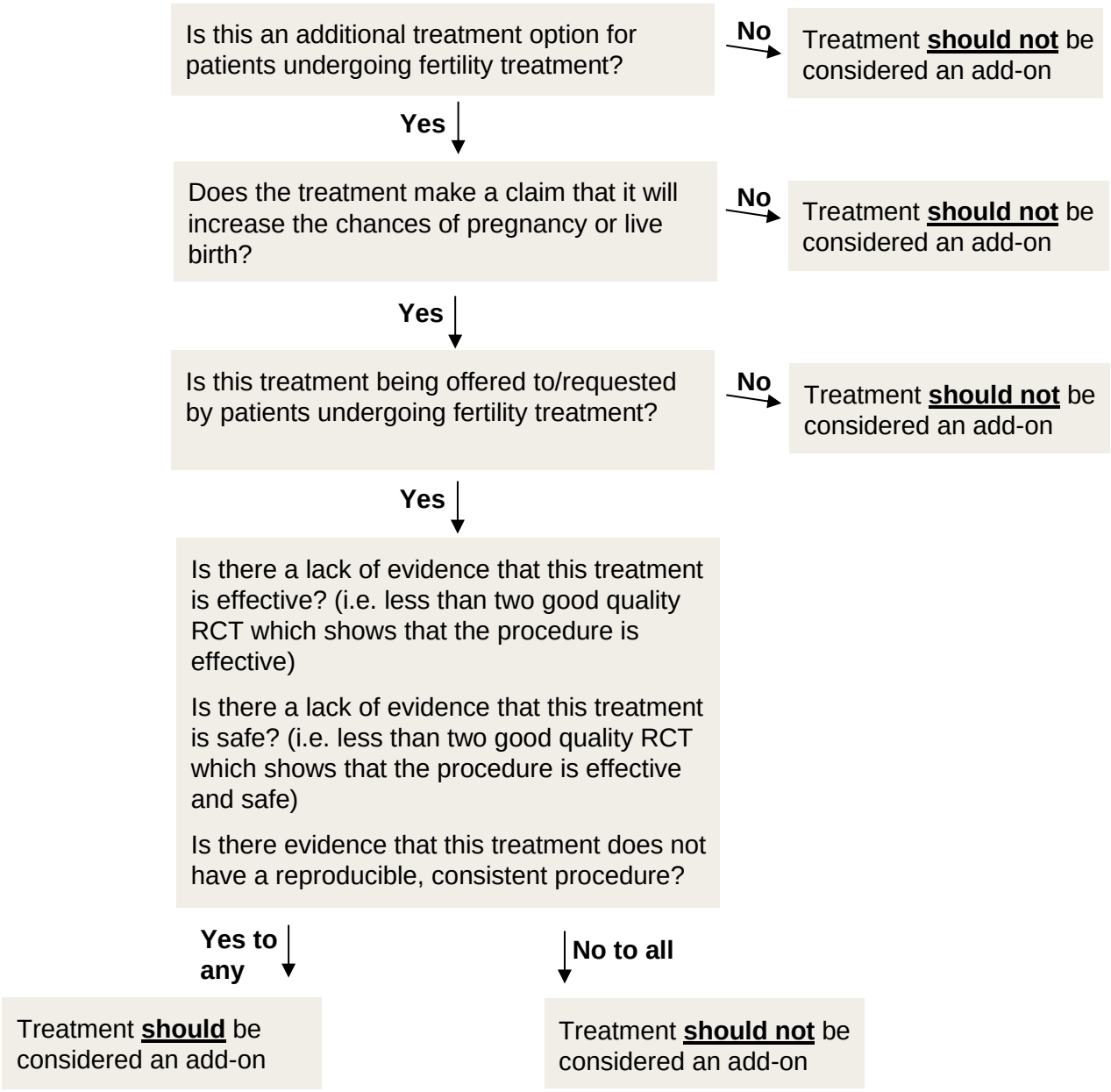
This form should be submitted, with any associated papers and information, to **enquiriesteam@hfea.gov.uk**.

Annex A – References

- Mahajan N. Endometrial receptivity array: Clinical application. *J Hum Reprod Sci* 2015;8:121-9
- Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero J.A, Alamá P.et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histological dating as diagnostic method for the endometrial factor. *Fertil Steril.* 2013; 99: 508-517
- Simón C. et al, A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. *Reproductive BioMedicine Online,* Volume 41, Issue 3, 2020, Pages 402-415
- Riestenberg C, Kroener L, Quinn M, Ching K, Ambartsumyan G. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. Fertil Steril. 2021 Apr;115(4):1001-1006.
- Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, Carrera J, Vilella F, Pellicer A, Simón C. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril.* 2013 Sep;100(3):818-24
- Tan J, Kan A, Hitkari J, Taylor B, Tallon N, Warraich G, Yuzpe A, Nakhuda G. The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers. *J Assist Reprod Genet*. 2018 Apr;35(4):683-692.
- Bassil, R., Casper, R., Samara, N. et al. Does the endometrial receptivity array really provide personalized embryo transfer?. *J Assist Reprod Genet* 35, 1301–1305 (2018)
- Igenomix (2019), Endometrial Receptivity Array (ERA) Informed consent and HIPAA, Available at: **http://www.igenomix.com/wp-content/uploads/2019/10/ERA-Consent-Form-EN.pdf** (Accessed 23rd April 2021)
- Will AJ, Sanchack KE. Endometrial Biopsy. [Updated 2020 Oct 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: **https://www.ncbi.nlm.nih.gov/books/NBK541135**

Annex B

SCAAC treatment add-on application decision tree



Artificial intelligence (AI)

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 (07/06/2021) 007
Meeting date:	07 June 2021
Author:	Victoria Askew, Policy Manager

Output from this paper

For information or decision?	For information
Recommendation:	Members are asked to: • advise the Executive if they are aware of any other recent developments in AI relevant to fertility treatments or research; • discuss their views of the impact AI will have on fertility treatment as technology advances, including practical and ethical challenges to their application; • discuss their views on the Authority's regulatory interest around AI systems – scope and limits; and • review whether any outputs from the HFEA are required, addressing the use of AI.
Resource implications:	None
Implementation date:	N/A
Communication(s):	None
Organisational risk:	Low

1. Background

1.1. Artificial intelligence (AI) is the theory and development of computer systems able to perform tasks normally requiring human intelligence, typically making predictions or decisions such as around visual perception, speech recognition, decision-making, and translation between languages.

1.2. AI and the machine learning that progressively improves specific AI task performance is driven by data. In healthcare, this could be related to data pertaining to patient characteristics or data from medical images. With a large enough dataset, machine learning can be applied to create algorithms independently and form systems such as artificial neural networks (ANNs) that are advanced enough to generate clinical judgements or predictions.

1.3. Within reproductive medicine current application of AI and data driven technologies includes assisting embryologists in the ranking and selection of embryos, automating semen analysis, predicting treatment success rates, aiding in clinical decision making and robotic surgery. Outside of the UK AI can also be used for facial matching of patients to potential gamete donors (this technology would not currently be permitted for use within UK regulations on managed information release about donors).

1.4. 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.

1.5. Numerous organisations and public bodies have addressed the introduction of AI processes into both clinical and industrial use. The House of Lords Liaison Committee report **AI in the UK: No room for complacency** concluded that *"Sector-specific regulators are better placed to identify gaps in regulation, and to learn about AI and apply it to their sectors. The [Centre for Data Ethics and Innovation (**CDEI**)] and **Office for AI** can play a cross-cutting role, along with the [Information Commissioners Office (**ICO**)] to provide that understanding of risk and the necessary training and upskilling for sector specific regulators."*

1.6. In February 2020 the **Committee on Standards in Public Life (CSPL)** produced a report into artificial intelligence and public standards. The report noted that the UK's regulatory and governance framework for AI in the public sector remains a work in progress and deficiencies are notable. As a follow up to this report the **CSPL surveyed regulators**, including HFEA, to determine how they are adapting to the challenge of AI.

1.7. As part of the HFEA's response to the CSPL survey, the executive summarised that *"The use of AI in the fertility sector is increasing, but not yet commonplace. As noted above, we have no specific powers related to the regulation of AI in the clinics we licence, nor do we have the resources to develop staff expertise at present. We are considering how we can best ensure that any AI systems that a licensed fertility clinic uses meets the requirements set out in laws*

such as GDPR or the Equality Act, or to inspect data security and the potential for data breaches, but without regulatory or industry guidelines produced by experts in the field of AI it will be difficult to regulate this area of technology effectively."

1.8. The **AI Council**, an independent expert committee that advises the government, published an **AI Roadmap** in January 2021 that provides recommendations to help the government's strategic direction on AI. The Office for AI has produced a **guide** to using AI in the public sector, **guidance** for ethics, transparency and accountability framework for automated decision-making in the public sector and announced the publication of a **national AI strategy** later this year.

1.9. The ICO have produced guides on **AI and data protection** and **explaining decisions made by AI**. The ICO should also be developing a training course for regulators in the ethical and appropriate use of public data and AI systems, its opportunities and risks. This should be developed in collaboration with CDEI, Office for AI and the **Alan Turing Institute** and is due to be rolled out in July 2021.

1.10. The **Accelerated Access Collaborative (AAC)**, in partnership with **NHSX** and the **National Institute for Health Research (NIHR)**, has made £140 million available over four years to accelerate the testing and evaluation of the most promising AI technologies which meet the strategic aims set out in the **NHS Long Term Plan**. Currently, applications for round 3 of the competition for awards are being accepted from June to September 2021.

1.11. In April 2021 the **National Institute for Health and Care Excellence (NICE)** updated their evidence standards framework for digital health technologies. NICE also announced the launch of an **Office for Digital Health** in May 2021.

2. Current developments in AI within the fertility sector

2.1. AI can be applied to many different aspects of treatment cycles and operating procedures within a clinic. Below is a summary of the research into implementing AI in the fertility sector and its relation to commercially available products. This review included paper published between June 2019 - May 2021, UK-based clinic websites and websites of companies offering products involving the use of AI to patients both within and outside of the UK.

Gamete analysis

2.2. Riordon et al. (2019) used a deep learning algorithm to automate semen analysis. The deep convolution neural network (CNN) was trained for classification into World Health Organisation (WHO) shape-based categories using the sperm head data sets HuSHeM and SCIAN. The algorithm was able to classify sperm with a high accuracy and performed well in comparison to other algorithms created using the same datasets. The authors concluded that their algorithm highlighted the potential for AI to exceed human experts in accuracy, reliability, and throughput.

2.3. Abbasi et al. (2021) created two deep learning algorithms for sperm morphology analysis, one using network based deep transfer learning approach and a second using Deep Multi-talk Transfer Learning. The algorithms were compared to a benchmark of the sperm morphology analysis dataset MHSMA. The two algorithms increased the accuracy of classifying the head, acrosome and vacuole of sperm by 6.66%, 3.00% and 1.33% respectively reaching accuracy rates of 84.00% (head), 80.66% (acrosome) and 94.00% (vacuole).

2.4. Tsai et al. (2020) reviewed the performance of a smartphone-based image recognition and cloud computing semen analysis system. The system allowed users to captured videos of sperm using a microscope and microfluidic modules that were designed to adapt to different types of smartphones. The video was then used to grade the sample according to the concentration of total and motile sperm and the sperm motility percentage. When compared to the grading of a professional with 10 years experience the system demonstrated good correlation for concentration of total sperm (r=0.65, P<.001), concentration of motile sperm (r=0.84, P<.001), and motility percentage (r=0.90, P<.001).

2.5. This home semen analysis AI technology is currently **available** in the UK, with 5 tests costing around £150. However, due to high demand, the current UK supplier is out of stock as of May 2021. Of note, semen analysis is not a **licensable activity**.

2.6. There is also a commercially available oocyte classification and prediction algorithm, **VIOLET**, with research presented as a short paper session at **Fertility 2021** (Nayot et al. 2020). This product is not currently available in the UK.

Embryo grading

2.7. Tran et al. (2019) tested the ability of their deep learning model, IVY, to predict the probability of fetal heart using outcome data and time-lapse imaging for 10638 embryos. The deep learning model was able to predict FH pregnancy from time-lapse videos with an area under the curve (AUC) of 0.93 in 5-fold stratified cross-validation. A hold-out validation test across eight laboratories showed that the AUC was reproducible, ranging from 0.95 to 0.90 across different laboratories with different culture and laboratory processes. Of note, this algorithm is used within **UK clinics**.

2.8. A study by Bormann et al. (2020) evaluated the consistency and objectivity of deep neural networks in embryo scoring and making decisions for biopsy and cryopreservation compared to trained embryologists. Embryologists exhibited a high degree of variability in grading embryos. When selecting blastocysts for biopsy or cryopreservation, embryologists had an average consistency of 52.14% and 57.68%, respectively. The neural network outperformed the embryologists in selecting blastocysts for biopsy and cryopreservation with a consistency of 83.92%.

2.9. VerMilyea et al. (2020) trained an AI based model using static two-dimensional optical light microscope images of 8886 embryos with known clinical pregnancy outcomes to provide a confidence score for prediction of pregnancy. Comparison to embryologists' predictive accuracy was performed using a binary classification approach and a 5-band ranking comparison. The results showed a combined accuracy of 64.3% across both viable and non-viable embryos. Binary comparison of viable/non-viable embryo classification demonstrated an improvement of 24.7% over embryologists' accuracy and 5-band ranking comparison demonstrated an improvement of 42.0% over embryologists. Of note this technology is commercially **available but not within the UK**.

2.10. Bormann et al. (2020) evaluated the use of a deep CNN, trained using single timepoint images of 742 embryos collected at 113 hours post-insemination and observed an accuracy of 90% in choosing the highest quality embryo available. Furthermore, a CNN trained to assess an embryo's implantation potential directly using a set of 97 euploid embryos capable of

implantation outperformed 15 trained embryologists (75.26% vs. 67.35%, p<0.0001) from five different fertility centers.

2.11. Chavez-Badiola et al. (2020) used 1231 static embryo images with known outcomes to train an Embryo Ranking Intelligent Classification Algorithm (ERICA). The group reviewed ERICA's ability to predict euploid embryos in comparison to ploidy prediction against randomly assigned prognosis labels and against senior embryologists, and the algorithms ability to grade euploidy embryos highly. An accuracy of 0.70 was obtained with ERICA, with positive predictive value of 0.79 for predicting euploidy. ERICA had greater normalized discontinued cumulative gain (ranking metric) than random selection (P = 0.0007), and both embryologists (P = 0.0014 and 0.0242, respectively). ERICA ranked a euploid blastocyst first in 78.9% and at least one euploid embryo within the top two blastocysts in 94.7% of cases, better than random classification and the two senior embryologists.

2.12. The use of AI to detect embryo ploidy from static images is available as a product to patients, both using **ERICA**, the algorithm discussed above, and **other providers**, although the executive have found no evidence of its use in the UK.

2.13. Also of note, a product called **PGTai 2.0** is offered within the UK with a claim of significantly increasing a patient's live birth rate, citing a conference paper (Buldo-Licciardi et al. 2020) presented at **ASRM 2020**. The technology uses an AI algorithm to analyse both copy number variation (CNV) and single nucleotide polymorphisms (SNP) and claims to detect ploidy, confirm genetic link to intended parents (or donors) and genetically identifies whether there are two pronuclei present.

Clinic processes

2.14. Letterie et al. (2020) created the first iteration of an AI algorithm to aid in vitro fertilisation (IVF) management including day-to-day decision making during ovarian stimulation. The algorithm was trained using 7376 clinic visits from 2603 treatment cycles and was used to predict four critical clinical decisions during ovarian stimulation for IVF. Algorithm accuracies for these four decisions are as follows: continue or stop treatment: 0.92; trigger and schedule oocyte retrieval or cancel cycle: 0.96; dose of medication adjustment: 0.82; and number of days to follow-up: 0.87. The group concluded that the algorithm was highly accurate and in agreement with evidence-based decisions by expert teams.

2.15. Lainas et al. (2020) created an algorithm that used measurements of grade of ascites, haematocrit, white blood cell count and maximal ovarian diameter in day 3 patients to predict the development of severe ovarian hyperstimulation syndrome (OHSS) on day 5 with an area under the curve of 0.93, a sensitivity of 88.5% and a specificity of 84.2% in high-risk patients triggered with hCG.

2.16. Noor et al. (2020) conducted a randomised control trial (RCT) to compare the oocyte yield using 3D automated and 2D ultrasound-based follicle tracking in women undergoing IVF-embryo transfer (IVF-ET). 130 patients were randomised into two groups, group A, follicular tracking using 3D Sonography- based Automated Volume Count (SonoAVC) and group B, follicular tracking was done by manual ultrasonography. The two groups had comparable treatment outcomes; however, Group B required more time for performing the scan. This result indicated an added advantage of saving time when applying artificial intelligence in follicular tracking.

2.17. A paper by Bormann et al. (2021) discusses the use of AI as part of the quality management system within a fertility clinic laboratory to monitor key performance indicators into staff competence for individual embryologists and culture conditions. The group suggests that this could be able to provide systemic, early detection of adverse outcomes, and identify clinically relevant shifts in pregnancy rates, providing critical validation for two statistical process controls: intracytoplasmic sperm injection (ICSI) fertilization rate and day 3 embryo quality.

2.18. Some UK licensed clinics offer their patients access to apps during their treatment cycle. These apps differ slightly in function but are largely used to offering medical and emotional support, managing appointments and receive notifications or communication from the clinic. Examples include **MediEmo**, **Dia** and **Salve**.

Outcome prediction

2.19. Barnett-Itzhaki et al. (2020) compared the machine learning algorithms support vector machine (SVM) and artificial neural network (NN) with logistical regression to predict IVF outcomes based on age and BMI. Machine learning algorithms (SVM and NN) based on age, BMI, and clinical features yielded better performances in predicting number of oocytes retrieved, mature oocytes, fertilized oocytes, top-quality embryos, positive beta-hCG, clinical pregnancies, and live births, compared with logistic regression models. While accuracies were 0.69 to 0.9 and 0.45 to 0.77 for NN and SVM, respectively, they were 0.34 to 0.74 using logistic regression models.

2.20. Apricity have **two outcome prediction tools** available on their website. The first 'The Fertility Treatment Predictor' was launched in 2019 and uses HFEA register data from 2010-2016 to predict the percentage chance of success for having a baby based on one cycle of IVF treatment. After asking a few questions about the length of time trying to conceive and known fertility issues the tool makes comparisons for chances of success between a patient having fresh and frozen embryo transfer, IVF and ICSI, and the risks of multiple pregnancy. However, to receive these individualised results a person is asked to input their name and email address and asked to give permission to contact the person for marketing purposes.

2.21. The second tool 'The Natural (Lifestyle) Fertility Predictor' was created in 2020 using results from a systematic review of 29 research papers (reference on the website). The papers looked at the effect of various lifestyle factors on fertility outcomes, either whilst undergoing fertility treatment or trying to conceive naturally. People can complete a short questionnaire about their lifestyle, including BMI, smoking status and alcohol intake. The tool will give them a percentage 'current chance of fertility' based on their age and lifestyle and a percentage 'optimum chance of fertility' based only on their age. The tool then makes recommendations for lifestyle changes to improve a person's chance of fertility, for example, 'quitting smoking multiplies your chances by x1.49'.

3. Conclusion

3.1. The use of AI in reproductive medicine could encompasses most aspects of a patient's treatment cycle, from patient management and clinical decision making to gamete and embryo grading.

3.2. There is a lack of high-quality research into the effectiveness of many of these algorithms, with few RCTs having taken place. There are also potential conflicts of interest with commercial companies often funding or being named authors on the research into their product.

3.3. Other concerns with the use of AI include a lack of transparency over decision making, a need for vast amounts of data for training models, a risk of unintended bias in training data and lack of accountability over each element of a model's output.

3.4. As suggested by the House of Lords Liaison Committee there is a need for regulators to identify gaps in regulation, and to learn about AI and apply it to their sectors. The use of AI in the fertility treatment would raise questions about how the Authority would inspect their suitability and appropriate use in centres as well as that of quality assurance systems in place. It is likely that regulators as currently resourced will need significant external support and guidance from government and professional expert bodies to be able to regulate AI and data-driven technologies effectively. This is an issue common to regulators globally in several sectors. For the time being, ongoing proactive efforts between HFEA and other health regulators are taking in order to share innovation and good practice so far as is possible, within the resources and legal powers that we currently have.

3.5. Despite concerns and regulatory questions, the use of AI in reproductive medicine is developing rapidly with new technologies frequently being introduced to the sector for commercial use, raising questions of prioritisation and resource for HFEA.

4. Recommendations

4.1. Members are asked to:

- advise the Executive if they are aware of any other recent developments in AI relevant to fertility treatment or research;
- discuss their views on the impact AI will have on fertility treatment as technology advances, including practical and ethical challenges to their application;
- discuss their views on the Authority's regulatory interest around AI systems – scope and limits; and
- review whether any outputs from the HFEA are currently required addressing the use of AI.

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