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

Wednesday 7th October 2026

Date	Action	Responsibility	Due date	Progress to date
03/06/2026	Issue a Clinic Focus article reminding clinics of the treatment add-ons consensus statement.	Dharmi Deugi, Scientific Policy Officer	07/10/2026	Actioned.
03/06/2026	Consider how research priorities could be highlighted.	Mina Mincheva, Policy Manager	07/10/2026	Actioned. Research priorities will be highlighted in Data Research Update Newsletters.
03/06/2026	Draft and publish treatment add-on information on microbiome testing to the website.	Dharmi Deugi, Scientific Policy Officer	07/10/2026	Actioned. Text has been approved by the Chair and published on the website.
03/06/2026	Draft and publish treatment add-on information on sperm DNA fragmentation testing to the website	Rebecca Taylor, Scientific Policy Manager	07/10/2026	Text has been approved by the Chair and will be published on the website.

Updating SCAAC horizon scanning and treatment add-on review processes

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (07/10/2026) 005
Meeting date:	7 October 2026
Author:	Rebecca Taylor, Scientific Policy Manager
Annexes	Annex A: Overview of current horizon scanning and add-on review processes

Output from this paper

For information or recommendation?	For recommendation

Decision:	Members are asked to:
	• consider the proposed updates and changes to SCAAC
	  ○ horizon scanning process
	  ○ treatment add-on review process
	And decide whether to
	• Approve as proposed
	• Amend further/differently
	• Revert to existing processes

Resource implications:	None
Implementation date:	From SCAAC decision
Communication(s):	Publication of committee papers, minutes. No other communications are envisaged.
Organisational risk:	Low

1. Background

2. HFEA Executive held a brainstorming meeting in July 2026 to think about ways to improve SCAAC horizon scanning and treatment add-on review rating processes. The focus was to identify ways to perform these tasks in a more efficient manner through streamlining processes further. This generated some ideas, which were then discussed further with the SCAAC Chair in August and refined. This paper further develops those ideas into concrete proposals for change.

Horizon scanning process

2.1. The HFEA's horizon scanning function is an annual cycle that feeds into HFEA business planning, the SCAAC workplan and the Authority's consideration of scientific and ethical matters. It comprises of the horizon scanning process (including 3 yearly literature reviews and topic specific papers), the annual HFEA horizon scanning meetings and Executive attendance at meetings and conferences.

2.2. The purpose of horizon scanning is to identify and monitor emerging and ongoing topics that impact the fertility sector and the regulatory remit of the HFEA.

2.3. Horizon scanning enables the HFEA to:

- Keep up to date with scientific and regulatory developments
- Build relationships with researchers and clinicians and strengthen the HFEA's reputation
- Use the knowledge gained to shape current and future work.

2.4. An overview of the current horizon scanning process can be found in Annex A.

Treatment add-on rating reviews

2.5. The aim of treatment add-ons rating reviews is to provide patients with an independent unbiased assessment of the evidence supporting the use of treatment add-ons. In particular, the reviews consider the evidence on whether an add-on is effective at improving live birth and/or other relevant outcomes.

2.6. An overview of the current treatment add-ons rating review process can be found in Annex A.

3. Proposed changes to Horizon Scanning Process

3.1. Currently the Executive should undertake a full literature search of all topics every three years in addition to topic papers including literature reviews for each topic being brought to SCAAC meetings every 2-3 years. The resource/workload implications of this full literature search arguably outweigh the additional value it brings.

3.2. It is proposed that the full literature search of all topics every three years is replaced by a system of ongoing monitoring to assess whether a paper of each horizon scanning topic is needed.

3.3. The Executive will develop a monitoring plan that would include undertaking and recording the results of:

- Regular OVID alerts
- Relevant studies in clinical and scientific databases
- Upcoming and published studies flagged by SCAAC members under agenda item 4

- Media monitoring
- Blogs/live discussions from key journals
- International regulators
- Professional society agendas
- Monitoring online and other advertising
- Intelligence from conferences

3.4. The possibility of using AI to assist this monitoring will be investigated and its implementation feasibility considered.

3.5. The monitoring will be used to identify:

- Significant scientific developments or progress
- Evidence likely to affect regulation
- Emerging ethical and regulatory concerns
- New topics

3.6. The results of the monitoring would feed into the yearly work planning and prioritisation that takes place at the February SCAAC meeting.

3.7. It is proposed to introduce this new approach starting in 2027. Should SCAAC consider it necessary, a review of the new approach could be put on the SCAAC agenda after one year of implementation.

4. Proposed changes to treatment add-on rating review process

4.1. Currently, a full review of all treatment add-ons should be undertaken every 5 years as agreed by the SCAAC and the Authority. The last review took place in 2023, so the next review is due in 2028, but the work would start in 2027.

4.2. A full review of all add-ons is a significant and resource intensive task which involves:

- The Executive undertaking a 5-year literature search for 17 add-ons to identify new studies as per the evidence decision tree for rating treatment add-ons:
  - If the add-on was previously reviewed with 3 good RCTs, only new RCTs would be sought.
  - If the add-on was previously reviewed with NRSIs, RCTs and NSRIs would be sought.
- If no new studies are identified, no review takes place and this outcome is reported to SCAAC.
- Statistical analysis of previous and any new studies for each add-on by an external expert statistician where new studies are identified.
- Statistician's report and new recommended rating for each add-on where new studies are identified.
- The Executive prepare a background paper on the add-on review
- SCAAC consideration of the background paper and statistician's report and rating for each add-on where new studies are identified.

4.3. A new two-phase approach is proposed which would result in an add-on only being reviewed if necessary. This would involve:

- Phase 1 (partial) review: A SCAAC panel comprising the chair and one or two SCAAC members with appropriate expertise would be convened to assess whether the new studies identified merit a review being undertaken.

- Should the panel decide the studies do not merit a statistician review of the add-on rating, then this would be recorded and no further review (phase 2 review) would take place. In addition, the HFEA website would be updated to inform the public that the add-on rating had been subject to a phase 1 review.
- Phase 2 (full) review: Should the panel decide a full review including statistician's review is needed, the newly identified studies will be shared with one of the external expert statisticians for a revised statistical analysis using GRADE methodology. The statistician will prepare a report with suggested new rating, which would go to SCAAC for consideration and decision on the rating along with a background paper.

5. Recommendations

5.1.

Members are asked to:

- consider the proposed updates and changes to SCAAC horizon scanning process and treatment add-on review process

And decide whether to:

- Approve as proposed
- Amend further/differently
- Revert to existing processes

Annex A: Overview of current horizon scanning and add-on rating review processes

Horizon scanning

Step/stage/task	Details	Proposal to change?
Horizon scanning criteria for topic inclusion	• Within HFEA remit • Timescale for likely introduction (now or within 3 years) • High patient demand/clinical use if introduced • Technically feasible • Ethical issues raised or public interest	No
Topic prioritisation and workplan agreed at February SCAAC meetings	• Executive proposes topic prioritisation – high, medium, low and watching brief • Proposed prioritisation is presented to February SCAAC meeting for Committee consideration and decision. • SCAAC workplan, including horizon scanning activities, is agreed.	No
Literature searches	• OVID Medline is used to undertake literature searches for horizon scanning (agreed in 2025, first introduced ahead of February 2026 SCAAC meeting) • Identified studies are run through retraction tool (agreed in 2025, first introduced ahead of February 2026 SCAAC meeting).	No
SCAAC papers for priority topics	• Literature search that covers period since last review (typically every 2-3 years) for review in a meeting paper. • 10-year literature search performed for any new topic. • Paper provides a summary of research developments and spreadsheet of studies as annex (latter introduced February 2026). • Frequency of reviews depends on prioritisation of topic and whether there are known to be new developments. • External experts are invited to present on some priority topics.	No
All topic literature search	• Undertaking a literature search of all high, medium and low priority topics.	Yes

	• A spreadsheet of studies for each topic is presented to the SCAAC every 3 years as part of the prioritisation and workplan discussions at the February meetings. This is to help prioritise topics and identify new ones.	
SCAAC agenda standing item	• Standing item on every SCAAC meeting agenda on "Relevant public health developments and research findings". This is designed to help identify new developments in priority topics between SCAAC papers.	No
Annual HFEA horizon scanning meeting	• Invite only international meeting held alongside ESHRE annual meeting focusing on new/future developments.	No

Treatment add-on rating review

Step/stage/task	Details	Proposal to change?
Treatment or test add-ons criteria for rating consideration	An application can be made if an add-on is offered to patients in UK clinics and the following apply: • Claim that the add-on will increase live birth rate and/or improve other treatment outcomes; • No conclusive evidence of the add-on's effectiveness at improving live birth rate or other outcomes; • Not on HFEA's rated list of add-ons; or • Evidence that the add-on may reduce treatment effectiveness or has potential safety concerns • There is new evidence about an add-on already on the HFEA's rated list.	No
SCAAC decision	• SCAAC considers applications for including an add-on and decides whether it meets the criteria for inclusion on the HFEA's list of rated add-ons.	No
SCAAC review panel	• SCAAC review panel is convened comprising Committee Chair plus one or two members with relevant expertise. • Panel agrees relevant patient groups and outcomes to be evaluated.	No
Literature search	• 10-year literature search uses OVID Medline to find relevant studies. • RCTs and systematic reviews are sought in first instance.	No

	• If there are 3 good RCTs, no NRSIs (non-randomised studies of intervention) are sought. • If there are insufficient RCTs, NRSIs are also sought.	
Statistical analysis	• An external expert statistician undertakes statistical analysis using GRADE methodology on the studies identified. • Statistician prepares report outlining the statistical analysis with suggested rating	No
SCAAC decision	• SCAAC considers a background paper and the statistician's report and agrees a rating.	No
Publication	• Executive drafts text for publication on HFEA website. • Text is reviewed by Chair and panel members (if needed). • Text is reviewed by PEF (Patient Engagement Forum) volunteers. • SCAAC Chair final sign-off.	No
Periodic review of add-on ratings	• Add-on ratings are reviewed every 5 years (agreed in February 2024). • Literature search identifies new evidence, and an external expert statistician performs analysis again and prepares an updated report and recommended rating. • SCAAC considers a background paper and the statistician's reports on all add-ons and agrees a rating. • Between reviews Committee and Executive monitors publication of studies that could be significant enough to trigger an ad-hoc review of the rating of an existing add-on (through standing agenda item 4 "Relevant public health developments and research findings").	Yes

New process application- Calcium ionophore for embryo development

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item	6
Paper number	HFEA (07/10/2026) 006
Meeting date	7 October 2026
Author	Dharmi Deugi, Scientific Policy Officer
Annexes	Annex A – New process application form Annex B – Supporting evidence Annex C – Authorised processes decision tree Annex D – Authorised processes list

Output from this paper

For recommendation or decision?	For decision
Recommendation:	Members are asked to: • consider whether the process is a new process that requires authorisation; • consider whether there the evidence is sufficient to satisfy the Committee that the process does not render the tissues or cells clinically ineffective or harmful to the recipient; and • consider whether there is any evidence to indicate that the process renders the tissues and cells harmful to the recipient (including the resulting child). • if the Committee authorises the process, to define the criteria for mandatory reporting as per General Direction 0008; and • consider and define any conditions for authorisation (if applicable).

Resource implications:	TBC
Implementation date:	Following SCAAC discussion
Communication(s):	As needed
Organisational risk:	Low

1. Introduction

1.1. As the UK regulator of fertility clinics, the HFEA maintains a list of authorised processes, which was first introduced in May 2011, that clinics can use to carry out the licensable activities set out in the Human Fertilisation and Embryology Act 1990 (as amended), (the HFE Act). If a centre wishes to carry out a process which does not appear on the list, it must apply to the Authority for permission. In March 2024, the Authority approved revisions to the authorised processes list and delegated the authorisation of new processes to the Scientific and Clinical Advances Advisory Committee (SCAAC) in March 2024.

1.2. SCAAC should consider a new process application as follows (see Annex B for authorised processes decision tree):

1.2.1. SCAAC should agree that the process is sufficiently different from any of the processes currently authorised to be considered as new.

1.2.2. The Committee should make a judgement on whether the evidence is sufficient to satisfy committee members that the process does not render the tissues or cells clinically ineffective or harmful to the recipient. In the event of the evidence not being fully conclusive, SCAAC members should use their judgement based on a compound level of risk and the strength of the evidence.

1.2.3. If approved, the SCAAC define the criteria for mandatory reporting including the data requirements (KPIs), timeframe and intervals for reporting. The HFEA Executive propose that SCAAC consider a standard 3-year initial period of mandatory reporting upon approval to ensure that the use of a new authorised process is reconsidered within a minimum timeframe. Depending on the perceived level of risk associated with the process or its anticipated frequency of use, the SCAAC may wish to reduce the timeframe for mandatory reporting to enable reconsidering a process at an earlier date.

1.2.4. If upon reconsideration of an authorised process, the evidence to support its ongoing use (arising from mandatory reporting requirements) is inconclusive, the SCAAC may:

a) reinstate/extend the requirement for mandatory enhanced reporting,
b) place additional conditions on the use of a process (eg restrict the process to a defined patient group),
c) monitor on a more regular basis through committee discussions, or
d) (in exceptional circumstances) suspend the process until a decision can be taken.

1.3. Regarding activities with a research purpose, the Licence Committee grants research licenses for activities specified in Paragraph 3 (1), (2) or (3), or Paragraph 2 (1) or (1A) of Schedule 2 in the HFE Act (as amended). Briefly summarised these are:

- bringing about the creation of embryos (or human admixed embryos) in vitro for the purposes of a project of research
- keeping or using embryos (or human admixed embryos) for the purposes of a project of research
- mixing sperm with the egg of a hamster, or other animal specified in directions, for the purpose of developing more effective techniques for determining the fertility or normality of sperm, but only where anything which forms is destroyed when the research is complete and, in any event, no later than the two cell stage

1.4. The research activities applied for are considered against the relevant licensable activities under Paragraph 1 (1) of Schedule 2 of the HFE Act (as amended). The Authority grants a research licence for one or more of the permitted research purposes defined in Paragraph 3A (1) and (2) of Schedule 2 in the HFE Act (as amended). Research licences are not required to conduct research on sperm or eggs.

1.5. The authorised processes list has been designed to encompass high-level processes, focusing on processes more broadly rather than on different methodologies used to perform them and the purpose(s) for which they may be used. This means that there may be several methodologies and purposes by which an authorised process can be undertaken, unless specified by the Authority. Fertility clinics that hold an HFEA licence are permitted to undertake the appropriate authorised process as part of their clinical practice, in accordance with the licence they hold.

1.6. The current use of calcium ionophore is approved for artificial oocyte activation (AOA) as an HFEA authorised process under "processing gametes". Calcium ionophore for AOA was reviewed by the SCAAC in 2018: Reviewing novel processes: egg activation with calcium ionophore where the SCAAC decided that it should remain on the authorised processes list.

1.7. At the October 2023 SCAAC meeting, the Committee confirmed that clinics using calcium ionophore for AOA are expected to do so in accordance with relevant professional body (ACRS/BFS) guideline. The SCAAC considered the use of Calcium Ionophore as an egg activation technique and highlighted the theoretical risks relating to embryo viability (eg, premature activation and triploid embryos). Given the theoretical risks of Calcium Ionophore activation, centres using it are expected to do so only in selected patients, such as those with PLCz deficiency, or in accordance with professional guidelines. Centres are expected to document their rationale for using Calcium Ionophore for individual cases. As with all treatments and processes, centres should ensure that patients are fully informed about the efficacy and potential risks and that validation is carried out.

2. Recommendations

2.1. Members are asked to:

- consider whether the process is a new process that requires authorisation;
- consider whether the evidence is sufficient to satisfy the Committee that the process does not render the tissues or cells clinically ineffective or harmful to the recipient; and
- consider whether there is any evidence to indicate that the process renders the tissues or cells harmful to the recipient (including the resulting child).
- if the Committee authorises the process, to define the criteria for mandatory reporting as per General Direction 0008; and
- consider and define any conditions for authorisation (if applicable).

3. Annex A – New process application form

Application to authorise a new process to carry out a licensed activity

1. Introduction

The Authorised processes list describes the processes clinics can use to carry out the licensable activities set out in the Act.

If you wish to use a process, which does not appear either on the authorised or the prohibited processes lists, you will need to apply to the HFEA to seek permission to use it in clinical practice.

Please note certain processes may be subject to prohibitions under the HFE Act and therefore cannot be authorised. Please contact your clinic inspector if you are uncertain whether authorisation of a new process is in conflict with the Act.

This application form should be used by centres that wish to carry out a licensed activity using a process that has not previously been authorised by the Authority.

2. The authorisation process

Applications will be reviewed by the HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) who will:

- consider whether the process is a new process that requires authorisation;
- consider whether there is evidence to suggest that the process renders the tissues and cells ineffective; and
- consider whether there is any evidence to indicate that the process renders the tissues and cells harmful to the recipient (including the resulting child)[1].

It is therefore important that applications contain sufficient evidence to allow the Committee to make an assessment of the effectiveness and the potential harm of the process. If the SCAAC is not provided with sufficient evidence they may adjourn their decision until additional information has been provided, which will delay processing of the application.

[1] Such requirements are derived from the third Directive of the European Tissues and Cells Directive, retained in UK legislation by the Retained EU Law (Revocation and Reform) Act 2023. Further details of the statutory requirements are set out in the March 2024 Authority paper. For information on processes excluded under Recital 6, please contact your clinic inspector.

A process may be restricted to use in a sub-population of patients where the evidence suggests that its application in the wide patient group is lacking or would not meet the legal requirements (eg egg activation using calcium ionophore). When providing evidence, please ensure that it is clear which patient population the evidence has been derived from.

The SCAAC will then decide whether or not to add the process to the authorised processes list and determine which licensed activity/activities the process should fall under. If it decides that it should add the process to the authorised processes list, any clinic or laboratory may use the process (subject to any conditions imposed by SCAAC), provided they are licensed to carry out the associated licensed activity.

Upon approval, the process will then be subject to an initial period of mandatory reporting as set out by section D of General Direction 0008. The criteria for reporting will be determined by the SCAAC during the consideration of the application.

It is important that the language used in this application is clear and as far as possible, understandable to non-specialists. All abbreviations should be explained.

New process application form

1. Current centre information

Person Responsible: Rehan Salim

Centre name: Lister Fertility at The Portland Hospital

Centre number: 0387

2. Process details

2.1. What is the name of the process?

Use of Calcium Ionophore to Support Blastocyst Development

2.2. To which cell or tissue type(s) is the process applied?

Oocytes

2.3. Please provide a description of the process and its intended purpose/application.

Note: Please indicate whether you plan to implement this process as part of a clinical trial.

This application seeks approval for a novel laboratory process involving the controlled use of calcium ionophore following ICSI for blastocyst development. The process would be applied selectively to patients with a documented history of poor or absent blastocyst development despite adequate fertilisation. For this process application specifically, it would be used for patients with a history of poor or absent blastocyst development. The use of calcium ionophore would still be applied for patients with poor fertilisation where appropriate under the current HFEA authorised process under “processing gametes”. There may be some patients who fall into both treatment groups

The proposed process extends the established use of calcium ionophore beyond fertilisation rescue, targeting patients where impaired downstream embryonic development is suspected to be related to deficient calcium-mediated signalling. Following ICSI, oocytes are briefly exposed to a calcium ionophore solution (as per manufacturer's instructions; see attached SOP) and subsequently cultured under standard laboratory conditions.

This is not part of a clinical trial.

3. Licensed Activity

3.1. Please indicate which licensed activity/activities the new process is applicable to:

Activity	
Procuring gametes	☐
Keeping gametes	☐
Processing gametes	☒
Distribution of gametes	☐
Use of gametes	☐
Storage of gametes	☐
Storage of embryos	☐
Creation of embryos	☐
Procuring embryos	☐
Keeping embryos	☐
Testing gametes	☐
Testing embryos	☐
Processing embryos	☐
Distribution of embryos	☐
Placing any permitted embryo in a woman	☐
Using embryos in training	☐

3.2. Is this an application to extend the use of an existing process (for example to remove conditions of authorisation, such as its use in a restricted population)? If so, please indicate which authorised process this relates to:

Yes. The process applied for is to extend the use of calcium ionophore for artificial oocyte activation (AOA) which is an HFEA authorised process under "processing gametes".

4. Evidence to support application

Effectiveness

4.1. Please provide a summary of the evidence that demonstrates that this process does not render the tissues or cells clinically ineffective, clearly indicating the patient populations from which the evidence is derived (if relevant). Include copies of any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include data from animal studies, research on human embryos or clinical trial data.

Note: this should include all available evidence including that which may indicate ineffectiveness.

Review of the literature

Calcium ionophore-assisted oocyte activation (AOA) has been used clinically for more than two decades as an adjunct to intracytoplasmic sperm injection (ICSI), primarily in cases of previous total fertilisation failure, low fertilisation rates, or suspected oocyte activation deficiency. Published studies demonstrate that embryos derived from oocytes exposed to calcium ionophore can progress through cleavage-stage development and blastocyst formation at rates comparable to, or in specific patient populations (previous low fertilisation or poor embryo development groups) higher than, those achieved following conventional ICSI. These studies have reported improvements in fertilisation rate, implantation rate, clinical pregnancy rate, and live birth rate without evidence of adverse effects on embryo morphology or developmental competence (Ebner et al., 2015, Ruan et al., 2023, Kim et al., 2023).

As such, the available evidence indicates that exposure of oocytes to calcium ionophore under controlled laboratory conditions does not appear to adversely affect embryo development, showing that AOA application does not render embryos clinically ineffective. On the contrary, its selective application has been associated with improved blastocyst formation and sustained implantation potential in patient groups where conventional approaches have repeatedly failed (Shan et al., 2022; Zhang et al., 2025).

The outcome of specific use of AOA for patients with previously reported poor embryo development is limited and consists predominantly of retrospective observational studies, with most of the studies confined to the poor fertilisation patient groups (Chen et al., 2022, Zhang et al., 2025). Whilst mixed, these studies have largely shown a beneficial outcome on embryo development in poor embryo development patients (Ebner et al., 2015, Ruan et al., (2023) Karagianni et al., 2026) although it may be restricted to certain age groups (Chen et al., 2022). However, under certain conditions AOA has shown not to improve blastocyst development for poor embryo development patients, but the methodology in this paper involved a double application process and may not be comparable (Cardona Barberán et al., 2023).

In-house studies

The information on in-house studies, pages 17-19, has been removed for confidentiality reasons.

4.2. To ensure patient safety all products that come into contact with patients, gametes and embryos must be appropriately CE marked (Class IIa) and approved by the relevant UK Approved Body prior to application.

Please list all reagents and materials used in the new process that come into contact with patients, gametes or embryos, providing details of the supplier and quality/safety specification. Please expand the below table as necessary.

Note: If authorised, this process may be used by other licensed centres, and it is acknowledged that there may be variations in the reagents used however any clinic using the process will be expected to show that they are using products of similar specification with the necessary CE marking to those referenced below.

Reagent/material	Manufacturer or supplier	Product code	Specification e.g. CE marking (specify level and approved purpose), clinical grade, reagent grade, etc.
CultActive (GM508)	Gynemed (Nexpring)	4 GM 508CULT-active1	CE IVD European Pharmacopoeia and/or USP standard (see attached risk assessment re use of a non-CE marked product)

Safety and risks

4.3. Please provide a summary of the evidence that demonstrates that this process does not render the tissues and cells harmful to the recipient (including the resulting child).

Clearly indicate the patient populations from which the evidence is derived (if relevant). Include copies of any relevant published and/or unpublished data as appendices to this form. For example you may wish to include data from animal studies, research on human embryos, or clinical trials data.

Note: this should include all available evidence including that which may indicate potential harm.

A systematic review and meta-analysis published Shan et al., (2022) evaluated 22 clinical studies investigating calcium ionophore AOA. The review found that use of calcium ionophore was associated with improved fertilisation, implantation, clinical pregnancy, and live birth rates in appropriately selected patients (reduced fertilisation or oocyte activation groups or with globozoospermia). Importantly, the analysis found no evidence of increased miscarriage rates or adverse neonatal outcomes among pregnancies resulting from AOA compared with conventional ICSI.

The same meta-analysis specifically assessed available neonatal safety data and reported no increase in the incidence of congenital birth defects among children born following calcium ionophore AOA compared with standard ICSI treatment. The authors concluded that current

evidence does not indicate an increased risk of congenital abnormalities attributable to calcium ionophore exposure.

Although few, there are several studies on the continuous follow-up of children born after AOA. These have shown that neurodevelopmental outcome of children aged between 12 and 60 months (Miyazaki et al., 2025) and 3 and 10 years (Vanden Meerschaut et al., 2014) is within expected ranges as is their language development (D'haeseleer et al., 2018). A further small study also showed that children followed to the age of 6 showed no influence of calcium ionophore on physical development, although one baby was shown to be trisomy 21 (age of the patient was not stated). However, it is difficult to make conclusions from this given the very small size of the study and the unknown age of the patient where the trisomy was seen which is likely to influence the chance of this occurring (Irie et al., 2018).

The concerns associated with the use of AOA appear to be more theoretical in nature concerning the possible unknown epigenetic consequences of calcium ionophore exposure which have not been adequately investigated as represented by the lack of studies examining gene expression profiles or epigenetic modifications in this treatment group (Ebner and Montag, 2016, Bolton et al., 2023). To date, no large human studies have demonstrated increased rates of imprinting disorders (e.g., Beckwith–Wiedemann syndrome, Angelman syndrome, Silver–Russell syndrome) and direct molecular studies examining DNA methylation and epigenetic programming in offspring remain very limited. However, a study has shown that that when AOA was used the alteration in gene expression was less than expected compared with conventional IVF. Indeed, the combination of ICSI with a chemical activation step resulted in a gene expression pattern that was found to be closer to IVF than to ICSI alone, suggesting that AOA effectively mimics the fertilisation process (sperm entry) at the genetic level (Bridges et al., 2011).

In summary, the data provided largely from patient cohorts in the low or no fertilisation group have shown that where AOA was used during ART, birth characteristics, congenital malformation rates, growth parameters and early childhood development have been reported to be within expected ranges for ART populations, with no consistent evidence of increased adverse outcomes. As such, this could be similarly applied to the use of AOA for embryo development. Whilst the current evidence is reassuring and does not indicate harm to the resulting child, the centre recognises that continued long-term follow-up remains warranted as the number of children assessed remains relatively small and data regarding long-term neurodevelopmental and epigenetic outcomes are limited.

4.4. Please indicate if any professional body guidance, UK or international, covers the use of this process:

To our knowledge, calcium ionophore has not been covered under UK or international professional body guidance for the specific purpose of poor embryo development/blastulation.

4.5. Please note that clinics using this process will be expected to be able to show that they:

- will provide suitable information to patients about the nature of the treatment including any consequences and risks arising as a result of the use of this process;
- that staff have been suitably trained in the application of the new process and can provide evidence of the assessment of their competence;
- that the process and any equipment used in the process has been fully validated;
- there are mechanisms in place for monitoring the effectiveness of the process through regular audit.

Please provide brief details of your plans, with timelines, to ensure that these requirements are met.

Patients are provided with suitable information about the nature of the treatment which includes the potential risks arising as a result of the use of this process. Patients are made aware that this is considered as an experimental process. Patient information and consent form for use of calcium ionophore for blastocyst development attached.

Staff involved in the application of calcium ionophore have been suitably trained in its application and are required to undergo a competency assessment. A formal competency assessment is in place for the use of calcium ionophore following ICSI (attached) and assigned to all ICSI practitioners.

There is no specialised equipment required for the use of calcium ionophore other than standard ability to move and transfer oocytes between solutions at the designated times as per the protocol. No additional equipment is used for the processing of gametes using calcium ionophore to that already in place for reduced/failed fertilisation. SOP for use of calcium ionophore attached.

Mechanisms in place for monitoring the effectiveness of the process through regular audit.:

Annual audit of treatment outcomes where calcium ionophore is used – plan for next audit November 2026 for patients already in use (the data included in this report summarises the audit between 2023-2025. Audit to include, fertilisation, blastulation, utilisation, PGT-A outcome and clinical pregnancy rates.

Going forward, the centre has had discussions with the Portland Hospital Director of Quality and Risk and one of the hospital's fetal medicine specialist with regard to development of the most appropriate monitoring strategies.

Following the use of calcium ionophore in treatment (segregated by reason for use in treatment) a validated questionnaire will be issued to all parents of children born where ionophore was used at annual intervals (some may only be appropriate at certain ages).

Birth and Pregnancy

Were there any problems during the pregnancy?

Were there concerns on ultrasound scans?

Was the baby born on time, early, or late?

What was their birth weight?

Did they require special care, NICU admission, or resuscitation?

Were there any feeding difficulties in the newborn period?

Did anyone comment on unusual physical features at birth?

General Health and Physical Development

Growth

- What is your child's current height and weight?
- Has your child been following a normal growth pattern according to healthcare professionals?
- Has your child ever been diagnosed with growth delay or growth acceleration?

General Health

- How would you rate your child's overall health?
- Does your child have any chronic medical conditions?
- Has your child required hospital admission? If so, for what reason and at what age?
- Is your child taking any regular medications?

Vision and Hearing

- Has your child been diagnosed with any vision problems?
- Does your child wear glasses?
- Has your child had any hearing difficulties or hearing assessments?

Motor Development

- At what age did your child:
    - Sit unsupported?
    - Crawl?
    - Walk independently?
- Has your child experienced difficulties with balance, coordination, or fine motor skills?

Neurodevelopmental Milestones

Early Development

- Were there any concerns raised by health visitors, paediatricians, or teachers regarding development?
- Did your child meet developmental milestones within the expected age range?

Speech and Language

- At what age did your child say their first words?
- At what age did your child begin using sentences?
- Has your child received speech and language therapy?
- Do you have any concerns about communication skills?

Learning and Cognition

- Does your child learn at the same pace as their peers?
- Has your child experienced difficulties with memory, attention, or problem solving?

- Has your child undergone any educational or psychological assessments?

Behavioural and Emotional Development

Behaviour

- Have there been concerns about hyperactivity, impulsivity, or inattention?
- Does your child have difficulty following instructions or completing tasks?
- Have teachers expressed concerns regarding behaviour?

Social Development

- Does your child make and maintain friendships easily?
- Does your child participate in social activities with peers?
- Are there concerns regarding social interaction or communication?

Emotional Wellbeing

- Have there been concerns regarding anxiety, low mood, or emotional regulation?
- Has your child received support from mental health services?
- How would you rate your child's emotional wellbeing?

Neurodevelopmental Diagnoses

Has your child ever been diagnosed with:

- Autism Spectrum Disorder (ASD)?
- Attention Deficit Hyperactivity Disorder (ADHD)?
- Learning disability/intellectual disability?
- Developmental coordination disorder (dyspraxia)?
- Speech and language disorder?
- Dyslexia?
- Other neurodevelopmental conditions?

If yes:

- At what age was the diagnosis made?
- Who made the diagnosis?
- What support or interventions are currently being provided?

Educational Outcomes

- What type of school does your child attend?
- Does your child require additional educational support?
- Does your child have an Education, Health and Care Plan (EHCP) or equivalent?
- Are academic achievements in line with age expectations?
- Have there been concerns raised by teachers regarding learning or behaviour?

Physical Activity and Daily Function

- Does your child participate in sports or physical activities?
- Can your child perform age-appropriate self-care activities independently?
- Are there limitations in daily activities due to physical or developmental issues?

Quality of Life

- How would you rate your child's quality of life?
- Does your child's health affect school attendance?
- Does your child's health affect family activities?
- Are there any ongoing health or developmental concerns not already discussed?

5. Declaration

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

Signature: 

Date: 15 September 2026

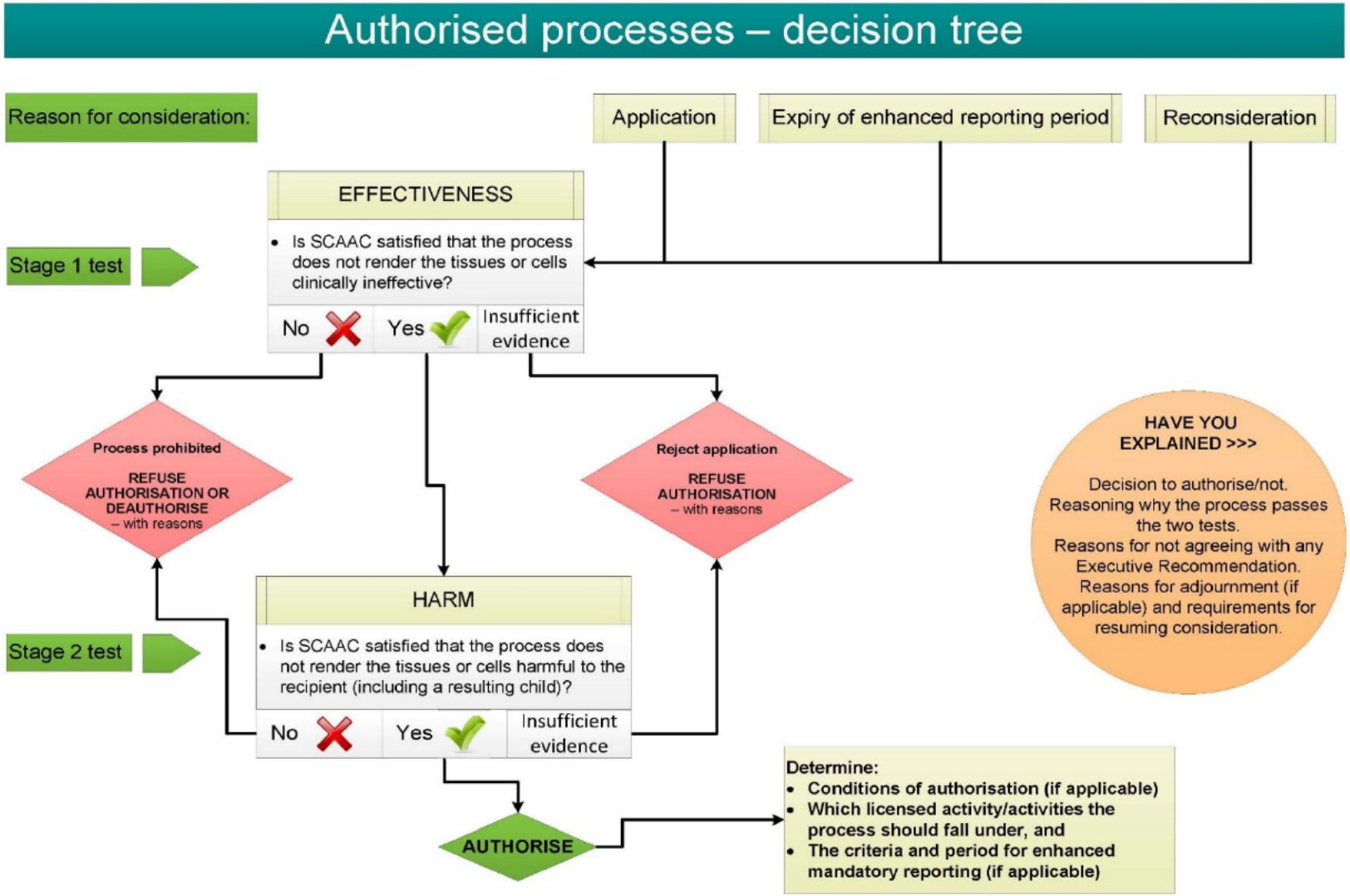
This must be completed by the Person Responsible of the licensed centre applying for authorisation of the process. The form should then be submitted, with any associated papers and information to your inspector.

4. Annex B – Supporting evidence

4.1. Provided as separate files:

- Calcium ionophore for embryo development – Supporting information
- Calcium ionophore for embryo development – References

5. Annex C – Authorised processes decision tree



6. Annex D – Authorised processes list

Licensed activity	Authorised processes
Procuring gametes	Egg collection Surgical sperm collection Ovarian tissue collection Testicular tissue collection
Keeping gametes	Culture of eggs Culture of sperm
Processing gametes	Semen preparation (including the use of reagents to increase sperm motility) Egg preparation Grading of gametes In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles) Cryopreservation of gametes Thawing/re-warming gametes Polar body biopsy Egg activation using Calcium Ionophore (only in selected patients or in accordance with professional guidelines* - see below for further guidance)
Distribution of gametes	Transfer of sperm between centres Transfer of eggs between centres Supply of sperm from a licensed centre to unlicensed premises in thawed or thawing state for home insemination - this should only be done in **exceptional circumstances** as per the Code of Practice
Use of gametes	IUI GIFT IVF ICSI

Licensed activity	Authorised processes
Storage of gametes	Cryopreservation of eggs Cryopreservation of sperm Cryopreservation of testicular tissue (HTA licence may be required depending on the reasons for storage and intended use) Cryopreservation of ovarian tissue (HTA licence may be required depending on the reasons for storage and intended use)
Storage of embryos	Cryopreservation of embryos (including at the pronucleate and blastocyst stage)
Creation of embryos	IVF ICSI
Procuring embryos	Lavage
Keeping embryos	Culture system
Testing gametes	Genetic testing associated with polar body biopsy
Testing embryos	PGT-M PGT-A PGT-SR PTT (formerly PGD-HLA)**
Processing embryos	Culture Biopsy Assisted hatching Embryo grading (including non-invasive assessments, see T91 for limitations) Manipulation Thawing/re-warming of blastocysts and embryos Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same person)

Licensed activity	Authorised processes
Distribution of embryos	Transfer of embryos between centres
Placing permitted embryo in a woman	Embryo transfer
Using embryos in training	Embryo biopsy Blastocyst biopsy Cryopreservation and thawing/re-warming techniques Assisted hatching Embryo handling and manipulation Assessment of embryos

*The HFEA's **Scientific and Clinical Advances Advisory Committee (SCAAC)** considered the use of Calcium Ionophore as an egg activation technique and highlighted the theoretical risks relating to embryo viability (eg, premature activation and triploid embryos). Given the theoretical risks of Calcium Ionophore activation, centres using it are expected to do so only in selected patients, such as those with PLCz deficiency, or in accordance with professional guidelines. Centres are expected to document their rationale for using Calcium Ionophore for individual cases. As with all treatments and processes, centres should ensure that patients are fully informed about the efficacy and potential risks and that validation is carried out.

In August 2023, the Association of Reproductive and Clinical Scientists (ARCS) and the British Fertility Society (BFS) published 'The use of ICSI in ART: Evidence for practice' which includes guidelines on the best practice use of artificial egg activation.

The use of pre-implantation tissue typing (PTT), also known as human leukocyte antigen (HLA) tissue typing, requires patient-specific authorisation. Should you wish to undertake PTT, an application can be made via the Clinic Portal 'New licences, returns and applications' webpage. An application must be made for each patient case. For further information, please contact the PGTM team at **pgtm@hfea.gov.uk.

New process application- In Vitro Maturation of immature oocytes recovered during ovarian tissue processing

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item	7
Paper number	HFEA (07/10/2026) 007
Meeting date	7 October 2026
Author	Mina Mincheva, Policy Manager
Annexes	Annex A – New process application form Annex B – Supporting evidence Annex C – Authorised processes decision tree Annex D – Authorised processes list

Output from this paper

For recommendation or decision?	For decision

Recommendation:	Members are asked to: • consider whether the process is a new process that requires authorisation; • consider whether the evidence is sufficient to satisfy the Committee that the process does not render the tissues or cells clinically ineffective or harmful to the recipient; • consider whether there is any evidence to indicate that the process renders the tissues or cells harmful to the recipient (including the resulting child); • If the Committee authorises the process, to define the criteria for mandatory reporting as per General Direction 0008; • consider and define any conditions for authorisation (if applicable).
Resource implications:	TBC
Implementation date:	Following SCAAC discussion
Communication(s):	As needed
Organisational risk:	Low

1. Introduction

1.1. As the UK regulator of fertility clinics, the HFEA maintains a list of authorised processes, which was first introduced in May 2011, that clinics can use to carry out the licensable activities set out in the Human Fertilisation and Embryology Act 1990 (as amended), (the HFE Act). If a centre wishes to carry out a process which does not appear on the list, it must apply to the Authority for permission. In March 2024, the Authority approved revisions to the authorised processes list and delegated the authorisation of new processes to the Scientific and Clinical Advances Advisory Committee (SCAAC) in March 2024.

1.2. SCAAC should consider a new process application as follows (see Annex B for authorised processes decision tree):

1.1.1. SCAAC should agree that the process is sufficiently different from any of the processes currently authorised to be considered as new.

1.1.2. The Committee should make a judgement on whether the evidence is sufficient to satisfy committee members that the process does not render the tissues or cells clinically ineffective or harmful to the recipient. In the event of the evidence not being fully conclusive, SCAAC members should use their judgement based on a compound level of risk and the strength of the evidence.

1.1.3. If approved, the SCAAC define the criteria for mandatory reporting including the data requirements (KPIs), timeframe and intervals for reporting. The HFEA Executive propose that SCAAC consider a standard 3-year initial period of mandatory reporting upon approval to ensure that the use of a new authorised process is reconsidered within a minimum timeframe. Depending on the perceived level of risk associated with the process or its anticipated frequency of use, the SCAAC may wish to reduce the timeframe for mandatory reporting to enable reconsidering a process at an earlier date.

1.1.4. If upon reconsideration of an authorised process, the evidence to support its ongoing use (arising from mandatory reporting requirements) is inconclusive, the SCAAC may:

a) reinstate/extend the requirement for mandatory enhanced reporting,
b) place additional conditions on the use of a process (eg restrict the process to a defined patient group),
c) monitor on a more regular basis through committee discussions, or
d) (in exceptional circumstances) suspend the process until a decision can be taken.

1.3. Regarding activities with a research purpose, the Licence Committee grants research licenses for activities specified in Paragraph 3 (1), (2) or (3), or Paragraph 2 (1) or (1A) of Schedule 2 in the HFE Act (as amended). Briefly summarised these are:

- bringing about the creation of embryos (or human admixed embryos) in vitro for the purposes of a project of research
- keeping or using embryos (or human admixed embryos) for the purposes of a project of research
- mixing sperm with the egg of a hamster, or other animal specified in directions, for the purpose of developing more effective techniques for determining the fertility or normality of sperm, but only where anything which forms is destroyed when the research is complete and, in any event, no later than the two cell stage

1.4. The research activities applied for are considered against the relevant licensable activities under Paragraph 1 (1) of Schedule 2 of the HFE Act (as amended). The Authority grants a research licence for one or more of the permitted research purposes defined in Paragraph 3A (1) and (2) of Schedule 2 in the HFE Act (as amended). Research licences are not required to conduct research on sperm or eggs.

1.5. The authorised processes list has been designed to encompass high-level processes, focusing on processes more broadly rather than on different methodologies used to perform them and the purpose(s) for which they may be used. This means that there may be several methodologies and purposes by which an authorised process can be undertaken, unless specified by the Authority. Fertility clinics that hold an HFEA licence are permitted to undertake the appropriate authorised process as part of their clinical practice, in accordance with the licence they hold.

1.6. In June 2026 SCAAC discussed the scope of the authorised process 'in vitro maturation (IVM) for oocytes that are retrieved from antral or pre-ovulatory follicles' for clinical practice and concluded that the authorisation does not include its use for the maturation of oocytes obtained from ovarian tissue. The SCAAC noted that the current evidence base is limited and emphasised the need for appropriate pre-clinical and clinical safety data before embryos derived from such oocytes are used in treatment.

2. Recommendations

2.1. Members are asked to:

- consider whether the process is a new process that requires authorisation;
- consider whether the evidence is sufficient to satisfy the Committee that the process does not render the tissues or cells clinically ineffective or harmful to the recipient;
- consider whether there is any evidence to indicate that the process renders the tissues or cells harmful to the recipient (including the resulting child);
- If the Committee authorises the process, to define the criteria for mandatory reporting as per General Direction 0008;
- consider and define any conditions for authorisation (if applicable).

3. Annex A – New process application form

Application to authorise a new process to carry out a licensed activity

1. Introduction

The Authorised processes list describes the processes clinics can use to carry out the licensable activities set out in the Act.

If you wish to use a process, which does not appear either on the authorised or the prohibited processes lists, you will need to apply to the HFEA to seek permission to use it in clinical practice.

Please note certain processes may be subject to prohibitions under the HFE Act and therefore cannot be authorised. Please contact your clinic inspector if you are uncertain whether authorisation of a new process is in conflict with the Act.

This application form should be used by centres that wish to carry out a licensed activity using a process that has not previously been authorised by the Authority.

2. The authorisation process

Applications will be reviewed by the HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) who will:

- consider whether the process is a new process that requires authorisation;
- consider whether there is evidence to suggest that the process renders the tissues and cells ineffective; and
- consider whether there is any evidence to indicate that the process renders the tissues and cells harmful to the recipient (including the resulting child)[1].

It is therefore important that applications contain sufficient evidence to allow the Committee to make an assessment of the effectiveness and the potential harm of the process. If the SCAAC is not provided with sufficient evidence they may adjourn their decision until additional information has been provided, which will delay processing of the application.

A process may be restricted to use in a sub-population of patients where the evidence suggests that its application in the wide patient group is lacking or would not meet the legal requirements (eg egg activation using calcium ionophore). When providing evidence, please ensure that it is clear which patient population the evidence has been derived from.

The SCAAC will then decide whether or not to add the process to the authorised processes list and determine which licensed activity/activities the process should fall under. If it decides that it should add the process to the authorised processes list, any clinic or laboratory may use the process (subject to any conditions imposed by SCAAC), provided they are licensed to carry out the associated licensed activity.

Upon approval, the process will then be subject to an initial period of mandatory reporting as set out by section D of General Direction 0008. The criteria for reporting will be determined by the SCAAC during the consideration of the application.

It is important that the language used in this application is clear and as far as possible, understandable to non-specialists. All abbreviations should be explained.

[1] Such requirements are derived from the third Directive of the European Tissues and Cells Directive, retained in UK legislation by the Retained EU Law (Revocation and Reform) Act 2023. Further details of the statutory requirements are set out in the March 2024 Authority paper. For information on processes excluded under Recital 6, please contact your clinic inspector.

New process application form

1. Current centre information

Person Responsible: Dusko ILIC

Centre name: Assisted Conception Unit, Guy's Hospital

Centre number: 0102

2. Process details

2.1. What is the name of the process?

In vitro maturation of immature oocytes recovered ex vivo during ovarian tissue processing for fertility preservation

2.2. To which cell or tissue type(s) is the process applied?

Immature human oocytes, including germinal-vesicle and metaphase-I stage oocytes, recovered ex vivo during processing of human ovarian cortical tissue. This may include oocytes recovered during ovarian tissue cryopreservation processing and oocytes recovered from ovarian tissue removed for other clinical indications, such as oophorectomy/ovariectomy for cancer, risk-reducing surgery or other pathology, where the ovarian tissue is not intended or suitable for transplantation.

2.3. Please provide a description of the process and its intended purpose/application.

Note: Please indicate whether you plan to implement this process as part of a clinical trial.

The proposed process is the in vitro maturation (IVM) of immature oocytes recovered ex vivo during ovarian tissue processing for fertility preservation.

The process involves identification of immature oocytes or cumulus-oocyte complexes during ovarian tissue processing, followed by culture in defined IVM conditions and assessment of maturation progression from germinal vesicle (GV) or metaphase I (MI) to metaphase II (MII).

The intended application is fertility preservation for patients from whom ovarian tissue is removed or processed for clinical reasons and from whom immature oocytes may be recovered ex vivo. This includes patients undergoing ovarian tissue cryopreservation and patients undergoing oophorectomy/ovariectomy or partial ovarian tissue removal for other clinical indications, such as cancer, risk-reducing surgery or other pathology, where ovarian tissue is not intended or suitable for transplantation.

The risk-benefit rationale is that these are immature oocytes recovered opportunistically during clinically indicated ovarian tissue processing that might otherwise have no reproductive use. The

process is intended as an additional fertility-preservation opportunity and not as an alternative to established controlled ovarian stimulation, oocyte cryopreservation or embryo cryopreservation where these are feasible.

If immature oocytes successfully mature to MII following the proposed process, their subsequent clinical use would depend on patient circumstances, consent and HFEA/SCAAC authorisation. Possible downstream clinical pathways may include vitrification/storage of mature MII oocytes, or, where clinically appropriate and fully consented, fertilisation of mature MII oocytes, embryo culture to the blastocyst stage where appropriate, and blastocyst vitrification/storage for future patient use.

The centre does not propose to implement this process as a clinical trial at this stage. Any clinical introduction would occur only following HFEA/SCAAC authorisation, completion of local validation, approved SOPs, patient information, consent documentation, staff competency assessment and QMS approval.

The centre is seeking authorisation for the IVM of immature oocytes recovered ex vivo during ovarian tissue processing for fertility preservation. It is not seeking authorisation in this application for embryo testing, embryo transfer or any separate embryo-based validation activity.

3. Licensed Activity

3.1. Please indicate which licensed activity/activities the new process is applicable to:

Activity	
Procuring gametes	☐
Keeping gametes	☒
Processing gametes	☒
Distribution of gametes	☐
Use of gametes	☐
Storage of gametes	☒
Storage of embryos	☐
Creation of embryos	☐
Procuring embryos	☐
Keeping embryos	☐
Testing gametes	☐
Testing embryos	☐
Processing embryos	☐
Distribution of embryos	☐
Placing any permitted embryo in a woman	☐
Using embryos in training	☐

The centre has ticked only the gamete-related licensed activities directly engaged by the proposed new process: keeping, processing, use and storage of immature/mature oocytes.

Downstream embryo-related activities have not been ticked because fertilisation, embryo culture, embryo storage and embryo transfer are not proposed as part of the new process itself.

If oocytes matured using this process are subsequently used in treatment, this would occur only after HFEA/SCAAC authorisation and in accordance with the centre's existing licensed treatment pathway, patient/partner consent, clinical governance and any conditions specified by HFEA/SCAAC.

3.2. Is this an application to extend the use of an existing process (for example to remove conditions of authorisation, such as its use in a restricted population)? If so, please indicate which authorised process this relates to:

This is not an application to remove conditions from, or extend the patient population for, an existing authorised process.

The application is related by analogy to the existing authorised process "In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles)". However, HFEA/SCAAC has indicated that IVM of immature oocytes obtained ex vivo from ovarian tissue is outside the scope of that existing authorised process and requires consideration as a new authorised process.

The authorisation sought is therefore specifically for in vitro maturation of immature oocytes recovered ex vivo during ovarian tissue processing for fertility preservation, rather than for standard IVM of oocytes retrieved from antral or pre-ovulatory follicles.

4. Evidence to support application

Effectiveness

4.1. Please provide a summary of the evidence that demonstrates that this process does not render the tissues or cells clinically ineffective, clearly indicating the patient populations from which the evidence is derived (if relevant). Include copies of any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include data from animal studies, research on human embryos or clinical trial data.

Note: this should include all available evidence including that which may indicate ineffectiveness.

The available evidence base is limited and heterogeneous. It includes published human observational experience and systematic-review level evidence relating to immature oocytes recovered from ovarian tissue/ovarian tissue cryopreservation processing. The evidence is not equivalent to the evidence base for routine clinical IVM of oocytes retrieved from antral or preovulatory follicles.

Published human evidence supports the biological feasibility of recovering immature oocytes from ovarian tissue and achieving in vitro maturation to metaphase II (MII) in a proportion of cases. Relevant publications include four published studies discussed below (Fasano et al., 2017; Fouks et al., 2020; Mohd Faizal et al., 2020; Segers et al., 2024). These data derive primarily from fertilitypreservation contexts, including oncology patients and, in some reports, pre-pubertal/adolescent populations.

The evidence should be interpreted cautiously. The strongest evidence relates to recovery of immature oocytes and maturation to MII. Evidence for functional developmental competence, including fertilisation, cleavage, blastocyst formation, pregnancy, live birth and offspring safety, is substantially more limited.

A summary of the published evidence is provided below and full papers are included as appendices.

Study 1: Fasano G, Dechène J, Antonacci R, Biramane J, Vannin AS, Van Langendonckt A, Devreker F, Demeestere I. Outcomes of immature oocytes collected from ovarian tissue for cryopreservation in adult and prepubertal patients. Reprod Biomed Online 2017;34:575-582. doi:

10.1016/j.rbmo.2017.03.007.

Affiliation: Université Libre de Bruxelles, Brussels, Belgium.

- **Population:** 136 patients: 130 postpubertal/adult, mean age 27.6 ± 5.6 years; 6 prepubertal girls, mean age 8.7 ± 2.3 years
- **Tissue source / context:** Oocytes collected ex vivo during ovarian tissue cryopreservation; adult patients mainly ovarian biopsies, prepubertal patients mainly unilateral oophorectomy
- **Oocytes assessed:** 705 oocytes collected; 559 subjected to IVM
- **MII after IVM:** 145/559 matured to MII after IVM, excluding 6 MII oocytes already retrieved during procedure
- **Maturation %:** Overall 25.9%; adults 28.1%; prepubertal 10.3%
- **Fertilisation / embryo development:** 139 mature oocytes vitrified in 72 patients; 7 pronuclear-stage embryos obtained after ICSI of 12 MII oocytes and vitrified in 5 patients
- **Pregnancy / live birth:** 4 adults returned to use oocytes/embryos; one biochemical pregnancy, no live birth reported in this cohort
- **Main limitation:** Observational cohort; low warming survival in used oocytes; limited clinical use; prepubertal numbers small; developmental competence not established

Study 2: Fouks Y, Hamilton E, Cohen Y, Hasson J, Kalma Y, Azem F. In-vitro maturation of oocytes recovered during cryopreservation of pre-pubertal girls undergoing fertility preservation. Reprod Biomed Online 2020;41:869-873. doi: 10.1016/j.rbmo.2020.07.015.

Affiliation: Sackler Faculty of Medicine, Tel-Aviv, Israel

- **Population:** 93 oncology patients aged 0–25 years: 33 pre-menarche, 60 post-menarche.
- **Tissue source / context:** Laparoscopic oophorectomy for OTC before chemotherapy/radiotherapy/oncotherapy; oocytes recovered from medium after OTC.

- **Oocytes assessed:** 879 immature oocytes: 216 pre-menarche, 663 post-menarche
- **MII after IVM:** Overall table reports 205 MII excluding MII oocytes retrieved during the procedure; post-menarche 227/597 and pre-menarche 46/182 in the abstract/table denominator.
- **Maturation %:** Overall 23.3%; post-menarche 38.0%; pre-menarche 25.3%; age 1–5 years only 3.4% reached MII.
- **Fertilisation / embryo development:** No use for actual fertility purposes as of April 2020
- **Pregnancy / live birth:** No pregnancies/live births from this study material.
- **Main limitation**: Retrospective; focused on young/premenarche patients; no reproductive use outcomes; very young girls had particularly low maturation.

Study 3: Mohd Faizal A, Sugishita Y, Suzuki-Takahashi Y, Iwahata H, Takae S, Horage-Okutsu Y, Suzuki N. Twenty-first century oocyte cryopreservation-in vitro maturation of immature oocytes from ovarian tissue cryopreservation in cancer patients: A systematic review. Womens Health (Lond) 2022;18:17455057221114269. doi: 10.1177/17455057221114269.

Affiliation: St. Marianna University School of Medicine, Kawasaki, Japan.

- **Population:** Systematic review of 12 studies; 590 cancer patients undergoing concurrent OTC/ovarian tissue oocyte (OTO)-IVM; 42 prepubertal and 548 postpubertal.
- **Tissue source / context:** Immature oocytes obtained during ovarian tissue cryopreservation, mostly non-stimulated ovaries; one stimulated-cycle study included.
- **Oocytes assessed:** 5,724 immature oocytes.
- **MII after IVM:** 1,937 MII after IVM.
- **Maturation %:** 33.84%
- **Fertilisation / embryo development:** 118 embryos obtained after IVF/ICSI; mean fertilisation rate 64.53%; all embryos cryopreserved.
- **Pregnancy / live birth:** No pregnancy, biochemical pregnancy, clinical pregnancy or live birth rates recorded in the included FP cohorts.
- **Main limitation:** Heterogeneous studies; mainly cancer FP; limited prepubertal evidence; no pregnancy/live-birth outcomes in review dataset.

Study 4: Segers I, Mateizel I, Wouters K, Van Moer E, Anckaert E, De Munck N, De Vos M. Ovarian Tissue Oocyte-In Vitro Maturation for Fertility Preservation. J Vis Exp 2024;17:207. doi: 10.3791/65255.

Affiliation: Vrije Universiteit Brussel, Brussels, Belgium

- **Population:** Updated single-centre clinical programme: 98 patients aged 1-38 years; 11 prepubertal and 87 adult/postpubertal.
- **Tissue source / context:** OTO-IVM during oophorectomy or ovarian biopsy for OTC.
- **Oocytes assessed:** 1,417 cumulus oocyte complexes (COCs)/oocytes collected.
- **MII after IVM:** 563 MII.
- **Maturation %:** Overall 40%; prepubertal 26%; adult/postpubertal: 42%.
- **Fertilisation / embryo development:** 13/98 patients requested embryo creation; 64 MII inseminated, 40 2PN fertilised, 27 good-quality embryos cryopreserved; 5 patients later warmed OTO-IVM oocytes, survival 58/77, fertilisation 28/58, 8 good-quality embryos.
- **Pregnancy / live birth:** 10 patients returned to use OTO-IVM material; 3/10 had healthy babies.

- **Main limitation:** Single-centre experience; OTO-IVM still described as experimental/add-on; limited numbers returning to use material; further data needed on vitrification efficiency, developmental capacity and offspring outcomes.

Taken together, the published evidence supports biological feasibility of recovering immature oocytes from ovarian tissue processing and achieving maturation to MII in a proportion of cases. The evidence is strongest in adult/postpubertal fertility-preservation patients and weaker in prepubertal children, particularly those under 5 years of age. Evidence for downstream developmental competence is more limited but includes fertilisation, embryo cryopreservation and a small number of reported live births. The centre therefore considers that the evidence supports further controlled introduction of ovarian-tissue-oocyte IVM as an additional fertility-preservation option, subject to HFEA/SCAAC authorisation, defined patient selection, clear consent, local QMS/process approval, and enhanced audit/reporting.

The centre has also generated preliminary local Stage 1 rescue-IVM data using consented surplus post-ICSI GV oocytes from patients who had consented to their use for training/validation. These oocytes were not recovered from ovarian tissue processing and therefore do not directly validate the proposed ovarian-tissue-derived oocyte process. However, they demonstrate local capability to culture, monitor, stage, photograph and document immature-oocyte maturation under controlled laboratory conditions.

In this preliminary dataset, 18 GV oocytes were cultured: 9 in G-IVF medium and 9 in dedicated IVM medium. Final maturation to MII was observed in 8/9 G-IVF-cultured oocytes and 9/9 IVM-mediumcultured oocytes, with no degeneration observed in either group. These data support local laboratory capability for rescue-IVM culture and documentation, but do not establish developmental competence, implantation potential, live-birth outcome or clinical safety for ovarian-tissue-derived oocytes. Full details are provided in Appendix.

The centre does not propose fertilisation, embryo culture, blastocyst cryopreservation or embryo transfer as validation activity. Clinical use would only occur prospectively after HFEA/SCAAC authorisation, under the authorised clinical pathway, with appropriate consent, SOPs, QMS approval, staff competency and outcome monitoring.

4.2. To ensure patient safety all products that come into contact with patients, gametes and embryos must be appropriately CE marked (Class IIa) and approved by the relevant UK Approved Body prior to application.

Please list all reagents and materials used in the new process that come into contact with patients, gametes or embryos, providing details of the supplier and quality/safety specification. Please expand the below table as necessary.

Note: If authorised, this process may be used by other licensed centres, and it is acknowledged that there may be variations in the reagents used however any clinic using the process will be expected to show that they are using products of similar specification with the necessary CE marking to those referenced below.

Reagent/material	Manufacturer or supplier	Product code	Specification e.g. CE marking (specify level and approved purpose), clinical grade, reagent grade, etc.

Culture dish (5 well)	Vitrolife	16004	CE
Culture dish (40-mm)	Vitrolife	16001	CE
Culture dish (60-mm)	Vitrolife	16002	CE
Culture dish (90-mm)	Vitrolife	16007	CE
Centre Well Dish	Vitrolife	16005	CE
Serological Pipettes (5-mL)	Vitrolife	16205	CE
Serological Pipettes (10-mL)	Vitrolife	16206	CE
Pipette tips (200-µL)	Hunter Scientific	003001004	general laboratory use
Pipette tips (1000-µL)	Hunter Scientific	0030010060	general laboratory use
Needle (21G)	BD	304432	CE
Fine dosage syringe	Hunter Scientific	9166017/V	CE
Sterile Pasteur Pipette (150mm)	Hunter Scientific	PPS150	CE, class IIa, gamete handling
S-Cryolock®	Hunter Scientific	S-CL(B)	CE, vitrification device
Flexipet® pipette (135-µm)	Cook	G26712	CE, oocyte manipulation
Flexipet® pipette (170-µm)	Cook	G26713	CE, oocyte manipulation
Flexipet® pipette (300-µm)	Cook	G46020	CE, oocyte manipulation
Polystyrene containers (150-mL)	ThermoFisher	11319133	general laboratory use
Gx-IVF	Vitrolife	10171	CE, clinical ART medium
Human serum albumin	Vitrolife	10064	CE, clinical ART medium
G-MOPS	Vitrolife	10129	CE, clinical ART medium
G-MOPS Plus	Vitrolife	10173	CE, clinical ART medium
HYASE-10X	Vitrolife	10176	CE, clinical ART medium
OVOIL HEAVY	Vitrolife	10174	CE, clinical ART medium
Vit Kit – Freeze NX	Irvine Scientific	90188	CE, clinical ART medium
MediCult IVM System	Cooper Surgical	82214010	CE, clinical ART medium
Gonal-f 900 IU*	Merck	PLGB 11648/0270	Licensed medicinal product
Menopur 1200 IU*	Ferring	PL 03194/0107	Licensed medicinal product
Buserelin/Suprecur injection**	Sanofi-Aventis	PL 45043/0051	Licensed medicinal product

*Used only as defined hormonal supplements within the approved IVM protocol. **Included, where required, as a defined GnRH agonist component of the IVM protocol

Safety and risks

4.3. Please provide a summary of the evidence that demonstrates that this process does not render the tissues and cells harmful to the recipient (including the resulting child).

Clearly indicate the patient populations from which the evidence is derived (if relevant). Include copies of any relevant published and/or unpublished data as appendices to this form. For example you may wish to include data from animal studies, research on human embryos, or clinical trials data.

Note: this should include all available evidence including that which may indicate potential harm.

The centre recognises that the safety evidence for ovarian-tissue-derived oocyte IVM is limited. Maturation to metaphase II (MII) does not, by itself, establish clinical safety, developmental competence or equivalence with oocytes matured in vivo or with oocytes matured after conventional follicular retrieval.

No specific safety signal has been identified in the limited published human evidence; however, available numbers are insufficient to establish equivalence with conventionally matured oocytes or to exclude uncommon or long-term developmental or offspring risks.

Potential safety considerations include the following:

Oocyte and laboratory handling

Immature oocytes recovered during ovarian tissue processing may be exposed to variable tissue transport conditions, temperature changes, tissue dissection, blood contamination, mechanical handling, denudation and extended culture. These factors could affect oocyte survival, maturation kinetics, cytoplasmic competence or degeneration rate.

To mitigate these risks, the process would be performed under controlled laboratory conditions using approved SOPs, defined media and consumables, appropriate equipment, witnessing, traceability, staff competency assessment and QMS oversight. The centre would monitor recovery, survival, degeneration, maturation timing, GV/MI/MII progression and oocyte morphology.

Maturation, developmental competence and future clinical use

Potential risks include failed maturation, delayed or abnormal nuclear/cytoplasmic maturation, oocyte degeneration, reduced fertilisation competence and impaired embryo development if mature oocytes are subsequently used in treatment. Published evidence supports the biological feasibility of maturation to MII in a proportion of ovarian-tissue-derived immature oocytes, but developmental competence remains less well established.

The published evidence includes limited downstream reproductive outcome data, including small numbers of reported live births, but these data are insufficient to establish equivalence with conventionally matured oocytes or to exclude uncommon or long-term risks. Patients would therefore receive specific information and counselling regarding the limited evidence base, alternative fertility-preservation options, and any additional follow-up or reporting requirements specified by HFEA/SCAAC.

The centre is seeking authorisation for the IVM of immature oocytes recovered ex vivo during ovarian tissue processing for fertility preservation. It is not seeking authorisation in this application for embryo testing, embryo transfer, or any separate embryo-based validation activity.

If the process is authorised for clinical use, any future use of oocytes matured through this process would be undertaken prospectively under the authorised clinical pathway, with appropriate consent, counselling, witnessing, documentation, storage consent, QMS approval, staff competency assessment and ongoing outcome monitoring.

4.4. Please indicate if any professional body guidance, UK or international, covers the use of this process:

The centre is not aware of UK professional-body guidance specifically recommending the clinical use of in vitro maturation of immature oocytes recovered during ovarian tissue processing, also referred to as ovarian tissue oocyte–in vitro maturation (OTO-IVM). However, the process is addressed in international professional guidance on fertility preservation and in vitro maturation.

The American Society for Reproductive Medicine (ASRM) Committee Opinion on fertility preservation in patients with medical indications (2026) recognises that cumulus-oocyte complexes may be aspirated from small follicles or identified during ovarian tissue dissection and processing, and that these oocytes may subsequently undergo in vitro maturation and cryopreservation before or after fertilisation **[1].** ASRM identifies this as a potential additional fertility-preservation opportunity, including in circumstances where avoiding subsequent ovarian tissue transplantation may be advantageous. However, it also emphasises that clinical outcome data remain limited and that more established fertility-preservation methods should be pursued whenever feasible.

The 2025 **American Society of Clinical Oncology (ASCO)** fertility-preservation guideline describes IVM as an emerging fertility-preservation method that may be offered in selected circumstances, while recognising the low quality of the available evidence and uncertainty regarding pregnancy and live-birth outcomes in cancer survivors **[2]**.

More general professional guidance on IVM, including the **ASRM Committee Opinion on In Vitro Maturation** (2021), recognises the biological and clinical feasibility of IVM while highlighting limitations in developmental efficiency and the relatively limited evidence regarding offspring outcomes **[3].** These recommendations predominantly concern oocytes retrieved from antral follicles rather than oocytes recovered during ovarian tissue processing and therefore provide supportive context rather than direct evidence for the proposed process.

The centre therefore considers that international professional guidance supports the biological and clinical rationale for OTO-IVM as a potential additional fertility-preservation strategy, while consistently recognising that the evidence base remains limited and that OTO-IVM should not replace established fertility-preservation methods where these are clinically feasible.

Human Fertilisation and Embryology Authority (HFEA). Clinic Focus. July 2026. Clarification on authorised IVM process and immature oocytes obtained from ovarian tissue. The July 2026 HFEA Clinic Focus update confirms that the existing authorised IVM process for oocytes retrieved from antral or pre-ovulatory follicles does not encompass immature oocytes obtained from ovarian tissue, and that use of this process therefore requires consideration as a new authorised process.

References

1. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients with medical indications: a committee opinion. Fertil Steril 2026;125:247–259. doi: 10.1016/j.fertnstert.2025.12.001
2. Su HI, Lacchetti C, Letourneau J, Partridge AH, Qamar R, Quinn GP, Reinecke J, Smith JF, Tesch M, Wallace WH, Wang ET, Loren AW. Fertility Preservation in People with Cancer: ASCO Guideline Update. J Clin Oncol 2025;43:1488–1515. doi: 10.1200/JCO-24-02782
3. Practice Committees of the American Society for Reproductive Medicine, the Society of Reproductive Biologists and Technologists, and the Society for Assisted Reproductive Technology. In vitro maturation: a committee opinion. Fertil Steril 2021;115:298–304. doi: 10.1016/j.fertnstert.2020.11.018

4.5. Please note that clinics using this process will be expected to be able to show that they:

- will provide suitable information to patients about the nature of the treatment including any consequences and risks arising as a result of the use of this process;
- that staff have been suitably trained in the application of the new process and can provide evidence of the assessment of their competence;
- that the process and any equipment used in the process has been fully validated;
- there are mechanisms in place for monitoring the effectiveness of the process through regular audit.

Please provide brief details of your plans, with timelines, to ensure that these requirements are met.

The centre will not introduce ovarian-tissue-derived oocyte IVM into clinical practice until HFEA/SCAAC authorisation has been granted and all local governance, QMS and training requirements have been completed.

Following HFEA/SCAAC authorisation, the centre would implement the process using the following indicative timeline:

Within 4 weeks of authorisation

The centre would review any conditions or reporting requirements specified by HFEA/SCAAC and confirm the authorised scope of the process. The relevant SOPs, risk assessment, patient information, consent pathway, laboratory records, witnessing requirements and traceability documentation would be finalised and submitted through local QMS change control.

Within 8 weeks of authorisation

The centre would complete QMS approval of the final SOPs and associated documents. All media, consumables and equipment required for the process would be confirmed as suitable for clinical use, with relevant certificates, lot-release documentation and traceability arrangements in place. The process would be incorporated into the ovarian tissue processing workflow so that oocyte recovery and IVM do not compromise ovarian tissue cryopreservation.

Within 10–12 weeks of authorisation

Relevant embryology and clinical staff would complete documented training and competency assessment. This would include oocyte identification during ovarian tissue processing, transfer into IVM culture, monitoring of GV/MI/MII progression, identification of MII oocytes,

documentation, witnessing, cryostorage records, consent checks and escalation/reporting requirements.

Initial clinical implementation

Routine documentation, witnessing, traceability, consent checks, deviation reporting and adverseevent reporting would be undertaken in accordance with existing centre procedures and HFEA requirements.

In addition, the first clinical cases using ovarian-tissue-derived oocyte IVM would be subject to enhanced prospective review. This review would focus on feasibility of integration into the ovarian tissue processing workflow, oocyte recovery, maturation outcomes, degeneration, timing to MII, any impact on ovarian tissue cryopreservation workflow, documentation completeness, deviations, incidents and any amendments required to the SOP, risk assessment or patient information.

Governance review

The process would be reviewed after the initial cohort of cases, or earlier if required by HFEA/SCAAC. The review would assess feasibility, compliance with the authorised process, maturation outcomes, deviations, incidents, patient information/consent issues and any further changes required to SOPs or risk assessment. A further review would be undertaken at 6 and 12 months after first clinical use, with reporting to HFEA/SCAAC as required by any conditions of authorisation.

5. Declaration

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

Signature: 

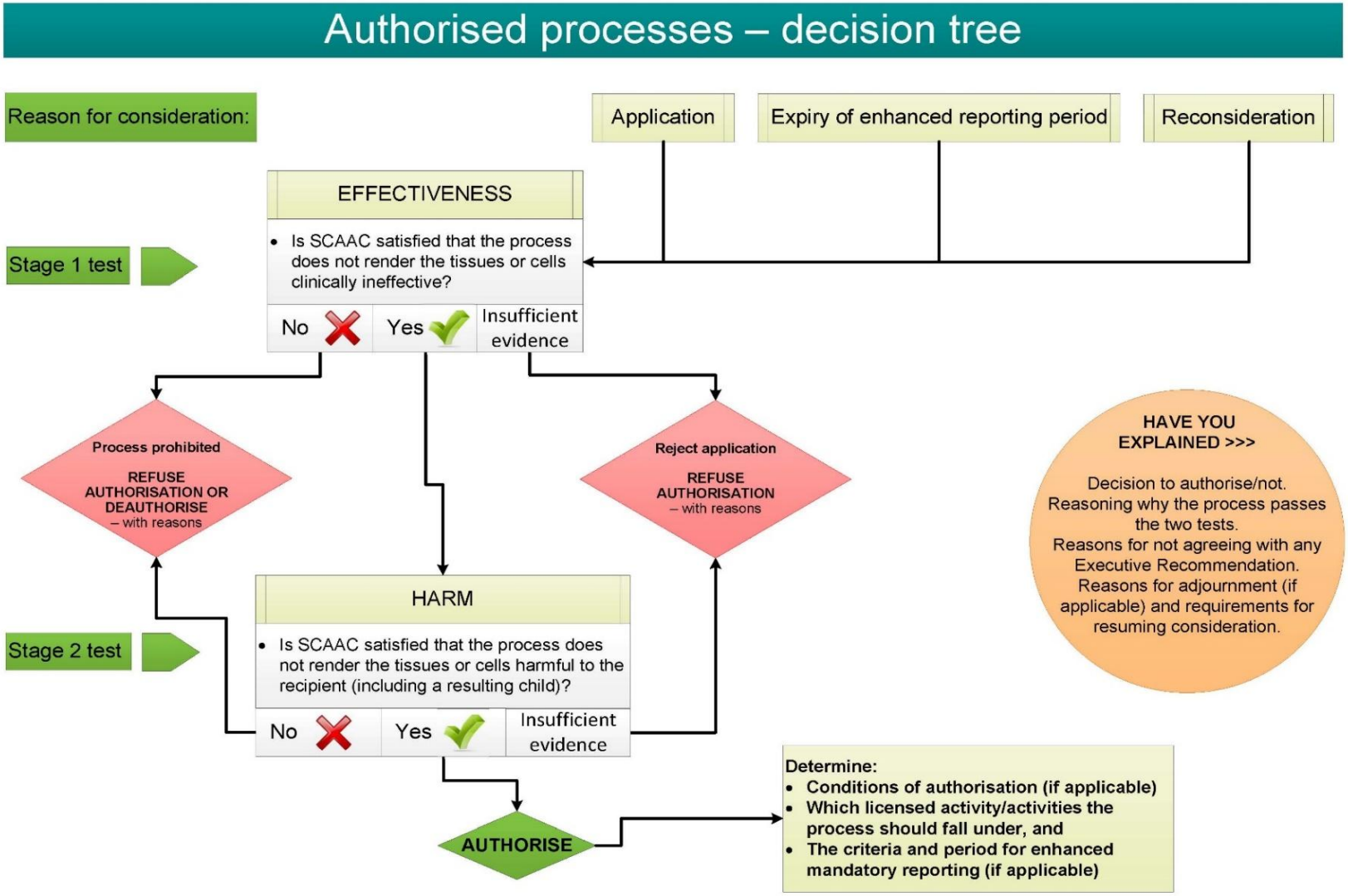
Date: 13 September 2026

This must be completed by the Person Responsible of the licensed centre applying for authorisation of the process. The form should then be submitted, with any associated papers and information to your inspector.

4. Annex B – Supporting evidence

4.1. Provided as a separate file (referred to as Appendix in the application form)

5. Annex C – Authorised processes decision tree



6. Annex D – Authorised processes list

Licensed activity	Authorised processes
Procuring gametes	Egg collection Surgical sperm collection Ovarian tissue collection Testicular tissue collection
Keeping gametes	Culture of eggs Culture of sperm
Processing gametes	Semen preparation (including the use of reagents to increase sperm motility) Egg preparation Grading of gametes In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles) Cryopreservation of gametes Thawing/re-warming gametes Polar body biopsy Egg activation using Calcium Ionophore (only in selected patients or in accordance with professional guidelines* - see below for further guidance)
Distribution of gametes	Transfer of sperm between centres Transfer of eggs between centres Supply of sperm from a licensed centre to unlicensed premises in thawed or thawing state for home insemination - this should only be done in **exceptional circumstances** as per the Code of Practice
Use of gametes	IUI GIFT IVF ICSI

Licensed activity	Authorised processes
Storage of gametes	Cryopreservation of eggs Cryopreservation of sperm Cryopreservation of testicular tissue (HTA licence may be required depending on the reasons for storage and intended use) Cryopreservation of ovarian tissue (HTA licence may be required depending on the reasons for storage and intended use)
Storage of embryos	Cryopreservation of embryos (including at the pronucleate and blastocyst stage)
Creation of embryos	IVF ICSI
Procuring embryos	Lavage
Keeping embryos	Culture system
Testing gametes	Genetic testing associated with polar body biopsy
Testing embryos	PGT-M PGT-A PGT-SR PTT (formerly PGD-HLA)**
Processing embryos	Culture Biopsy Assisted hatching Embryo grading (including non-invasive assessments, see T91 for limitations) Manipulation Thawing/re-warming of blastocysts and embryos Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same person)

Licensed activity	Authorised processes
Distribution of embryos	Transfer of embryos between centres
Placing permitted embryo in a woman	Embryo transfer
Using embryos in training	Embryo biopsy Blastocyst biopsy Cryopreservation and thawing/re-warming techniques Assisted hatching Embryo handling and manipulation Assessment of embryos

*The HFEA's **Scientific and Clinical Advances Advisory Committee (SCAAC)** considered the use of Calcium Ionophore as an egg activation technique and highlighted the theoretical risks relating to embryo viability (eg, premature activation and triploid embryos). Given the theoretical risks of Calcium Ionophore activation, centres using it are expected to do so only in selected patients, such as those with PLCz deficiency, or in accordance with professional guidelines. Centres are expected to document their rationale for using Calcium Ionophore for individual cases. As with all treatments and processes, centres should ensure that patients are fully informed about the efficacy and potential risks and that validation is carried out.

In August 2023, the Association of Reproductive and Clinical Scientists (ARCS) and the British Fertility Society (BFS) published 'The use of ICSI in ART: Evidence for practice' which includes guidelines on the best practice use of artificial egg activation.

The use of pre-implantation tissue typing (PTT), also known as human leukocyte antigen (HLA) tissue typing, requires patient-specific authorisation. Should you wish to undertake PTT, an application can be made via the Clinic Portal 'New licences, returns and applications' webpage. An application must be made for each patient case. For further information, please contact the PGTM team at **pgtm@hfea.gov.uk.

Scientific considerations relevant to the 14-day rule

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	8
Paper number:	HFEA (07/10/2026) 008
Meeting date:	07 October 2026
Author:	Dharmi Deugi, Scientific Policy Officer (HFEA)
Annexes	Annex B – Literature review and scope of the Scientific considerations relevant to the 14-day rule

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • advise the executive if they are aware of any other recent developments; • consider the research findings, drawing conclusions on the scientific considerations relevant to the 14-day rule; and • review whether any outputs from the HFEA are required.
Resource implications:	Within budget
Implementation date:	N/A
Communication(s):	Minutes of committee discussion to be published on the SCAAC webpage and communicated to the sector via Clinic Focus newsletter.
Organisational risk:	Low

1. Background

1.1. The legal limitation prohibiting the culturing of human embryos in vitro beyond 14 days, known as the '14-day rule', originated in the UK from recommendations in the Warnock Committee report (1984). Initially implemented as guidance, the 14-day rule was incorporated into UK legislation by the **Human Fertilisation and Embryology (HFA) Act 1990**.

1.2. Research using human embryos and human admixed embryos requires a research licence from the HFEA. The Authority considers applications for research licences and may grant a licence where the use of embryos is considered necessary or desirable for one or more purpose specified in the HFE Act (2008). These purposes include increasing knowledge about the development of embryos, the causes of miscarriage, serious disease and other medical conditions, developing treatments and promoting advances in infertility treatment.

1.3. Advances in embryology and embryo culture techniques now have the potential to enable researchers to culture human embryos beyond the 14-day limit. However, such research is not currently permitted under UK legislation. These developments have increased scientific interest in studying later stages of early human development in vitro and have prompted international discussions about extending the 14-day limit

1.4. The HFEA published **proposals for modernising the HFE Act** in November 2023. One of the four areas where recommendations were made was in future scientific developments and innovation. These proposals identified the 14-day rule for human embryo research as a matter that may require re-consideration in light of scientific developments.

1.5. The 'Scientific considerations relevant to the 14-day rule' topic was last discussed at the **October 2024** SCAAC meeting where the Committee considered the arguments for keeping and extending the time limit, focusing on the scientific and technical aspects. The SCAAC agreed that there is a case to be made for extending the 14-day rule. The Committee did not agree on any specific future upper limit, although 28 days was most commonly discussed and noted to be subject to international consideration.

1.6. In **November 2024**, the Authority considered both the scientific and technical case as well as the wider ethical arguments for a consensus on proposals for the 14-day rule. The Authority agreed that there is a case for recommending that the law is changed to extend the time limit on embryo research and that 28 days would be an appropriate new fixed upper limit. It was also agreed that any research project seeking to use human embryos beyond 14 days should be required to meet additional criteria, such as justifying the time limit proposed. The Authority decision was then shared with the DHSC as part of the process of modernising the HFE Act.

1.7. Any amendment to the 14-day limit would require a change to legislation and is therefore a matter for Government and Parliament. However, it continues to be important for the HFEA to lead the discussions and understand the scientific, legal and ethical implications of extending the 14-day limit of in vitro embryo culture.

1.8. Professional and scientific bodies have continued to consider appropriate limits for human embryo research. The **European Society of Human Reproduction and Embryology (ESHRE)** has recommended extending the 14-day limit to 28 days, based on the potential

scientific and medical benefits of studying later stages of embryonic development. The International Society for Stem Cell Research (ISSCR) has also recognised the potential scientific value of research beyond 14 days. Its guidelines recommend that, where there is broad public support and local regulations permit, research beyond 14 days could be considered through a specialised scientific and ethical oversight process, following appropriate public discussion.

1.9. The Nuffield Council of Bioethics is undertaking a project to explore the current and future ethical, scientific, social, and policy considerations related to the 14-day rule for human embryo culture, with the aim of informing potential UK legislative reform. As part of the project, the HFEA took part in the public dialogue work on the future of the 14-day rule. The findings are expected to be published this year.

1.10. This paper presents literature published between 1st September 2024 and 21st August 2026 reviewing scientific developments relevant to the 14-day rule. The Executive notes that this paper provides a summary of the findings described in published literature and is not an assessment of study validity.

2. Summary of research developments

2.1. The literature demonstrates continued advances in the study of human embryonic development around and beyond the 14-day rule, including consideration of the potential scientific value of extending the 14-day limit. Advances in embryo culture have enabled human embryos to be maintained in vitro to approximately 13–14 days, providing opportunities to study developmental stages that are currently poorly understood. In particular, the literature identifies gaps in understanding of post-implantation development, including gastrulation, cell differentiation, morphogenesis and early organogenesis. The literature also highlights the continued development of stem cell-based embryo models and other in vitro approaches as important complementary developments.

Early human embryonic development

Implantation and embryo-maternal interactions

2.2. Two studies on co-culture systems has enabled the study of human embryos alongside endometrial cells or organoids, providing opportunities to investigate communication between the embryo and endometrium during implantation and early post-implantation development. In addition to this study, a study on transcriptome analysis as well as ex vivo, and in vitro models have provided some insight into molecular and cellular processes involved in trophoblast proliferation and differentiation, as well as the role of mechanical forces in implantation. Such research may help to improve understanding of implantation failure, early pregnancy loss and placental development, although their potential clinical applications remain at an early stage.

Pre-implantation and embryo development

2.3. A few studies using molecular analyses and live imagining have identified mechanisms associated with developmental arrest, including chromosomal abnormalities, mitotic errors, DNA damage and cellular stress. These studies have provided further information on the regulation of early embryonic gene expression, including zygotic genome activation, pluripotency and lineage specification, potentially contributing to further understanding of embryo arrest during early development.

Development around 14 days and gastrulation

2.4. A small number of studies investigating development around the 14-day limit and early gastrulation have provided insights into the diversification and organisation of human embryonic cells. For example, three studies on spatial transcriptomics and a study on single-cell analyses have identified distinct developmental trajectories related to gastrulation. Some studies examining signalling pathways have further characterised the roles of pathways, such as WNT in early development. These studies provide some insight into the transition from implantation to gastrulation and early post-implantation development, although knowledge of these stages remains limited.

Experimental models and approaches

Stem cell-based embryo models

2.5. Stem cell-based embryo models and other in vitro approaches continue to provide complementary systems for investigating human development, including stages around and

beyond 14 days. They may provide opportunities to investigate developmental processes that cannot currently be studied directly in human embryos beyond 14 days, although differences between embryo models and human embryos remain an important consideration when interpreting their relevance to human development.

Extended embryo culture and non-human primate models

2.6. There has also been continued progress in extended embryo culture and non-human primate models. A few studies describe advances in culturing and modelling peri-implantation and early post-implantation development, while non-human primate models provide an additional system for investigating developmental processes that are difficult to study directly in human embryos. These approaches may provide information on morphogenesis, lineage specification and tissue organisation, while also highlighting the limitations of extrapolating findings between species and between embryo and stem-cell-based models.

Knowledge gaps

2.7. These developments highlight continuing gaps in knowledge, particularly during the transition from implantation through gastrulation and early post-implantation development. Advances in culture systems, imaging, single-cell and spatial analyses, and stem cell-based models are beginning to address some of these gaps. The findings may also have longer-term relevance to understanding developmental disorders, congenital conditions, miscarriage, implantation failure and placental development, although further research would be required before these findings could translate into clinical applications.

Implications for the 14-day limit

Scientific rationale for extending the limit

2.8. A number of publications describe the scientific rationale for studying human development beyond 14 days. This includes improving understanding of developmental disorders, congenital conditions and miscarriage, as well as informing regenerative medicine. The emerging evidence therefore suggests that the scientific case for extending the limit is based not only on the technical ability to culture embryos for longer, but also on the potential to address important gaps in knowledge about human development.

Regulatory and international considerations

2.9. There has also been continued international consideration of an appropriate alternative to the 14-day limit. The **Dutch Health Council** has advised extending the limit to 28 days and other publications similarly discuss 28 days as a potential new limit, reflecting the period during which important post-implantation developmental processes can be investigated. There is increasing consideration of different approaches to extending research beyond 14 days, although there remains variation in proposed approaches and limits.

2.10. A number of regulatory considerations would need to be addressed if the limit were extended. This includes the need for a clear framework governing how research could progress beyond 14 days and the need for research governance in order to implement and monitor any future extension. It would also be important to distinguish between natural embryos and embryo models, while recognising areas where their developmental characteristics overlap.

Ethical, legal and societal considerations

Ethical and legal considerations

2.11. Some publications relevant to the wider policy debate consider whether the 14-day rule remains ethically or conceptually appropriate in light of developments in embryo research, while others examine particular perspectives on the moral status and governance of embryos.

Public engagement and societal perspectives

2.12. There remains continued discussion of the ethical, legal and societal implications of extending the 14-day limit, including the importance of public engagement in any reconsideration of the rule. A few studies identify potential challenges in communicating the scientific and ethical issues to policymakers and the public and highlights the need for further empirical research into public understanding and attitudes.

2.13. Overall, the literature demonstrates scientific progress alongside continuing knowledge gaps in human embryonic development. The studies provide some insight into embryonic development, while advances in embryo culture and stem cell-based models are providing new opportunities to investigate previously inaccessible stages of human development. The literature supports continued consideration of the scientific opportunities associated with research beyond 14 days while highlighting the need for appropriate scientific governance, ethical consideration and public engagement if the limit were to be extended.

3. Recommendations

3.1. Members are asked to:

- Advise the executive if they are aware of any other recent developments;
- Consider the research findings, drawing conclusions on the scientific developments relevant to the 14-day rule; and
- Review whether any outputs from the HFEA are required.

4. Annex A – Literature review and scope of Scientific considerations relevant to the 14-day rule

4.1. Annex A has been circulated to the committee as a separate Excel document, which provides details on the available research on the scientific considerations relevant to the 14-day rule published between 1st September 2024 and 21st August 2026. Where possible literature has been separated by relevant subheadings.

4.2. This topic includes research into:

- the characterisation of human embryos in early-stage development (up to 14 days). This includes research studying gastrulation, early organogenesis and neural development, advances in embryo culture systems (including optimisation and extended in vitro cultivation of non-human primates), and the use of stem cell-based embryos models.

- Papers considering the ethical and/or legal aspects of extending embryo culture beyond 14 days are additionally within scope.

4.3. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search. Searches were also conducted on PubMed with the original search strategy to ensure comprehensive coverage.

Human stem cell-based embryo models (SCBEMs)

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item	9
Paper number	HFEA (07/10/2026) 009
Meeting date	07 October 2026
Author	Rebecca Taylor, Scientific Policy Manager
Annexes	Annex A: Scientific literature review (excel document)

Output from this paper

For information or recommendation?	For recommendation
Recommendation	Members are asked to: • Consider the progress of research into SCBEMs; • Advise if they are aware of any other recent developments in the field of SCBEMS; and • Review whether any outputs from the HFEA are required addressing SCBEMs.
Resource implications	NA
Implementation date	NA
Communication(s)	Minutes of committee discussion to be published on the SCAAC webpage and communicated to the sector via Clinic Focus newsletter.
Organisational risk	Low

1. Introduction

1.1. "Stem cell-based embryo model", abbreviated to SCBEM, is an umbrella term for a variety of organised structures mainly derived from human pluripotent stem cells that aim to mimic key developmental phases of early-stage human embryo development, including cellular heterogeneity and patterning.

1.2. Currently, SCBEMs are formed from either human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), or from cells that are in the process of reprogramming but that have not yet reached full iPSC identity. In the UK, hESCs can be newly derived from donated embryos, or established stem cell lines from the UK Stem Cell Bank (sole public repository of all UK-derived human embryonic stem cell lines) or from international repositories. iPSCs can be obtained from donated tissue and resource banks such as the Human Induced Pluripotent Stem Cells Initiative.

1.3. There are currently a range of stem cell-based embryo models which mimic early embryonic development to varying degrees and can be broadly broken down into blastoid, gastruloid, and axioloid models:

1.3.1. Blastoids seek to replicate the pre-implantation embryo (days 4-7 post fertilisation), containing cell types of the trophectoderm, hypoblast and epiblast, used to enable improved understanding of cell fate determination, implantation mechanisms and early embryo-uterine interactions. When cultured for an extended period in vitro, blastoids can form post-implantation cell types including indicators of the primitive streak and early gastrulation.

1.3.2. Gastruloids and peri-gastruloids, and structured stem cell-based embryo models (such as bilaminoids, heC-embryoids and E-assembloids) seek to replicate developmental stages of pre- and early post-gastrulation (days 10-16 post fertilisation), where germ layer formation (ectoderm, mesoderm, endoderm) and body axis specification takes place.

1.3.3. Axioloids and somitoids seek to replicate the body axis formation of the embryo such as the early steps of creating the anterior-posterior and dorsal-ventral axes, which may help researchers to gain insights into spinal cord development, nervous system organisation and the mechanisms underlying body symmetry and segmentation.

1.4. There are in addition, assembloids. In general terms, these are self-organising three-dimensional models generated through the integration of an organoid with one or more additional organoids or specialised cell types. They seek to replicate interactions between cells or tissues and organ systems. In the context of SCBEM research, an assembloid might combine cells/tissues or reproductive organoids with an embryo model (such as blastoids). This includes assembloids to study embryo implantation, endometrial growth, differentiation and disease[1] [2].

1.5. SCBEM research has not yet developed embryo models of the zygote or early cleavage stages.

1.6. In August 2025 the International Society for Stem Cell Research (ISSCR) updated its guidance on definitions of SCBEMs to retire the integrated vs non-integrated terminology due to the complexity

[1] Pașca, S.P., Arlotta, P., Bateup, H.S.*et al* A nomenclature consensus for nervous system organoids and assembloids. *Nature* 609, 907–910 (2022). https://doi.org/10.1038/s41586-022-05219-6

[2] Kanton, S and Pașca, S.P. Human assembloids, *Development* (2022) 149 (20): dev201120, https://doi.org/10.1242/dev.201120

of newer models which make this binary distinction increasingly difficult to apply. The guidance is as follows:

- All embryo models to be described as “stem cell-based embryo models” (SCBEMs) and to cease using the integrated and non-integrated embryo models definitions.
- That all 3D SCBEMs should have a clear scientific rationale, a defined endpoint, and be subject to an appropriate oversight mechanism.
- Human SCBEMs must not be transferred to a human uterus or animal host (unchanged from 2021).
- Recommending that a prohibition on the in vitro culture of SCBEMS to the point of potential viability— ie ectogenesis.

2. Background

2.1. SCAAC most recently considered SCBEMs in October 2024 when comments and recommendations were made in relation to the science, potential application and regulation of embryo models as follows:

- SCBEMs and embryos are not the same, so if embryo models are to come under the HFE Act (as amended), their definition would need to be distinct from embryos;
- Clearly defined upper limits on SCBEM research should be established without inadvertently banning good research;
- Prohibited activities such as transferring embryo models into a human or animal uterus, and not developing SCBEMs all the way to viability, should be made clear; and
- Members supported the suggestion that projects should be reviewed on a case-by-case basis, with the time limit for each individual project, below the upper limit, being specified by a review committee.

2.2. The above-mentioned recommendations were included in a paper on SCBEM regulation (Act reform) discussed (pages 57-66) at the January 2025 Authority meeting. The Authority agreed (pages 8-9) the following:

- That there was a case for recommending that SCBEMs are subject to some form of statutory regulation;
- That SCBEMs should be regulated on their own terms, separately from human embryos;
- That it should be explicit in law that SCBEMs must not be transferred to a human;
- That having a fixed upper limit on embryo model culture time is important and will be necessary in the future, but that this limit could not be fixed now and should be informed by consensus over time.

2.3. The Authority decision was then shared with the DHSC as part of the process of modernising the HFE Act.

2.4. This paper summarises the results of published studies identified between 1 September 2024 to 31 August 2026. The summary of developments is not an assessment of the studies validity. Annex A explains the scope of this topic and provides a review of the literature on SCBEM published between 1 September 2024 and 31 August 2026.

3. Summary of research developments

SCBEM reviews

3.1. The 2025 International Dutch Embryo Model Meeting heard from researchers working on a wide range of SCBEM topics, with a particular focus on advances in blastoids and gastruloids and included a session on ethics.

3.2. Reviews highlight that SCBEM are becoming more sophisticated and increasingly being used as a research tool to understand human development, in particular early-stage embryogenesis. Researchers are now using SCBEMS to answer specific scientific and clinical questions, not only in early embryogenesis, but also in reproductive medicine and disease modelling. For example, embryo models are being used to study implantation failure, causes of infertility, aneuploidy and early pregnancy loss.

3.3. The studies looking specifically at implantation frequently mention the potential of SCBEMs to allow researchers to study stages of human development that were previously inaccessible due to ethical, technical and legal constraints, the latter including the 14-day rule on embryo research. Authors remark that recent advances in SCBEM offer unprecedented windows into what has been a developmental “black box” including for example how embryo models can be used to obtain mechanistic insights into human implantation and trophoblast invasion.

Pre-implantation models

3.4. Typically, current SCBEMs bypass the zygote to morula stages of embryogenesis, self-organising directly into an early blastocyst-like structure containing components resembling the inner cell mass, an outer cell layer resembling the trophectoderm, and a fluid-filled cavity.

3.5. Blastoid research has moved from developing methods to using them to study embryo development, disease, toxicology, genetics and reproductive medicine. Using blastoids in research brings a number of benefits including being scalable, enabling functional studies difficult to do in human embryos, and allowing investigation of implantation and lineage specification.

3.6. New ways of generating blastoids:

3.6.1. Several studies focused on improving blastoid generation from naïve pluripotent stem cells (nPSCs) which may be embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs). They include the use of DMSO to produce blastoids with improved trophectoderm organisation, implantation-like attachment, lumen formation, and post-implantation development, as well as miR-200 family microRNAs to reprogramme somatic fibroblasts for blastoid generation.

3.7. Programming specific lineages:

3.7.1. Studies looking at directing development of specific cell types. For example a murine study using integrated, three-lineage stem cell-derived embryo model to recapitulate the epiblast (EPI), visceral endoderm (VE), and extraembryonic ectoderm (ExE) and other studies using inducible GATA4 expression to create blastoids.

3.8. Understanding developmental mechanisms:

3.8.1. Studies on cavitation, including one which finds that lysosomes, proton pump V-ATPase and lysosomal acidification are essential for blastoid cavitation.

3.8.2. Research uncovering that at least one human-specific LTR5Hs (a class of recently evolved endogenous retrovirus) is essential for blastoid-forming potential, and identifying important differences between human and mouse development particularly in relation to TCF/LEF DNA binding transcription factors and their impact on WNT signalling responses.

3.8.3. Research showing that human blastoids can be induced to enter a paused state (diapause) which temporally and reversibly reduces the capacity for blastoids to implant.

3.8.4. A study using blastoids to investigate the role of metabolism, specifically the levels of a-ketaglutarate, in early lineage specification.

3.9. Recent studies have expanded the engineering and application of blastoids including:

3.9.1. CRISPR-based approaches in human blastoids using cyanine-labelled ssODNs improved homology-directed repair, cell survival, and editing efficiency,

3.9.2. Blastoids have also emerged as toxicology models, demonstrating adverse effects of BPA, nano-polystyrene, and nano-carbon black on blastoid formation, implantation potential, DNA integrity, structure, and lineage specification.

3.9.3. Implantation research included a 3D implantation model using blastoids together with endometrial cells to better understand implantation failure. The same study tested FDA approved compounds to identify those which improved the efficiency with which blastoids implanted into endometrial cells from patients with recurrent implantation failure. Another study showed that blastoids could undergo implantation and early post-implantation development in an in vitro model of the endometrium. The blastoid/endometrial model was used to identify possible embryo – endometrial cell communication pathways.

Post-implantation models

3.10. Several papers report on SCBEMs that can recapitulate features extending from implantation through gastrulation toward systems capable of neurulation, somitogenesis, haematopoiesis and early organogenesis. These include:

3.10.1. STAT3-driven post-implantation models resembling embryos at Carnegie stages 5–7 (approximately 7-23 days post-fertilation) inducible SCBEMs (iSCBEMs) recapitulating amniotic and chorionic cavity formation, yolk sac-like tissues, anterior–posterior axis establishment and early gastrulation.

3.10.2. Organogenetic primate embryoids derived from cynomolgus totipotent blastomere-like stem cells (cTBLCs) that progress from organised blastoids through gastrulation to early organogenesis.

3.11. Recent SCBEM studies have revealed developmental quality-control mechanisms that promote embryonic robustness and error correction:

3.11.1. 3D epiblast models revealed that TGF-β signalling regulates pluripotent epiblast identity, with TGF-β signalling inhibition preventing epithelial identity.

3.11.2. Separately, bioprinted hiPSC-derived epiblast models demonstrated a role for endogenous WNT signalling in self-organisation into disc-like epiblast structures.

3.12. There is research using some models to fill gaps in mechanistic knowledge:

3.12.1. Separately, bioprinted hiPSC-derived epiblast models demonstrated a role for endogenous WNT signalling in self-organisation into disc-like epiblast structures.

3.13. There were also studies looking at how to scale and standardise embryo models for screening, toxicity testing and mechanistic studies. This includes a microwell screening platform using XEn/EpiCs developed to scale and standardise peri-implantation embryo models for compound screening, enabling detection of development-disrupting morphological changes termed "morphotoxicity."

3.14. Using SCBEMs to form other cells

3.14.1. Researchers developed a "haematoid" model, which replicates some tissue types of embryos at Carnegie stages 12-16 (30-40 days post fertilisation). This resulted in the generation of haemotopoetic stem cells, which if scaled up, could potentially be used in clinical applications.

3.15. Studies on other post-implantation models focus on development of CRISPR-programmed murine embryo models and a bilaminoid model.

Gastruloids and peri-gastruloids

3.16. Key themes found in gastruloid research include progress in the sophistication of models, identifying regulators of gastrulation, cell fate control and lineage commitment and the use of gastruloids in toxicology.

3.17. Peri-gastrulation models are now emerging as a distinct class of SCBEMs, which can capture developmental stages between implantation and gastrulation:

3.17.1. Described models include PTED embryoids that recapitulate features such as a trilaminar embryonic disc, amnion- and yolk-sac-like tissues and primitive haematopoiesis. Another model is human extra-embryoids (hEEs) that model coordinated embryonic and extraembryonic development.

3.18. Increasing sophistication of gastruloid models:

3.18.1. Recent advances in gastruloid models have expanded their developmental complexity, demonstrating mesoderm formation and differentiation of cardiac and skeletal muscle lineages.

3.18.2. The development of anterior–posterior (AP) gastruloids by combining anteriorly and posteriorly patterned pluripotent stem cell populations. This has also addressed the limited representation of anterior structures, generating models with brain-like domains and neural tube-like structures that approximately resemble Carnegie stage 11 embryos.

3.19. Using gastruloids to break symmetry and establish body axes:

3.19.1. Recent gastruloid studies have provided further insight into the mechanisms underlying early anterior–posterior axis formation, showing that polarisation can arise autonomously before Wnt stimulation, with distinct TBXT-positive and TBXT-negative populations and robust patterning across aggregate sizes.

3.19.2. Nodal heterogeneity also precedes detectable Wnt activity, with cell sorting consolidating Wnt-active regions into a single posterior pole.

3.19.3. A very recent study describes a new human SCBEM called a 'disc gastruloid, which aims to recreate formation of the primitive streak and early gastrulation. The disc gastruloid was grown in suspension culture and formed an elongated structure with clear axis patterning. Researchers reported gene expression changes occurring from early disc gastruloid to elongated structure, which recapitulated transcriptional changes in Carnegie stages 6-7 human embryos.

3.20. Identifying new regulators of gastrulation:

3.20.1. Recent gastruloid studies have identified key signalling and regulatory mechanisms controlling germ-layer specification, primitive streak formation, symmetry breaking, and axial organisation.

3.20.2. These include distinct roles for FGF4, FGF17 and FGF8, interactions between retinoic acid and FGF signalling, a role of RARγ, YAP1 and QSER1 in gastruloid development and developmental signalling. Research has identified a primate-specific requirement for the ILF2/3 complex in three-germ-layer differentiation.

3.20.3. Disease modelling using PTEN-mutant gastruloids further demonstrated excessive elongation, enhanced epithelial-to-mesenchymal transition (EMT), and increased AKT signalling.

3.21. Cell fate control and lineage commitment:

3.21.1. Studies have provided insight into the cellular and molecular mechanisms governing self-organisation, lineage commitment, and normal development.

3.21.2. Key findings include cross-talk between the spinal cord and paraxial mesoderm, required for spinal cord development. Evidence has emerged on the regulation of axial elongation and lineage commitment through T-UCstem1–DKK1–WNT signalling, a role for E- to N-cadherin switching in morphogenesis, and the inheritance of developmental biases through multiple cell divisions before gastruloid formation.

3.21.3. Spatial single-cell mapping further demonstrated highly reproducible cellular composition, spatial organisation, and differentiation trajectories across gastruloids.

3.22. Gastruloids as toxicology platforms

3.22.1. Toxicity testing studies identify adverse effects of NHC (the active metabolite of molnupiravir), amiodarone, dronedarone, and vinpocetine on human and/or mouse gastruloid development at clinically or pharmacologically relevant concentrations.

Axioloids and Somitoids

3.23. Research using somitoid and axioloid models investigated mechanisms underlying human embryonic patterning and phenotypic variation.

3.23.1. Somitoids revealed reciprocal signalling between the neural tube and somites, involving ALDH1A2 and retinoic acid signalling in spontaneous neural-tube patterning.

3.23.2. Evidence on axioloids demonstrated that divergent metabolic states can drive and predict phenotypic variation in embryo models.

Assembloids

3.24. A study used a microfluidic endometrial epithelium–blastoid platform to assess functional endometrial receptivity through blastoid adhesion, providing a potential model for evaluating therapeutic interventions for infertility.

Regulation, policy and ethics

3.25. Papers here covered a wide range of topics including the need for specific governance mechanisms, how to characterise SCBEMs for regulatory purposes, the importance of terminology, public understanding and what features or stages of development raise ethical concerns. Several papers each with a different main focus, raise the concern that scientific progress may be advancing faster than public debate and regulation.

3.26. On governance and regulation, there was agreement that SCBEMs require their own specific frameworks. Factors discussed in the literature included:

- Requirement for projects to have a clear scientific rationale;
- Consideration of developmental capacity and the challenges assessing it;
- Desirability of case-by-case approval;
- Transparency in decision making and research e.g. public registers of approved projects
- Desirability of regulation and governance arrangements that can adapt as the science advances;

The above aligns well with the HFEA position on regulation of SCBEMs and also with the updated ISSCR guidance.

3.27. Debate on the moral status of SCBEMs continues:

3.27.1. A challenge to arguments that human embryos and SCBEMs are morally equivalent opining that embryo models may require different ethical treatment. Also made was a suggestion that multiple forms of value including direct moral status, symbolic value, relational value and instrumental value should be considered.

3.28. There were some new proposals on SCBEM ethical oversight including:

3.28.1. An "embedded ethics" model requiring iterative reassessment during projects to address emerging ethical concerns. This makes ethical review an ongoing process not a one-off approval.

3.28.2. Defining the specific characteristics that should trigger ethical scrutiny including developmental stage, tissue integrity, foetal potential and neural development. Also considered important was establishing intended use, public perception and researcher responsibility.

3.28.3. A proposed two-tier oversight system for SCBEM is proposed based on a single guiding principle: SCBEMs should never attain sentience. Tier 1 would correspond roughly to day 28 post fertilisation (neural tube closure or defined somite/limb-bud stage) and tier 2 to day 56 post fertilisation.

3.29. There are developments in national regulation of SCBEMs to report:

3.29.1. Japan introduced revised SCBEM guidance in April 2026 to bring all human embryo model research under a single case-by-case oversight system requiring ethics review and notification to the national government. The guidance aligns very closely with the revised ISCCR revised guidance.

3.29.2. Calls for a comprehensive review of the current Australian legislation on embryo research because of the challenges presented by SCBEMs (some of which, like blastoids, are captured under the definition of embryos in Australia and are regulated as such) and extended culture technologies.

3.29.3. 2024 report of the Nuffield Council on Bioethics making the case for flexible governance, future-proofing regulation and proportional oversight in the UK. This included backing the UK SCBEM Code of Practice, amending the HFE act to cover SCBEMs, setting an upper culture limit (acknowledging associated uncertainty), identifying some red lines around sentience, and recommending the use of regulatory sandboxes.

3.30. Several papers look at terminology and public trust as governance issues:

3.30.1. Terminology should be scientifically accurate and ethically transparent; the terms “synthetic embryos” and “artificial embryos” can mislead scientists and the public.

3.30.2. A review of competing terms like embryo models, embryoids, synthetic embryos etc, noted that different terms carry assumptions about developmental capacity and moral status.

3.31. Please note that the HFEA Executive will attend a workshop on the ethical limits of SCBEM research at the Lorentz Centre in Leiden, Netherlands from 21-25 September and will report back on the workshop at the Committee meeting.

Methods, benchmarking and validation

3.32. This is a new area of research in SCBEMs. It no doubt reflects progress in the field that researchers now feel able to seek to benchmark and validate embryo models, something which has been long called for including by the SCAAC. A common message is that SCBEMs are now sufficiently sophisticated that the challenge is not merely generating them, but assessing their reliability, reproducibility and potential contribution to biology.

3.33. Several studies focus on improving reproducibility and reducing variability in SCBEM generation including:

3.33.1. Development of an optimised pre-culture protocol for mouse ESCs prior to gastruloid formation, providing workflows for optimising cell-line-specific conditions, guidance on reproducible germ-layer formation and approaches for evaluating protocol performance.

3.33.2. Presentation of an improved protocol for long-term gastruloid culture, which reported embedding gastruloids in Matrigel at 96 hours, extending culture to 168 hours and maintaining derivatives of all three germ layers.

3.33.3. Development of a microfluidic droplet platform for PSC culture and differentiation, creating a confined microenvironment which enhanced cell-cell signalling, tissue organisation, and gastruloid patterning.

3.34. Researchers have sought to establish standards and benchmarking frameworks, in particular how to benchmark against in vivo development:

3.34.1. Proposal of criteria for evaluating SCBEMs based on efficiency, reproducibility, fidelity and developmental relevance.

3.34.2. Development of a comprehensive human embryo reference atlas by integrating multiple human single-cell datasets spanning development from zygote to gastrula. This enabled the creation of a tool to allow researchers to project SCBEM datasets onto a common reference, assign cell identities and identify mis-annotation.

3.34.3. Proposal of a comparative framework for evaluating blastoid fidelity created by comparing seven published human blastoid systems using single-cell transcriptomics. Undertaking such

comparisons revealed that naïve PSC-derived blastoids more closely resemble blastocysts, whereas EPSC-derived blastoids often show aberrant lineage composition.

3.35. Another theme in this area of research is increasing use of AI and machine learning tools to validate, classify and quality control embryo models:

3.35.1. A deep-learning approach for assigning cell identities in embryo models to assess whether SCBEM-derived cells truly resemble their embryonic counterparts. The tool integrates scRNA-seq datasets, classifies in vitro-derived cells, and provides confidence scores for identity assignments.

3.35.2. Deep Blastoid, a deep-learning classifier for human blastoids, which analyses brightfield images only, evaluates >270 images/second and achieves up to 97% classification accuracy.

3.35.3. An AI framework to standardise embryo and blastoid grading combining multiple convolutional neural networks, visual explainability tools, and large language model reasoning to achieve near-human expert performance.

3.35.4. Application of deep manifold learning to analyse developmental trajectories in a post-implantation embryoid model. The framework captures hidden developmental states, reconstructs developmental trajectories, and generates realistic intermediate developmental stages computationally

3.35.1. Computational modelling suggests that axis formation is governed by a combination of local and longer-range cellular interactions.

3.36. Another area of focus is quantitative characterisation of embryo models at scale, which includes advanced imaging platforms:

3.36.1. Whole-mount imaging and computational analysis platform enabling deep two-photon imaging, nuclear segmentation, spatial gene-expression quantification and multi-scale tissue analysis. Applied to gastruloids, it links cellular morphology and gene expression to tissue organisation

3.36.2. A miniaturised LC-MS platform capable of profiling oxysterols in single gastruloids to study embryo model metabolism. This revealed significant metabolic heterogeneity between individual gastruloids, unexpected oxysterol species, and the feasibility of single-structure metabolomics.

3.36.3. A high-throughput morphometric screening platform using XEn/EpiC peri-implantation embryo models to quantify shape, texture, marker expression and morphotoxic effects.

3.37. AI models have also been used to help predict developmental failure and teratogenicity:

3.37.1. FATE-MAP, a computational framework incorporating deep learning, mechanistic modelling and phenotypic mapping can identify gastrulation failure modes, predict developmental outcomes and flag previously unrecognised candidate teratogens.

3.38. Some studies have looked at engineering approaches and technological innovation for next generation embryo models:

3.38.1. A review of human SCBEM technologies classifying platforms according to engineering principles including micropatterning, biomaterials, microwells, microfluidics, and dynamic culture systems. This review found that developmental fidelity depends heavily on physical and engineering constraints, not just signalling factors.

3.38.2. Technological innovations with applications in developmental biology, pregnancy loss, birth-defect research and developmental toxicology enabling advances in extended embryo culture systems and embryo models.

4. Questions for the committee

4.1. SCAAC members are asked to consider the following scientific questions related to SCBEMs:

- Consider the progress of research into SCBEMs;
- Advise if they are aware of any other recent developments in the field of SCBEMS;
- Review whether any outputs from the HFEA addressing SCBEMs are required.

5. Annex A: Scientific literature review

5.1. Annex A has been circulated to the committee as a separate Excel document, which provides details on the available research on SCBEMs published between 1 September 2024 and 31 August 2026.

5.2. This topic includes research into stem cell derived embryo models and their precursors:

- Pre-implantation models such as Morula-like models, blastoids, blastocyst-like models, and other preimplantation embryo models which do not meet morula/blastoid definitions
- Post-implantation embryo models and embryoids, including bilaminoids, heC-embryoids and related models
- Gastruloids and peri-gastruloids
- Axioloids and somitoids
- Assembloids

5.2.1. Studies using animal based SCBEM are included only where they are or could be translational to human research (mostly murine studies). Studies looking at livestock (bovine, porcine), species conservation etc are excluded.

5.2.2. Methods of developing, benchmarking and validating SCBEMs.

5.2.3. The regulation, public policy and ethical issues arising from SCBEMs.

5.2.4. This topic excludes techniques to derive embryonic and embryonic-like stem cells focused on their application to develop models investigating early embryonic development. It also excludes reproductive organoids which is a separate topic. However, assembloids combining cell/tissues or reproductive organoids with embryo models are considered within scope. The use of endometrial organoids to model the process of implantation using SCBEM is also within scope.

In vitro derived gametes (IVGs)

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	10
Paper number:	HFEA (07/10/2026) 010
Meeting date:	07 October 2026
Author:	Mina Mincheva, Policy Manager (HFEA)
Annexes	Annex A – Background of oocyte in vitro maturation Annex B – Literature review and scope of In vitro derived gametes (IVGs)

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • Consider the progress of research into IVG; • Advise if they are aware of any other recent developments; • Review whether any outputs from the HFEA are required addressing the use of IVGs; and • Advise on scope of literature search and animal models regarding IVM approaches to be considered (refer to points 3 and 4 at 5.2 in Annex B).
Resource implications:	Within budget
Implementation date:	N/A
Communication(s):	Minutes of the committee discussion will be published on the SCAAC webpage and communicated to the sector via our Clinic Focus newsletter.
Organisational risk:	Low

1. Background

1.1. Primordial germ cells (PGCs) are the common precursors of spermatozoa and oocytes. During early embryonic development, they undergo migration to and colonisation of the developing gonads alongside extensive epigenetic reprogramming and chromatin reorganisation events. Following gonadal sex determination, PGCs differentiate along sex-specific developmental trajectories, giving rise to pro-spermatogonia in the male and oogonia in the female. Pro-spermatogonia subsequently give rise to the spermatogonial lineage, whereas oogonia proliferate and enter meiosis during foetal development to form primary oocytes.

1.2. Approaches to generate in vitro derived gametes (IVGs) can be broadly divided into two categories depending on the initial source of cells:

- Two- (2D) and three-dimensional (3D) culture systems using immature germ cells (the committed germ cell lineage) retrieved from the gonads at various stages of gametogenesis. This includes embryonic primordial germ cells (PGCs) and germline stem cells postnatally.
- 2D and 3D culture systems for the generation of functional gametes from pluripotent stem cells. These can be embryonic stem cells (ESC) or somatic cells reprogrammed to induced pluripotent stem cells (iPSC) which can be induced to generate primordial germ cell-like cells (PGCLCs). For example, stem cell-based embryo models are a type of 3D model to generate IVGs.
- There are also 3D approaches where gonadal immature germ cells or pluripotent stem cell-derived gametes (eg PGCLCs) are co-cultured with gonadal tissue. However, reconstruction of a functional gonadal somatic niche from pluripotent stem cells has remained one of the major bottlenecks in IVG research.

1.3. Therefore, oocytes and spermatozoa derived in the laboratory from immature germ cells or stem cell sources can be referred to as in vitro derived gametes (IVGs).

1.4. The Human Fertilisation and Embryology (HFE) Act currently prohibits the clinical use of IVGs derived from pluripotent stem cell sources. Section 3ZA requires that eggs or sperm permitted for treatment are “produced by or extracted from the ovaries of a woman/testes of a man”. In January 2025, the HFEA recommended that **IVGs should be subject to statutory regulation** in time, which was one of a range of **recommendations for modernising fertility law**.

1.5. The use of immature sperm (i.e. spermatids) is prohibited in clinical practice under the **Authorised processes list** that describes the processes clinics can use to carry out the licensable activities set out in the HFE Act.

1.6. Whilst IVGs derived from pluripotent stem cell sources cannot be used in treatment in the UK, they can be used in research, for example research into germ cell development and cell differentiation. Researchers in the UK need an HFEA research licence if they wish to investigate whether human eggs and sperm derived in vitro from pluripotent stem cell sources could undergo fertilisation and the early stages of embryo development.

1.7. IVGs were last **discussed** by SCAAC in October 2024. The **discussion** was primarily focused on the Committee’s recommendations related to the current and anticipated future uses of IVGs

in research and treatment, and how the HFE Act may be 'future proofed' to accommodate technical and clinical advances. Members made recommendations on definition of gametes in the HFEA Act (as amended) and embryos generated from IVGs.

1.8. In vitro spermatogenesis for male fertility preservation **was discussed** at the HFEA's Annual Horizon Scanning Meeting at the European Society for Human Reproduction and Embryology (ESHRE) annual meeting in 2025. Highlights of the discussion covered challenges with implementation of cryopreserved immature testicular tissue auto-transplantation related to identifying patient groups, eligibility criteria, protocol optimisation and long-term follow-up. Consent practice, current good practice recommendations on setting up testicular cryopreservation programmes, as well as clinical and research activity in fertility preservation were also discussed.

1.9. In vitro maturation (IVM) – a method for supporting maturation of immature oocytes in vitro – is a blanket term applied to the process used to obtain mature oocytes from immature cumulus-oocyte complexes (COCs) retrieved from antral follicles. There are different methods of IVM, which typically involve some form of ovarian stimulation or gonadotropins and an in vitro maturation step. The most commonly used IVM methods are clinical IVM (standard IVM and rescue IVM), bi-phasic IVM (including capacitation in vitro maturation, CAPA-IVM), and ovarian tissue-derived oocyte IVM (OTO-IVM). Annex A provides further details as well as respective patient groups for whom these procedures are used.

1.10. In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles) is an authorised process on the **Authorised processes list** under licenses activity 'Processing gametes'. In June 2026 SCAAC discussed the scope of IVM for clinical practice. The Committee **concluded** that the current inclusion of IVM for oocytes on the authorised processes list does not include its use for the maturation of oocytes obtained from ovarian tissue.

1.11. Discussion around IVM of oocytes was held at the Horizon Scanning Meeting at ESHRE 2026. The discussion focused on capacitation in vitro maturation (CAPA-IVM) as an alternative approach to delivering ART for selected patient groups. Potential benefits highlighted included reduced treatment costs, prevention of ovarian hyperstimulation syndrome (OHSS), avoidance of ovarian stimulation, and a reduction in the physical and emotional burden of treatment. Participants also emphasised the need for further evidence on efficacy and safety before wider implementation.

1.12. This paper summarises the results of published studies identified within the specified time frame (1 September 2024 to 31 August 2026), during which the literature search was conducted. The summary of developments is not an assessment of the studies validity. When last discussed in October 2024, the summary of research developments on IVGs did not include literature search for the subtopic of IVM which was presented as a briefing.

2. Summary of research developments

2.1. In July 2026 the Regulatory Horizons' Council (RHC) published a **report** on modernising regulatory pathways for assisted reproductive technologies (ART), with a particular focus on IVGs. It looks at how the UK can maintain and develop its position as a scientific innovator, using IVGs as a case study. The RHC's preferred approach is to create regulatory readiness ahead of

technological readiness, by establishing a future-proof, technology-neutral framework for novel assisted reproductive technologies before they become clinically viable. The underlying principles are proactive governance to build legitimacy through ethical scrutiny and early public engagement, strong Parliamentary oversight, and a staged clinical evidence generation that enables innovation while maintaining public trust and patient safety.

2.2. The HFEA published a response to this report on 10 July 2026.

Human studies on in vitro gametogenesis

2.3. Research shows progress in directing human induced pluripotent stem cells (iPSCs) towards human primordial germ cell-like cells (hPGCLCs) and modelling subsequent germline development, with advances in defining the cellular niche, molecular regulators, and culture conditions required for germ cell specification and maturation.

- hPGCLCs can be generated from diverse somatic cell sources, including peripheral blood- and cumulus-derived iPSCs. This evidence demonstrated that the X-chromosome gene dosage in the different iPSC clones used to generate hPGCLCs showed aberrant variation depending on the starting iPSC clone, but the cell type of origin did not consistently affect the X-chromosome state of the iPSC lines. Other studies used defined long-term feeder- and serum-free systems to improve culture scalability of hPGCLCs.
- Studies of the hPGCLC niche demonstrate that somatic cell environment influences germline specification and maturation, with amnion-like cells promoting hPGCLC maturation and migration. Research using stem cell-based gastruloid models identified a shared amnion–PGC progenitor population at the amnion–epiblast boundary, indicating that stem cell-based embryo models can be a source of hPGCLCs. Germline maturation has also been modelled using xenogeneic testis systems supporting progression towards meiotic germ cells.
- Complementary approaches to modelling meiosis include mitomeiosis, which induces loss of chromosomes including at low frequency haploidisation of the somatic genome in somatic cell nuclear transfer (SCNT)-derived human oocytes. Others show iPSC-based transcription factor manipulation that recapitulates meiotic chromosome axis formation and synapsis while bypassing the PGCLC stage.

2.4. Three-dimensional (3D) culture systems based on decellularised testicular scaffolds or dissociated foetal testes support survival, maintenance and differentiation of spermatogonial stem cells, but efficient meiotic progression remains unresolved.

2.5. Transcription factor-based reprogramming enables efficient generation of oogonia-like cells from iPSCs, while 3D hydrogel systems preserve human cumulus granulosa cell viability and endocrine function long-term.

Animal studies on in vitro gametogenesis

2.6. Research on improving culture conditions for optimal in vitro growth and subsequent in vitro maturation of oocyte-cumulus granulosa cell complexes (OCGCs) has used porcine and murine models. Key advances include antioxidant supplementation and use of natural biomaterials or scaffold-free culture to support oocyte growth, maturation, steroidogenesis, cumulus expansion and blastocyst formation. Most of identified literature focuses on pre-clinical research, mechanistic and safety studies on in vitro maturation of immature oocytes (see below).

2.7. On the male side, dynamic bioreactor culture with decellularised human testicular matrix and exosomes promoted murine spermatogonial stem cell proliferation and differentiation towards elongated spermatids.

2.8. A seminal murine study (Yoshino et al., 2026)[1] stablished a fully pluripotent stem cell-derived model of testicular development by reconstituting the testicular somatic niche from mouse pluripotent stem cells. It recreated key aspects of sex determination and testis formation in vitro. The resulting tissue formed seminiferous tubule-like structures, supported pluripotent stem cell-derived PGCLCs, generated spermatogonial stem cells, and ultimately produced functional sperm after transplantation.

2.9. Another study advanced the field of reconstructing functional testicular somatic cells from pluripotent stem cells. The study (Sato et al., 2026)[2] used mouse embryonic stem cells to generate Sertoli-like and Leydig-like cells that closely resemble those found in the developing testis. These cells supported spermatogenesis in vitro and enabled the production of spermatids that generated viable offspring following round spermatid injection,

Opinion articles, commentaries and reviews on ethical, societal and legal perspectives on IVGs

2.10. The literature highlights the broad reproductive, ethical, legal and societal implications of IVGs, particularly their potential to expand reproductive options for infertility, age-related infertility, transgender/intersex and solo reproduction. It also covers themes on possibilities for mass production of donor gametes, genetic disease prevention and posthumous conception. These applications raise common concerns around safety, equitable access, parenthood, regulation, embryo and gamete use, and the potential for genetic enhancement and eugenics.

2.11. At a broader societal level, studies consider how IVGs could influence fertility rates, reproductive policy, population dynamics and geopolitical power, while stakeholder research highlights concern about technological control and the changing value of reproductive materials. The potential for somatic cell genome editing of iPSCs which can be used for generation of IVGs further raises the possibility of heritable genetic modification, intensifying concerns around safety, regulation and enhancement.

2.12. The committee of the National Academies of Sciences, Engineering, and Medicine published a commentary arising from a public **workshop** held in 2023. The workshop examined the scientific progress, potential applications, and remaining technical barriers to creating human eggs and sperm in vitro from embryonic and iPCSs. It considered the ethical and social implications of their use, alongside how current regulations address research and potential reproductive applications.

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[1] Yoshino T, Sasada H, Sato T, Nakamura T, Shirane K, Ohta H, Kamoshita M, Inoue M, Matsudaira Y, Liu C, Matsufuji M, Tachibana M, Morohashi KI, Ikawa M, Saitou M, Ogawa T, Hayashi K. Reconstitution of sex determination and the testicular niche using mouse pluripotent stem cells. Science. 2026;391(6788):eaea0296

[2] Sato T, Yoshino T, Ohtsuka M, Suzuki T, Matsumura T, Matsudaira Y, Ishikawa-Yamauchi Y, Maeda S, Yabukami H, Kanai Y, Inoue M, Shima Y, Tachibana M, Matoba S, Inoue K, Ogonuki N, Ogura A, Hayashi K, Ogawa T. Generation of functionally competent testicular somatic cells from pluripotent stem cells. Sci Adv. 2026 Feb 27;12(9):eadz0269[R

Reviews on scientific advances in culture methods for achieving IVGs

2.13. Many reviews on IVGs explore the molecular and cellular mechanisms underlying human gametogenesis, including primordial germ-cell specification, epigenetic reprogramming, meiosis, sex-specific germ cell differentiation. They also summarise research on the specification and differentiation of pluripotent stem cells (embryonic and iPCSs) to primordial germ cell like cells and attempts to differentiate and mature them in vitro. Reviews further focus on technological approaches and translational applications of IVGs, including two-dimensional/three-dimensional culture, organoids, artificial ovaries/testes, biomaterials, microfluidics and tissue engineering for fertility preservation and infertility treatment. The literature also highlights challenges around functional maturation, reproducibility, long-term safety studies, standardisation and clinical translation.

In vitro maturation (IVM) of human immature oocytes

2.14. Clinical evidence continues to evaluate standard IVM as an alternative to conventional ovarian stimulation, particularly in patients with polycystic ovary syndrome, PCOS (now renamed to polyendocrine metabolic ovarian syndrome, PMOS). In recent evidence comparing unstimulated IVM with conventional IVF in women with PCOS report a lower 36-month cumulative live birth rate following IVM, despite avoidance of severe ovarian hyperstimulation syndrome (OHSS). Natural-cycle IVF combined with IVM has also been investigated, showing that different sizes of the dominant follicle at hCG triggering did not affect laboratory and clinical outcomes. The updated Cochrane review concludes that IVM (and CAPA-IVM) for patients with PCOS substantially reduces moderate-to-severe OHSS compared with conventional IVF, though the effects on live birth remain uncertain. Human iPSC-derived ovarian support cells are also being developed as a clinical-grade product (Fertilo) to support oocyte maturation, representing a distinct strategy for recreating the somatic support normally provided by the ovarian follicular environment.

2.15. Studies have focused on identifying patients most likely to benefit from rescue IVM and improving the developmental competence of immature oocytes. A large retrospective analysis identified factors associated with oocyte immaturity and proposed an immaturity rate above 51% in retrievals yielding at least five oocytes as a potential criterion for selecting patients for future rescue-IVM studies. Culture-medium studies have also demonstrated that culture conditions influence maturation and developmental competence of rescued germinal vesicle (GV)-stage oocytes. An eight-year retrospective study in selected patients with unexpectedly low mature-oocyte yield found that GV rescue increased the number of mature oocytes and available euploid blastocysts despite lower blastulation of rescued oocytes. It concluded that rescue IVM was associated with a 20% relative increase in the number of patients achieving a live birth.

2.16. Research has focused on optimising the pre-maturation phase of biphasic IVM to better support oocyte developmental competence. Some evidence suggests that low (physiological) oxygen tension during pre-IVM alters cellular metabolism of COCs and may promote greater metabolic efficiency compared with atmospheric oxygen. A more recent study found altered gene expression for metabolic pathways at low oxygen during pre-maturation, fewer fertilised oocytes but not adversely affected subsequent embryo development. Recent data on five-year follow-up of children born from CAPA-IVM vs IVF in patients with high antral follicle count report no

significant concerns regarding the effects of CAPA-IVM on developmental progress and emotional wellbeing of children.

2.17. Research on in vitro follicle growth and ovarian tissue-derived oocyte IVM (OTO-IVM) has progressed along complementary pathways. In-vitro culture of follicles isolated from fresh or cryopreserved ovarian tissue has demonstrated that follicular development can be supported through multiple developmental stages. In parallel, recent studies have extended OTO-IVM towards fertility-preservation applications, including its use alongside ovarian tissue cryopreservation and evaluation of clinical and laboratory factors affecting oocyte recovery, quality and maturation. Clinical observational evidence indicates that gonadotropin administration before ovarian tissue collection is associated with higher maturation rates of ovarian tissue-derived oocytes, although maturation rates remain lower than those achieved following conventional ovarian stimulation. OTO-IVM has been investigated particularly where conventional ovarian stimulation may not be feasible or fertility preservation is urgent, although evidence on subsequent developmental and reproductive outcomes remains limited. Studies of FSH/LH signalling and paracrine cumulus–oocyte signalling have also provided insights into mechanisms regulating IVM of oocytes recovered from small antral follicles.

In vitro maturation (IVM) of oocytes – animal studies

Standard IVM

2.18. Translational animal studies increasingly move focus beyond improving maturation rate towards understanding how IVM differs from physiological maturation and how those differences affect downstream oocyte competence. Gene expression, proteomic and extracellular-matrix studies have identified persistent molecular differences between in-vitro- and in-vivo matured oocytes. Results from studies on metabolomics-guided media optimisation, microfluidic-based cultures, or culture systems incorporating stem cell-derived ovarian support cells indicate more physiologically informed approaches to improving IVM. Notably, ovarian-support-cell IVM has resulted in healthy murine offspring with multigenerational follow-up. Together, animal evidence implies that future optimisation of human IVM is likely to depend increasingly on reproducing the follicular microenvironment and demonstrating developmental and molecular competence rather than increasing MII rates alone.

Biphasic/CAPA-IVM

2.19. Preclinical work has focused on optimisation of the pre-maturation phase of biphasic IVM. Studies using C-type natriuretic peptide (CNP) and other meiotic-arrest strategies have investigated the maintenance of cumulus-cell physiology and the optimal conditions for controlled meiotic arrest before IVM. Follicular-fluid extracellular vesicles have also improved developmental competence when incorporated into simulated physiological oocyte maturation system, while use of CAPA-IVM on prepubertal goat oocytes has been found to have a different effect on maturation of oocytes from large vs small follicles. Together, the evidence shows that effects of interventions in the pre-maturation phase are assessed against maturation rate and blastocyst formation, but later developmental outcomes are not reported.

OTO-IVM

2.20. Animal studies continue to address biological limitations relevant to obtaining competent oocytes from ovarian tissue and immature follicles. Recent work demonstrates that isolation conditions,

preservation of granulosa–oocyte interactions and follicle structure in culture influence subsequent oocyte competence. Matrix-free three-dimensional culture improved meiotic and developmental competence in mouse follicles, while viable eggs have been produced from undeveloped oocytes in mouse preantral follicles following reaggregation of granulosa–oocyte complexes. Evidence from isolated primordial follicles has identified follicle survival following removal from the ovarian microenvironment as an additional challenge for developing in-vitro follicle-growth systems.

3. Recommendations

3.1. Members are asked to:

- Consider the progress of research into IVG;
- Advise if they are aware of any other recent developments;
- Review whether any outputs from the HFEA are required addressing the use of IVGs; and
- Advise on scope of literature search and animal models regarding IVM approaches to be considered (refer to points 3 and 4 at 5.2 in Annex B).

4. Annex A – Background of oocyte in vitro maturation

4.1. Standard IVM involves maturation in vitro of immature germinal vesicle (GV)-stage intact COCs in one step to MII, from unstimulated or FSH-primed patients.[3] Indications for standard/clinical IVM are patients with polycystic ovarian syndrome, PCOS (now renamed to polyendocrine metabolic ovarian syndrome, PMOS), cancer patients for fertility preservation before chemotherapy and women who do not respond to gonadotropin stimulation. [3] Standard IVM is routinely used in Belgium at **Brussels IVF fertility centre** for patients with PCOS and some cancer patients.

4.2. Rescue IVM entails maturation in vitro of cumulus denuded GV stage oocytes that have been needle aspirated in conventional IVF/ICSI cycles following controlled ovarian stimulation. [3]

4.3. Bi-phasic IVM entails maturation in vitro of immature GV-stage intact COCs in two steps, from unstimulated or FSH-primed patients. Intact COCs are GV-arrested in step one (called pre-IVM) and matured in step two. In the pre-IVM phase, intact COCs are deliberately arrested at the GV-stage, the purpose of which allow for cytoplasmic maturation of the oocyte. [3] Bi-phasic IVM has been reported in just three types of patients, including women diagnosed with PCOS, women with a high AFC, and women with gynaecological malignancies. [3]

[3] Gilchrist, R. B., Ho, T. M., De Vos, M., Sanchez, F., Romero, S., Ledger, W. L., Anckaert, E., Vuong, L. N., & Smitz, J. (2024). A fresh start for IVM: capacitating the oocyte for development using pre-IVM. Human Reproduction Update, 30(1), 3–25.

4.4. Ovarian tissue-derived oocyte IVM (OTO-IVM) or ex vivo IVM involves maturation in vitro of immature GV-stage intact COCs collected from ovarian tissue ex vivo, typically without any prior gonadotrophin stimulation. [3]

5. Annex B – Literature review and scope of in vitro derived gametes (IVGs)

5.1. Annex A has been circulated to the committee as a separate Excel document, which provides details on the available research on IVGs published between 1 September 2024 and 31 August 2026.

5.2. This topic includes research into:

1) methods for achieving in vitro gametogenesis (organoids, three-dimensional systems, scaffolds, etc) in both human and animal models. This includes the use of embryonic stem cells, induced pluripotent stem cells, immature gametes retrieved from the gonads.
2) recreating early stages of gametogenesis (ie primordial germ cells and primordial germ cell-like cells, and their induction to germ cells).
3) In vitro maturation (IVM) of oocytes, including clinical IVM (standard IVM and rescue IVM) as well as experimental approaches such as in vitro follicle growth and ovarian tissue-derived oocyte IVM (OTO-IVM), and translational stage approaches like bi-phasic IVM (including CAPA-IVM). The search includes both human and animal studies.
4) The selection criteria for including animal studies on oocyte IVM in the summary of evidence were studies that contextualised developments that could plausibly inform human IVM applications. These included mechanistic or protocol-optimisation studies with potential translational relevance, as well as studies addressing the efficacy, safety or biological limitations of biphasic/CAPA-IVM, standard IVM or OTO-IVM. Rescue IVM was not considered a separate category for the animal literature, as the term primarily describes a clinical scenario in which unexpectedly immature oocytes retrieved following ovarian stimulation are subsequently matured in vitro. In experimental animal studies, immature oocytes are generally collected with the intention of undergoing IVM as part of the study protocol and were therefore classified according to the maturation approach used rather than as rescue IVM.
5) Opinion articles on the ethical and legal perspectives relevant to this topic.

5.3. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search, and to ensure comprehensive coverage across platforms.