Scientific and Clinical Advances Advisory Committee (SCAAC) – Minutes

Monday 7th October 2024, 10:00am – 3:00pm
Microsoft Teams

Authority members	Present	Tim Child (Chair) Alex Kafetz Frances Flinter Christine Watson Zeynep Gurtin (virtually before 12pm)
External advisers	Present	Jason Kasraie Anthony Perry Scott Nelson (virtual) Kevin McEleny Richard Anderson Alison Campbell (virtual) Peter Rugg-Gunn Veronique Berman
	Apologies	Ying Cheong
Invited expert	Present	Robin Lovell-Badge (The Francis Crick Institute)
Speakers	Present	Mary Herbert (Newcastle Fertility Centre at Life) Louise Hyslop (Newcastle Fertility Centre at Life) Rekha Pillai (Newcastle Fertility Centre at Life) Meenakshi Choudhary (Newcastle Fertility Centre at Life) Robert McFarland (Newcastle Hospitals NHS Foundation Trust)
Executive	Present	Julia Chain (Chair of Authority) Peter Thompson (Chief Executive) Clare Ettinghausen (Director of Strategy and Corporate Affairs) Rachel Cutting (Director of Compliance and Information – virtual) Dina Halai (Head of Policy, Scientific) Rebecca Taylor (Scientific Policy Manager) Mina Mincheva (Policy Manager, Scientific) Molly Davies (Scientific Policy Officer; Committee Secretariat)
Observers	Present	Kath Bainbridge (Department of Health and Social Care) Ana Hallgarten (Department of Health and Social Care)

		Adrian Thompson (Boardroom Apprentice) Several HFEA staff observed the meeting virtually as relevant to their role or induction into the organisation.

1. Welcome, apologies, declarations of interest

1.1. The Chair welcomed the Committee, thanking them for attending.

1.2. Apologies were received from Ying Cheong.

1.3. The Chair reminded members of the advisory role of the SCAAC, highlighting that members should advise the HFEA on any significant implications for licensing and regulation arising out of scientific and clinical developments in assisted conception, embryo research and related areas.

1.4. The following conflicts of interests were declared concerning the meeting agenda:

- Scott Nelson highlighted that he is a co-author on the Nature Medicine paper titled 'Deep learning versus manual morphology-based embryo selection in IVF: a randomized, double-blind noninferiority trial' due to be discussed under item 4: Relevant public health developments and research findings.
- Kevin McEleney highlighted that he is employed as a Consultant Andrologist and Clinical Lead for the male factor clinic at Newcastle Fertility Centre at the International Centre for Life which operate the Mitochondrial Donation Programme.

1.5. No further conflicts of interest were declared.

2. Matters arising

2.1. The Executive updated the Committee on the matters arising:

2.1.1. During the June 2024 meeting, the Committee recommended that the Executive update the patient facing website information on preimplantation genetic testing (PGT-P) and intracytoplasmic sperm injection (ICSI) for non-male factor infertility.

2.1.2. With the support of Frances Flinter, the 'Embryo testing and treatments for disease' webpage has since been updated to clearly state that, in relation to PGT-P, there is currently a lack of evidence to support the use of preimplantation genetic testing for polygenic risk scores and that it is unlawful to do so under the current UK law.

2.1.3. Information on the 'Intracytoplasmic sperm injection (ICSI)' webpage has also been made more explicit, stating that there is no evidence to support the use of ICSI for non-male factor infertility and that its use for this purpose is not endorsed by professional body guidelines.

2.1.4. Following discussions at the June meeting, the SCAAC also recommended that testosterone supplementation should be rated as a treatment add on. The Executive is due to meet with the review panel (comprising of a small number of SCAAC members) to determine which outcomes/populations should be rated and is in the process of commissioning an expert literature review of the evidence. This will be bought back to the Committee for a rating once completed (anticipated February 2025).

3. Chair's business

3.1. The Chair updated members on the HFEA's annual Horizon Scanning Meeting held in July 2024 during the European Society of Human Reproductive Medicine (ESHRE) conference:

3.1.1. This year attendees discussed developments relevant to genetic screening of the early embryo, the promise of organoids, future uses of AI in the IVF lab, and emerging strategies in ovarian rejuvenation with invited speakers Professor Shai Carmi (Hebrew University of Jerusalem), Dr Margherita Yayoi Turco (Friedrich Miescher Institute for Biomedical Research), Daniella Gilboa (AIVF), and Professor Emri Seli (Yale School of Medicine).

3.1.2. Key takeaways and discussion points included:

- Genetic screening of the preimplantation embryo for polygenic diseases: patient populations to whom it may offered; ethical considerations; technical limitations and challenges surrounding validation
- Promise of organoids: clinical applications of female reproductive tract organoids; technical considerations related to method optimisation; good manufacturing practice for clinical implementation and model fidelity
- AI in the IVF lab: regulatory challenges arising from fast paced developments in AI use; validation, liability and standardisation considerations
- Ovarian rejuvenation: challenges with demonstrating efficacy of ovarian rejuvenation techniques and applicability for certain patient groups

3.2. The Chair agreed with the concerns around the use of platelet rich plasma (PRP) therapy (a form of 'ovarian rejuvenation') in reproductive medicine, highlighting that the limited evidence currently available shows no evidence of benefit. Despite this PRP is being offered within the UK fertility market. A member noted that PRP therapy use is unlikely to stop, and that variations in its administration will be used to challenge the evidence of recent randomised control trials which show no improvement.

3.3. The Chair invited the Executive to update the Committee on the conclusions of the work on Authorised Processes. The Policy Manager provided a brief summary of tasks which included: publication of the updated Authorised Processes webpage, revisions to the Statutory Approvals Committee (SAC) and SCAAC Standing Orders, an update of the procedures for the approval, review and deauthorisation of processes (including the revised decision tree and explanatory note), and changes to General Direction 0008 section D, as described in the July 2024 Chairs letter.

3.4. The Chair informed members that this is Jason Kasraie's final SCAAC meeting in his capacity as an External Adviser. The Committee recognised Jason's contributions to the SCAAC in both his capacity as an Authority member and Deputy Chair to the SCAAC, and subsequently as an External Adviser, thanking him for the expertise he has provided with regards to clinical embryology.

4. Relevant public health developments and research findings

4.1. Prior to the meeting, the Executive had highlighted the following papers to the Committee for consideration:

1. Deep learning versus manual morphology-based embryo selection in IVF: a randomized, double-blind noninferiority trial | Nature Medicine
2. Clinical effectiveness and safety of time-lapse imaging systems for embryo incubation and selection in in-vitro fertilisation treatment (TILT): a multicentre, three-parallel-group, double-blind, randomised controlled trial - The Lancet
3. Prednisone vs Placebo and Live Birth in Patients With Recurrent Implantation Failure Undergoing In Vitro Fertilization: A Randomized Clinical Trial | Pregnancy | JAMA | JAMA Network

4.2. In relation to the papers on time-lapse imaging (papers 1. and 2.) the Chair noted that neither paper showed any benefit for different time-lapse imaging approaches (including that using AI) in relation to improving clinical outcomes for patients. Both papers support the black HFEA add-ons rating for time lapse imaging and incubation, which indicates that, on balance, the findings from moderate/high quality evidence shows that this add-on has no effect on treatment outcomes.

4.3. The paper looking at the use of deep learning-based embryo selection (paper 1.) was noted to be more nuanced as it also looked at the operational benefits of introducing AI technologies into the embryology lab, including the impact on embryologists' time. Although the study was not able to demonstrate noninferiority of deep learning algorithms in terms of clinical pregnancy rates when compared to standard morphology-based selection, it did demonstrate that deep learning significantly accelerated evaluation time.

4.4. Given many patients are being charged for time-lapse imaging as a separate add-on without being informed that current evidence shows no patient benefit, concern was raised from a patient support perspective.

4.5. With regards to the paper comparing steroid medication (prednisone) to placebo as a treatment for recurrent implantation failure (paper 3.), the Chair commented that as well as no evidence of improvement in live birth rate with prednisone, the study showed increased risk of poor outcomes including pre-term delivery rate and biochemical pregnancy loss.

4.6. Despite some criticisms of the methodology, this study was noted to be of high quality. The Chair recommended a review of the wording regarding the use of steroids as a treatment add-on to ensure patients have updated information on the possible risks of such therapies ahead of use.

4.7. **Recommendation:** The Executive to review the patient information on the use of steroids (glucocorticoids) for fertility to make sure the risks associated are made clear.

4.8. A member highlighted that a number of trials on ICSI vs IVF for mild male factor infertility have recently been published, with an upcoming trial from Scandinavia due to be published in the coming months. It was noted that preliminary evidence has highlighted that ICSI used for mild male factor infertility results in lower live birth rates than IVF. A potential shift in practice in light of such evidence was highlighted, and the Committee recommended that publications relevant to this topic were brought for discussion under this standing item at the February meeting.

4.9. **Recommendation:** The Committee to discuss growing body of evidence against the use of ICSI for non-male and mild-male factor infertility at the February 2025 SCAAC meeting.

5. Mitochondrial Donation

5.1. A summary of key developments in mitochondrial donation therapies was presented to the Committee. This included alternative techniques of mitochondrial donation, such as polar body transfer and mitochondrial DNA gene editors, and the use of more established methods of mitochondrial donation (MST and PNT) as techniques to improve oocyte quality and rescue developmental competence for patients with infertility.

5.2. The Committee discussed the recent developments on the topic:

5.2.1. It was noted that two members of the SCAAC and the invited expert were on the expert panel who originally reviewed the evidence for approval of MST and PNT in 2016.

5.2.2. A member noted the importance of separating research into the validity of approaches for treating inherited mitochondrial disease, from evidence for using mitochondrial therapies to overcome infertility. As the indications for treatment differ between patient groups, evidence that mitochondrial donation therapies are effective in preventing the transmission of heritable mitochondrial disease should not be used to justify the treatment of women with infertility. Furthermore, members discussed whether heteroplasmy in these populations would be problematic. This may be dependent upon levels of heteroplasmy, but further study is needed.

5.2.3. The invited expert commented on the developments in heritable genome editing, noting that new mitochondrial gene editors appear to work, but show limited efficiency. At present they are not able to fully correct mitochondrial DNA mutations for treatment and may only be utilised for a limited number of mitochondrial disease forms where the underlying genetic mutation can be effectively manipulated using such techniques. The invited expert also highlighted the possibility of using genetic editing methods to prevent heteroplasmy following the use of mitochondrial DNA therapies. This would involve using gene editing techniques (eg mitoTALENS) to destroy faulty maternal mitochondria harbouring the mutated mitochondrial genome and prevent any subsequent carryover. This technique is currently being tested in somatic cell lines with some success and preliminary data on its application in combination with mitochondrial donation therapy on embryos has demonstrated proof of concept.

5.2.4. Members discussed the targeting of gene editors to the mitochondria and possible limiting factors to application including the heterogeneity of patient genomes, the volume of editors, and potential access to the nuclear genome during the cell cycle.

5.2.5. With reference to the 2023 Costa-Borges et al. study the invited expert highlighted that although this study was limited, outcomes were reasonably promising. Despite this, incomplete exploration of why such interventions may overcome infertility in certain patient populations was thought to require further research. Further work on oocyte precursor cells was mentioned.

5.2.6. The Chair indicated that the use of mitochondrial donation therapies for infertility treatment is being increasingly discussed by academics in the field of assisted reproduction.

5.2.7. The invited expert went on to highlight that all evidence from published studies on polar body transfer (PBT) indicates that it could be a very useful technique. It was noted that the mitoHope programme in Australia are looking into this technique as an alternative to MST and PNT.

5.3. The Chair welcomed the speakers from Newcastle Fertility Centre at Life to give an update on the Mitochondrial Donation Programme. Speakers were:

- Dr Rekha Pillai – Clinical Lead for the Mitochondrial Donation Programme;
- Professor Bobby McFarland – Professor of Paediatric Mitochondrial Medicine;
- Professor Mary Herbert – Professor of Reproductive Biology;
- Louise Hyslop – Principal Embryologist and licenced PNT practitioner; and
- Dr Meenakshi Choudhary – Senior Consultant in Reproductive Medicine Clinical Lead for the egg donor programme.

5.4. Updates on the Mitochondrial Donation Programme from the team at Newcastle (referred to as 'Newcastle' from here on) included the following:

5.4.1. A review of the patient pathway to treatment was given, whereby patients are first referred from clinics around the UK (including neurology, genetics and mitochondrial teams) to the Mitochondrial Reproductive Advice Clinic (MRAC) for a medical assessment of the mitochondrial disease and diagnosis confirmation. At the follow up clinic, patients undergo a fertility assessment, which includes an evaluation of the safety of carrying a pregnancy, and may be offered patient specific fertility treatment (including PGT-mito, PNT, or egg donation) depending on the clinical presentation of the disease and levels of heteroplasmy.

5.4.2. At the time of writing, 189 patients had been seen by the MRAC, with 131 patients going on for fertility assessments. Of these, 42 patients had undergone treatment using PGT-mito and 32 patients had been given HFEA approval for PNT. Live birth rates and ongoing pregnancies were shared but are redacted here to protect patient confidentiality.

5.4.3. Trends in new referrals indicate a slight increase in those being referred to the programme, however, there has been a slight drop in PNT sessions with most patients undergoing FETs and patients being clustered to conserve HVJ-E (Hemagglutinating Virus of Japan Envelope), which is used in a critical part of the mitochondrial replacement therapy process to promote membrane fusion.

5.4.4. There are three elements to the egg donor programme at Newcastle Fertility Centre at Life: recruitment solely for research, recruitment for 'whole egg donation' (inclusive of nuclear DNA), and recruitment for mitochondrial donation. Following various egg donor recruitment drives undertaken by the centre, recruitment has improved across the past three years and there is currently no wait list for donors on the mitochondrial programme, with donors awaiting recipients for fresh donation. However, the mitochondrial donation programme has seen an increase in known donors, which may be due to previous wait times, and recipients independently finding willing donors to accompany them for treatment. An increase in donors willing to donate to both the mitochondrial donation and 'whole' donation programmes has resulted in willing donors being directed into the relevant programme as per demand.

5.4.5. It was noted that current screening requirement for donors requires negative NAT and serology testing before embryos are frozen, and again when the embryos are to be thawed for use. This requires the donors to return for repeat testing, and the need for this was questioned.

5.4.6. An overview of the pregnancy and paediatric follow up pathway was presented to members. Details of the relevant pregnancies, delivery and live birth paediatric outcomes were shared.

5.4.7. Professor Mary Herbert provided further clinical research data.

5.4.8. It was noted that there is no evidence of complete reversion in vivo to date. However, possible mechanisms for reversion were considered, including: increased amount of cytoplasm in patient karyoplast, uneven distribution of maternal mitochondria in embryo resulting in subset enrichment (founder cell effect), and preferential amplification of maternal mitochondrial DNA during development, possibly due to specific differences in part of the D-loop giving this a slight advantage of the donor mitochondrial DNA.

5.5. Following the presentation members of the SCAAC discussed various aspects of the programmes with Newcastle, including the processes followed.

5.6. A member questioned why day three biopsies are performed for PGT-mito patients, which are thought to reduce the potential of having a euploid embryo by approximately a third and are no longer standard practice. This would indicate that the outcomes are not equivalent to PGT performed on day five blastocysts. Newcastle explained that PGT for mitochondrial disease has been largely tested on blastomere(s) biopsied on day 3, with evidence across a range of inherited mitochondrial mutations indicating that heteroplasmy levels show little variation between blastomeres and that low levels at this stage are predictive of low levels in babies born. It is less clear whether a trophectoderm biopsy provides a reliable indicator of heteroplasmy levels and further investigation of the reliability of trophectoderm biopsy to measure mitochondrial heteroplasmy is necessary.

5.7. Interest in the health of the women undergoing the PNT was raised, with specific reference to their ability to carry a pregnancy and whether there have been any requirements for surrogacy. To date, all patients on the PNT programme have been medically suitable to carry their own pregnancy, however, surrogacy will be considered if required.

5.8. The Committee thanked the team from Newcastle for their detailed presentation. It was noted that protocols, patient selection and clinical outcomes continue to improve and from the Committee's perspective there are no concerns.

6. Stem cell-based embryo models (SCBEM)

6.1. The Executive reminded the Committee of the ongoing work on modernising fertility law and the proposals surrounding future scientific developments and innovation which were published in November 2023. Specifically, these include improving the HFEA's ability to handle rapidly changing scientific developments, such as the introduction of new 'categories' of cells inclusive of stem cell-based embryo models (SCBEM) and in vitro derived gametes (IVGs).

6.2. As described by the supporting paper, the current regulatory landscape and scientific considerations for and against amending the regulation were summarised. The Committee was asked to address the questions laid out in the paper from a scientific and/or clinical perspective, considering the anticipated developments in research in order to best 'future proof' recommendations. It was noted that the Nuffield Council of Bioethics are currently undertaking a rapid review of embryo models, which should be published in November 2024.

6.3. The Committee thanked the Executive for the comprehensive paper and made the following comments and recommendations:

6.3.1. A member highlighted what the potential applications of SCBEM are in research, dividing this into three broad areas:

- Using preimplantation embryo models, such as blastoids, to support training or method development in the field of assisted reproduction. Examples include improving vitrification methods or testing for the quality and safety of embryo culture media. At present this is limited by incomplete modelling of the morula stage of development.
- Using models to study implantation, placentation and early post-implantation development. Many research groups are beginning to combine embryos and SCBEM with endometrial models to study processes of implantation. In vitro models are becoming increasingly sophisticated and able to match in vivo tissue physiology. This is increasing understanding of the molecules and signalling pathways involved in implantation and paving the way for in vitro models of diseased systems (such as recurrent implantation failure), and the identification of new pharmaceutical treatments.
- Using models to study gastrulation and early organogenesis. Here research is focused on improving understanding of development, with promising lines of translational research. This includes using embryo models to generate progenitor cells to overcome challenges associated with using traditional stem cell approaches, and promising therapeutic uses. In addition, there is ongoing work to obtain organ primordia as a source for making tissue specific organoids and with time full models (including primordial germ cells and gonadal tissue).

6.3.2. A member questioned whether integrated and non-integrated models should be treated differently. The invited expert highlighted that this terminology, as used by the International Society for Stem Cell Research (ISSCR), is likely to be revised and that all research using models should be looked at on an individual basis by an oversight committee. This is in line with proposals from the SCBEM Code of Practice published by Cambridge Reproduction. The review/oversight committee can address concerns and stipulate conditions at time of approval.

6.3.3. A member highlighted that most embryo model research does not seek to replicate the embryo in its entirety, but to mimic the function of a tissue or an aspect of development. Scientifically, embryo models are not human embryos, as they are created in a very different manner. Although a minority of embryo models do mimic embryos and embryogenesis, it may never be possible to assess their equivalence to a human embryo as it would be both unethical and is unlawful to conduct the necessary research (which would include transferring it into a human or animal for in vivo development). Should complete ectogenesis (implanting an embryo in an artificial womb and allowing it to develop to full term) become possible in future, it would need to be prohibited for embryo models. Instead, knowledge can be generated through in vitro culture experiments, animal models, etc. It was argued that too much emphasis is placed on the equivalence of embryo models to embryos, when the focus should be that there are many different embryo models with different uses.

6.3.4. While the special status assigned to human embryos has not been extended to embryo models, the question of their potential to behave in the same way was raised in relation to defining their moral status. Arguments about the moral status of embryos, as highlighted in the 14-day rule paper and the Warnock Report, consider individuality, sentience, and the ability to feel pain, which may never apply to embryo models. In addition, research indicates that pain and consciousness develop relatively late during fetal development, at stages far beyond those that are achievable by any current methods. Nevertheless, safeguards are needed to reassure the public that researchers are developing and utilising models in a safe and ethical way. A member noted that looking back at historic and ethical debates allows reflection on the changes in societal attitudes,

which may not have moved on as rapidly as the science. Evidence from the public dialogue conducted by the Wellcome-funded Human Developmental Biology Initiative (HDBI) highlighted three main public concerns: (1) transfer of embryo models into the human uterus, (2) transfer of embryo models into an animal uterus, and (3) developing an embryo model to viability (20-24 week equivalent).

6.3.5. It was highlighted that SCBEM are not currently regulated, so movement towards regulation would be desirable. A member suggested a prohibition on specific research or clinical use which raised ethical or other significant societal concerns, such as the transfer of a model to a human or animal uterus or reproductive tract, would be appropriate. A member indicated that bans on the transfer of models to the uterus may be more complex and may limit the use of cells derived from embryo models. It may also become possible to repurpose cells from embryo models for human reproduction in the form of IVGs. Therefore, if a ban was to be imposed, it may be necessary to make a distinction between implanting an embryo model itself, and implanting gametes derived from cells of the model.

6.3.6. It was noted that defining embryo models is challenging and there was a risk of being overly restrictive. The Executive highlighted that as this is an evolving area of science, it may be possible to resolve concerns through secondary legislation later once more is known. Any new definitions in the Act should clearly distinguish between a human embryo and human embryo model, but in relation to SCBEM there is a desire not to make this overly prescriptive.

6.3.7. Use of the term ‘live’ to define embryos was noted as ambiguous. Given SCBEM are not a product of direct bi-parental fertilisation, but created differently, a member suggested this distinction may be useful for distinguishing embryos from embryo models. Others proposed variances may be subject to change.

6.3.8. A member suggested that it may not be necessary to include embryo models within the HFE Act, and relying on the Cambridge Reproduction Code of Practice for governance could be sufficient. The member suggested that failure to comply with the Code could damage a research group’s ability to obtain funding, ethical approval impacting their ability to carry out and publish research.

6.3.9. A member suggested identifying red lines or taking a principles-based approach which are unlikely to change over time. This could future proof the legislation as the science develops if ethically and scientifically sound principles could be identified. Working backwards from what needs to be explicitly prohibited may be an appropriate starting point for setting any red lines or principles.

6.3.10. The Committee considered whether research using SCBEM should be restricted by a time limit, should the Act be broadened to cover research using models:

6.3.11. The Committee advised that a pragmatic time limit for embryo models would be difficult to agree as models vary widely and do not mimic the sequential stages of human embryo development; they could possibly mimic development far beyond day 28 within a much shorter timeframe. Moreover, consideration should be given to the fact that unless it is possible to culture human embryos past 14 days, it would be difficult to validate SCBEMs past day 14 development.

6.3.12. A member highlighted that although research has already provided new knowledge on embryo development prior to 14 days, further knowledge is yet to be gained from research prior to 14 days. Advances in cell and molecular biology techniques may reveal differences in molecular

behaviours between embryo models and embryos, indicating their functional equivalence/inequivalence. Should functional equivalence be validated, this will have implications on the moral status of SCBEM and how regulation of these models can be approached. It was agreed that the moral status of embryo models cannot be determined at this time.

6.3.13. A member highlighted that developing an embryo model to viability is the most challenging to regulate, as defining a timeline for viability in a model not following standard developmental processes will require an arbitrary line. It will also be challenging to find suitable language that does not risk prohibiting other stem cell research.

6.3.14. One member proposed a system of identifying embryo models of greatest concern and scrutinising appropriately, imposing time limits where appropriate. Additionally, it was thought that a blanket limit may unintentionally impede research on models of less concern.

6.3.15. A member noted that it may be appropriate to look at the legislation on human reproductive cloning which states that any person who places in a woman a human embryo created without fertilisation is guilty of an offence and liable to conviction.

6.4. The Committee made the following comments and recommendations:

6.4.1. SCBEMs and embryos are not the same, so if embryo models are to come under the HFE Act, their definition would need to be distinct from embryos;

6.4.2. Clearly defined upper limits on SCBEM research should be established without inadvertently banning good research;

6.4.3. 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

6.4.4. 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.

7. In vitro derived gametes (IVG)

7.1. The SCAAC was asked to advise on 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.

7.2. In relation to this topic, the Committee discussed the following:

7.2.1. Regarding updating various definitions in the HFE Act and suitable terminology:

7.2.2. It was considered a priority to update the definition of a gamete to accommodate IVGs given the growth in IVG research. The term 'live' in the current definition of human gametes is not sufficient to distinguish human gametes from IVGs. This was because any cell in culture could be described as 'live'; a more appropriate distinction could be made for a gamete that had undergone the process of meiosis in vivo.

7.2.3. Any changes to the definition of a gamete in the Act must ensure that any research facility storing stem cells would not become entangled in HFEA licence requirements or unintentionally

contravene the HFE Act. The current definition of a gamete as a cell of the [male/female] germ line at any stage of maturity, could be problematic as this could cover the structures of an embryo.

7.2.4. The Committee discussed whether the creation of an embryo using a single IVG in combination with a permitted gamete, or using two IVGs, should be considered an embryo model or an embryo. A member queried whether intended use could help define IVGs. This could mean that IVGs fertilised with the intention of human reproduction resulting in a live birth would meet the definition of an embryo, and those created for the purpose of research would be models.

7.2.5. The use of the term 'artificial' for IVG was thought inappropriate as it could be derogatory to individuals created using IVGs. Biologically, 'stem-cell derived' is the most accurate term for these structures, whether this is from embryonic stem cells, induced pluripotent stem cells, or spermatogonial stem cells.

7.2.6. A member noted a significant difference between IVGs and SCBEM in terms of the intent for clinical application, with IVGs ultimately aimed at fertility treatment use. Future clinical use is therefore much more likely and brings with it more immediate concerns.

7.2.7. A member added that, for IVG the source material is key. Research has shown that epigenetic errors can be traced back to the derivative population of stem cells and that induced pluripotent cells appear to have more genetic mutations than embryonic stem cells, which may make them less conducive to germ cell reprogramming. The process itself does not appear to be introducing new errors. The invited expert noted that recent research has started to overcome some of the previous epigenetic issues such as the ability to erase and reinstate maternal/paternal imprinting. The invited expert further explained that, in theory, it could be possible to create eggs as well as sperm using cells from XY men, as well as eggs from XX women, but it may not be possible to create sperm from XX women because of the missing Y-chromosome.

7.2.8. It will be critical to test the safety of IVG for clinical application before that takes place. However, establishing when IVG technology is sufficiently advanced for translation from research to clinical application will be challenging. This will require evaluating when and how it will be possible to use an IVG to create a fertilised embryo for transfer into a human uterus.

7.2.9. Evaluating and ensuring the long-term safety of IVGs is likely to require extending the 14-day rule to understand the longer-term outcomes of epigenetic correction and to validate the fertilised IVGs against conventional embryos post 14-days of culture. Pre-clinical testing would involve growing an IVG derived embryo for the maximum in vitro duration and testing safety prior to clinical application. Testing would be necessary ahead of offering fertility treatment using IVGs.

7.2.10. Currently three companies are actively pursuing research in this field, two in the USA and one in Japan. A member advised that it may be beneficial to look into regulatory developments and research on IVGs from Japan. While some companies have said that translation of IVGs into clinical practice will be possible within two to three years, SCAAC members were sceptical of such claims.

7.2.11. IVG methods are also being developed with the intent of conserving species at danger of extinction. Developments in these technologies can generate knowledge that may help translation to human gametes. In mice, primordial germ cell like cells need to be combined with somatic cells corresponding to the ovary or testis. In humans there are now methods of deriving ovarian or

testicular cells from induced pluripotent cells in culture, an approach now being combined with IVG research.

7.2.12. A member highlighted that the arguments in support of IVG technology are very compelling, particularly the possibility of significantly reducing the challenges many patients face in accessing fertility treatment (in terms of age, cost, and narrowing inequality). If successful, older patients could benefit from IVG technologies as they will extend the age at which women can procreate. There will also be less incentive for patients to freeze eggs or use donor eggs for treatment. IVGs could additionally be utilised by male same-sex couples, patients who have experienced premature infertility (such as cancer patients), or those with Klinefelter's syndrome and XXY.

7.2.13. Another consideration would be the introduction of age limits for IVG fertility treatment. Currently there is no legally imposed age limit on fertility treatment in the UK; this is something for individual clinics to decide.

7.2.14. A member considered that public engagement on IVGs would be valuable as public opinion has not currently been explored.

7.3. The Committee made the following comments and recommendations:

7.3.1. The definition of gametes within the Act should be updated to remove the statement that this covers germ cells at ‘any stage of maturity’ and consideration should be given to the use of the term ‘live’ for the current definition of gametes within the act.

7.3.2. The Executive should consider how to define embryos created from single or dual IVGs.

8. Scientific considerations relevant to the 14-day rule

8.1. The Committee was asked to address questions on the scientific rationale for maintaining or extending the 14-day rule and the possible benefits and drawbacks of doing so, as well as any conditionality needed should changes be considered.

8.2. In relation to this topic the Committee made the following comments:

8.2.1. One possible benefit of embryo research beyond 14-days includes looking at how the placenta forms during pregnancy. Late onset pregnancy complications, such as pre-eclampsia, still birth, and growth restrictions are thought to have origins in early-stage embryo development, when the placenta is beginning to form. The interaction between placenta and uterus, such as the depth of implantation which may lead to some of these conditions, cannot be fully studied before 14 days, leading to a gap in knowledge. This cannot be addressed through research using tissue from miscarriages or terminations as such material does not typically include placental tissue. Furthermore, tissue from miscarriages or terminations is only available from around 28 days onwards.

8.2.2. Across the first four weeks of embryo development, organ development (organogenesis) is also initiated and is thought to be the time frame within which the origins of many congenital defects arise, including those related to neural tube closure and cardiac disorders. If errors in signalling pathways, which play a crucial role in embryonic cell development were known, it could be possible to translate this research to screening programmes or even early interventions for

congenital disease. Growth of healthy embryos would also need to be studied to understand the pathways from which congenital pathologies deviate.

8.2.3. Testing of the safety of established techniques – including those of mitochondrial donation – could additionally be improved by allowing embryo culture past 14-days.

8.2.4. Despite recognising the hypothetical research benefits, a member challenged whether it was premature to revisit the 14-day rule at this time, indicating that more research could still be done on human embryos and other animal models (including non-human primate models) to extend knowledge and benchmark normal embryo development prior to 14-days. Members did not reach agreement over the current need to progress research beyond 14-days. The invited expert stating that processes differ significantly prior and following 14-days and that research across both periods calls on very different questions therefore having the limit is inhibiting the ability to conduct important research.

8.2.5. The Chair prompted members to consider an alternative upper limit for human embryo research in the event that it was allowed to go beyond 14 days.

8.2.6. The idea of a 28-day limit was discussed recognising that this is being considered in other jurisdictions, for example in the Netherlands. There is also a clear biological (morphological) marker, which is the moment when the anterior neural pore closes, as based on the Carnegie stages. However, as embryos have not yet been cultured in vitro beyond 14 days, it is not known whether this biomarker would arise the same way as it does in vivo, as in vitro embryos could develop slightly differently to their in vivo counterparts. A member highlighted a further reason which favoured a 28-day limit is that there is some tissue from abortions and miscarriages available as a valid alternative after 28 days.

8.2.7. For those interested in limb development or craniofacial abnormalities, a limit of 28 days could still prevent this research. Another member argued that alternative methods of culturing isolated structures, such as isolated limb buds from foetuses obtained from terminations or miscarriages, can enable such research, which falls outside the remit of the HFEA.

8.2.8. A member highlighted that while 28 days may be an appropriate new upper limit, it may take time until it is technically possible to culture to that boundary. The invited expert challenged this, noting improvements in culture techniques that have already enabled non-human primate embryos to be developed in vitro for up to the equivalent of 27/28 days.

8.2.9. Members discussed that although there is a lot we can learn from researching embryo development between 14-28 days, 28 days was in someways arbitrary. It was suggested that small incremental increases may be favoured as the research evolves.

8.2.10. The invited expert noted that the ISSCR guidelines committee could not agree on any new limit and concluded that no universal new limit should be set. Instead, a time limit should be based on the research justification for each project and determined by the nature of the research proposed, as part of the approvals process by an oversight committee. Having a different time limit for each study wishing to go beyond 14 days was supported by a member on the grounds that the time limit for embryo culture will depend on what the research is setting out to investigate. Different researchers may wish to investigate different developmental stages, and therefore a blanket new time limit may not be appropriate.

8.2.11. The Committee recognised that the absence of a fixed upper limit may generate public concern, in particular the idea of indefinitely extending the time limit of embryo research. There was a consensus reached that an upper limit should be set for both public reassurance and researcher clarity.

8.2.12. It was suggested that the specific time limit (within any new upper limit) could be agreed on a project-by-project basis as part of the research licence application. This could allow the HFEA to set the shortest duration required to achieve the scientific objectives of the research project. As all embryo research is licenced, oversight would be maintained.

8.2.13. There was consensus that human embryo research should not take place where a viable alternative could be used to undertake the same research. If a new upper limit was close enough to the point where alternative materials - e.g. from miscarriages or validated SCBEM - could be used, this would support extending the embryo research time limit to that point, but not further, to support continued research.

8.2.14. A member highlighted that any new proposed time limits on embryo research may be linked to known milestones in early pregnancy. This would include when pregnancy is first detected on ultrasound scan (around 5 to 6 weeks), up to 6 weeks when early miscarriages commonly occur, or at 6 to 7 weeks when foetal heart activity on scans is noted. It will be important to be mindful of public perception of these milestones, which may play a role in public support or opposition to any new time limit.

8.2.15. The invited expert highlighted the public engagement on embryo research which has taken place; However, public opinion on a specified new limit beyond 14 days has not been investigated. Despite limited public awareness of embryo research there is general interest in the justifications behind the research itself and that support for such research tends to align with the justification. It will be interesting to see public opinion on the anticipated assisted dying legislation, which may give an indication of likely public views on extending the 14-day rule.

8.2.16. Informing the public of the knowledge and discoveries generated through embryo research up to 14 days thus far, and what else may be learnt or discovered by extending the limit, will be important in the event of a proposal to extend beyond 14 days.

8.2.17. The Chair asked the Committee about applying any future proposed extension to research using human admixed embryos (including hybrids, transgene and chimeras), and it was agreed this should be clarified in any future changes considered. On the same topic, a member noted that research using embryos with significant human component should be subject to the same limit as human embryo research. However, some technical challenges could arise in relation to defining “significant component” as proportions can change during development.

8.2.18. There is currently no alternative way to study the so-called ‘black box’ period of embryo development, which is between 14-28 days, other than using human embryos. However, when SCBEMs and IVGs can be validated, it may be possible to use them in research covering this stage of development. Validation of SCBEMs beyond 28 days can be done against material from miscarriages or terminations.

8.2.19. It was argued that models are already able to mimic structures past 14-days and that validation of SCBEM requires comparison with human embryos. This was challenged by a member who stated

that that gaps in our understanding of normal embryo development prior to 14-days need to be addressed for model validation to be accurate.

8.2.20. Another member reiterated that at present embryos and embryo models are not equivalent and that research using both structures is more nuanced. Seeking to reduce or replace embryo research through the use of embryo models, would need careful consideration given their current limitations. Similarly, generating animal models instead of using surplus human embryos that individuals have chosen to donate to research, raises other ethical considerations.

8.2.21. A member noted the wider context of the UK's research environment, which has developed a reputation as world leading and resulted in high quality research and important discoveries including through embryo research.

8.3. Recommendations:

8.4. The SCAAC agreed that:

8.4.1. There is a case to be made for extending the 14-day rule, however the Committee did not agree on any specific future upper limit, although 28 days was most commonly mentioned in discussions and noted to be subject to international consideration. Beyond this determining small incremental increases through secondary legislation may be favourable as the research evolves.

8.4.2. It is important to define an upper time limit for embryo research, that should be clearly justified whether by reference to principles, developmental stages, cultural norms, or the benefits that might come from allowing research up to a new extended limit.

8.4.3. Members supported the suggestion that projects should be reviewed on a case-by-case basis, with the time limit for each individual project being specified by a review committee.

9. Any other business

9.1. The Chair reminded the Committee of the upcoming annual Committee Effectiveness Review. Recommendations will be discussed at the February meeting.

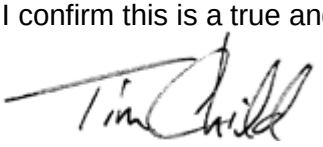
10. Meeting summary and close

10.1. The Chair closed the meeting by once again thanking Jason Kasraie for his contributions to the SCAAC and congratulated the standards of the papers from the Executive.

10.2. The next SCAAC meeting will be held in person on Monday 3rd February 2025 in a hybrid format.

11. Chair's signature

I confirm this is a true and accurate record of the meeting.



Chair: Tim Child

Date: 18th November 2024