

The regulation of scientific developments – part 2

Introduction

1. The introduction to the companion paper to this discussion paper ('The regulation of scientific developments – part 1') notes that the HFE Act 1990 (as amended in 2008) (hereafter 'the Act') can regulate only what it deems legally permissible. Permissibility reflects what was socially and political accepted at the time, and what was scientifically possible at the times the Act was debated, or what was on the near-horizon scientifically (such as novel techniques for the prevention of mitochondrial DNA disorders). Yet the science has developed considerably over the past 30 years and with it, what is possible to offer to patients clinically.
2. Over the same period, the fertility sector has become primarily self-funded in the UK, and the profile of patients using fertility treatments to start a family has become more diverse. Patient expectations of treatment possibilities have risen, in part due to the internet enabling wider access to information and opinion about scientific and clinical developments. The continued growth in the intersection of fertility treatments with advances in genetics and genomics offers new hope for families affected by serious genetic conditions, and in the future may present new options for more socially and medically contested reproductive options. The level of data available to assist clinicians with decision-making will expand greatly with the advent of AI into multiple aspects of the patient pathway, prompting important questions for all healthcare regulators about how to regulate data-driven technologies.
3. This paper provides an overview of the most significant developments in the science and sets out options for change. There is further detail provided for reference only on these various developments in various HFEA papers (noted in footnotes). LRAAG members need not read these further documents in order to express their views about the issues raised.

1. The 14-day limit

The current situation

4. The Act states that a license cannot authorise keeping or using an embryo after the appearance of the primitive streak.

“For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with [the day on which the process of creating the embryo began], not counting any time during which the embryo is stored.”

5. This legal limitation of not culturing embryos in vitro beyond 14 days originated from recommendations in the Warnock report in 1984. The '14-day rule' has since been legally implemented in several countries.¹

Issues

¹ For further, optional, information on the topic see the [Horizon Scanning Prioritisation of Issues](#) paper presented to SCAAC in 2022.

6. When the 14-day rule was introduced, researchers could not keep an embryo alive for that long in vitro, so even though the rule enjoyed considerable support the limit was in one sense theoretical. However, recent scientific work has demonstrated that keeping an embryo alive in vitro in a way that models in vivo development past 14-days is likely to be possible. This has caused some to question whether it should be revised. We understand that more than one research group outside of the UK is actively considering this issue.
7. The International Society for Stem Cell Research (ISSCR) has published new guidelines, allowing for the possibility of culturing intact human embryos beyond 14 days, subject to special oversight. The ISSCR guidelines state: *“Given advancements in human embryo culture, and the potential for such research to yield beneficial knowledge that promotes human health and wellbeing, the ISSCR calls for... public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research. Should broad public support be achieved within a jurisdiction, and if local policies and regulations permit, a specialised scientific and ethical oversight process could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days”*.
8. While the scientific case for culturing beyond 14 days in certain circumstances may be strong, the settlement on 14 days was not simply a scientific one. It represented a social agreement about what was acceptable. Proponents of change will therefore have to argue what benefit would be likely to be realised by extending the limit and what the new limit should be. We feel strongly that an open-ended period of embryo experimentation would be unacceptable.
9. Any new settlement would also need to be practical to enforce. One of the great virtues of the 14-day rule is that it is clear. Some have argued that a case-by-case approach might be justified depending on the likely benefits of a particular research project, but such a move might only make the regulatory process more contested and very time consuming.

Options for change

10. Given the sensitivities involved, change will require informed debate, whether involving the public or in Parliament. Some have argued that, given the likelihood that a research team will seek to go beyond 14 days somewhere in the world, it would be beneficial if the UK gave a clear signal that the debate and concerns are being anticipated and considered. This argument points to the UK's global reputation for clear and ethical regulation of assisted reproduction and embryology, rooted in public engagement as a pre-requisite of public trust. At this stage, we suggest three options for discussion.
11. In any options for change suggesting an amendment to the 14-day rule, a new 'upper limit' to research must be specified in the Act to ensure there is still a legal 'bright line'.
12. **Status quo** – the existing 14-day rule has largely stood the test of time and the explicit prohibition on the face of the Act stands as an important public commitment. Moreover, proponents of change might risk greater restrictions than currently, should they open this issue for debate.
13. **Change now** - to avoid delaying important research once it becomes feasible, Parliament could debate the principle of a new limit of >14 days now and decide to enshrine a clear new upper limit on the face of the Act or to delegate such a power to the HFEA. Under the delegated approach, the HFEA would then review advances and licence extended culture in the UK as appropriate without the need to revert to Parliament. Parliament would still retain its role as the democratic forum for deciding in principle what should happen with embryos and what new upper limit would exist, leaving the regulatory decision to the HFEA. The regulatory/administrative model used by the HFEA to approve the case-by-case licensing of PGD suggests that such an approach can maintain public confidence. While such a case-by-case approach could ensure there is limited delay in the translation of research

to patient benefit, it would be a complex process for HFEA to manage. Clear parameters would need to be set out to justify which projects would continue to be permitted to research up to 14-days, and those that would be permitted to research beyond this up to any new upper limit.

14. **Potential change later** – Parliament could decide to approach this issue in a manner similar to how it dealt with mitochondrial donation, by creating a commitment in the Act that it will review the limit in response to scientific advances, with regulations as the mechanism for any future change should the evidence warrant it. Under this option any revised Act would continue to permit keeping an embryo only up until the appearance of the primitive streak at 14-days, but be drafted in a way which allowed for regulations to be introduced in the future to amend this.

2. In vitro-derived gametes, embryo-like entities, and stem cell based embryo models

The current situation

15. The Act sets out rules regarding the creation, storage, and use of human gametes and embryos. At present the Act governs human embryos and gametes, and sets out prohibitions on human admixed embryos. These include, for example, human-animal chimeras, and cytoplasmic hybrids.
16. The legislation in the UK prohibits the use of in vitro-derived gametes in treatment. 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”.
17. Research into the development of gametes and embryos that are derived from human embryos and stem cells is resulting in cells that are becoming increasingly similar to ‘real’ *bona fide* human gametes and embryos. This poses new questions for regulation and their use in research and assisted reproduction.

In-vitro derived gametes

Issues

18. Research has led to the ability to derive functional gametes (eggs and sperm) from pluripotent stem cells, at least in mice.² This can challenge the definition of gametes and embryos, which in the Act are derived directly from gonads. The potential implications for human reproduction are profound: a near limitless supply of functional gametes from skin cells. Proponents note that this technology could theoretically support biological reproduction for people who could not otherwise produce gametes. However, scientific limitations mean that it would be challenging to create gametes of the opposite sex. Therefore it may not be possible to use in-vitro derived gametes in the treatment of same-sex couples wanting to have children that are genetically related to both partners.
19. Additionally, human embryonic stem cells could also in theory be reprogrammed and used to grow any of the 2-300 cell types in the body, with major implications for future opportunities in regenerative medicine. Deriving egg and sperm cells from HESCs for research use has been more complex for scientists to achieve than deriving other cell-types from HESCs, but the prospect of these in-vitro derived gametes raises important questions concerning how best to define ‘gametes’ and ‘embryos’ in legislation, and what as a society we want to secure from those terms via the HFE Act.

² For further, optional, information please see [this paper](#) presented to SCAAC in 2020.

20. If in vitro-derived gametes ever arise as a viable clinical proposition from ongoing research, it is reasonable to anticipate that there could be uses whereby a skin cell from a patient could be reprogrammed to become a stem cell that could then provide egg or sperm cells for the patient's own use in fertility treatment. The use of any such cells would create new challenges to concepts including biological parenthood and relatedness.
21. Consideration should be given to starting a public discussion on the possibilities of deriving gametes from other cells, as there could be calls to permit their use in assisted reproduction from some groups. This area would need careful consideration by Parliament if the relevant techniques were to be considered, on the basis of pre-clinical data, to be sufficiently safe and effective for clinical use in future.

Embryo-like entities

Issues

22. Significant advances have been made in the creation of human 'embryo-like entities' or 'stem-cell-based embryo models'. These embryo-like entities and models have significant potential for use within research.
23. These structures do not arise from gametes, but directly from reprogrammed embryonic stem cells³, or from induced pluripotent stem cells⁴ (which are derived by reprogramming of already-specialised adult cells) and may involve a combination of stem cells from more than one human donor (or from animals, in human/non-human chimeras).
24. At present, these entities sit outside the regulatory regime of the Act. It is an open question as to whether bringing them under the oversight of a revised Act might increase public trust and so encourage further responsible innovation in this area. This would have prospects for patient benefit and protection, whilst supporting further research.

Stem-cell based embryo models

Issues

25. Researchers have also exploited the potential of stem cells to derive embryo-like structures directly, without the need for a fertilisation step. This involves the creation of embryos from stem cells, rather than through fertilisation. A number of different terms have been used for such entities in recent years, but the 2021 ISSCR guidelines seek to standardise the terminology so that these entities are known collectively as 'stem-cell-based embryo models'.
26. Guidelines divide these stem-cell based embryo models into two categories. 'Integrated' stem-cell-based embryo models containing not just embryo-like cells, but also cells resembling extra-embryonic material – for example, cells of the kind that develop into the placenta.

³ Some embryo models require co-culture of different types of stem cells, not just HESC. See [In vitro attachment and symmetry breaking of a human embryo model assembled from primed embryonic stem cells - PubMed \(nih.gov\)](#).

⁴ See further information, optional, in [the Alternative methods to derive embryonic and embryonic like stem cells literature review](#) paper presented to SCAAC in 2022.

27. 'Non-integrated' stem-cell-based embryo models do not have (and cannot develop) such additional cells and resemble only the embryo proper (or a part of it).
28. Blastoids are not blastocysts but blastocyst-like embryo models derived from pluripotent stem cells. Blastoids are likely to be great tools for exploring cell fate control in human embryogenesis, and much more; but they are clearly not embryos and currently do not require regulation by the HFEA. If, for example, research in mice suggested that it was possible to derive live mice from an integrated embryo model, like a blastoid, this would have implications for attitudes to related human embryo models. It would also have implications for whether the use of *bona fide* human embryos could still be justified. If, through further research, they were to exhibit a developmental potential much more similar to *bona fide* embryos in the years to come, there is a strong argument that a revised Act should cover them.
29. The 2021 ISSCR guidelines require stricter oversight of integrated embryo models (such as blastoids) than for non-integrated embryo models. Furthermore, if an embryo model contains human cells, then – regardless of whether it is integrated or non-integrated – the Act and the guidelines prohibit any attempt to use it to establish a pregnancy.

Options for change

30. All of these developments – in vitro derived gametes, embryo like entities, and stem cell-based embryo models – pose significant challenges to our understanding of human reproduction and may therefore require wider public debate before any changes in regulation were contemplated. However, we can sketch out some key options at this stage.
31. Prior to any changes in regulation, informed Parliamentary debate should take place. Any changes in regulation would need clear articulation of the differences between use of these entities within scientific research and their use within human assisted reproduction.
32. **Status quo** – this work is progressing outside of any regulatory regime and there is therefore an argument for continuing as is. However, drawbacks of this approach include the lack of security and safety accorded to researchers, and the lack of regulatory oversight and control if at some point, there were moves to use these developments within assisted reproduction.
33. **Bring some, or all of these developments under regulatory oversight** - the benefits of bringing in-vitro derived gametes, embryo-like entities, and stem-cell based models under the regulatory framework is that this would ensure that as they become increasingly similar to their human counterparts, there is strong regulatory oversight. Some scientists are proactively requesting the HFEA for cooperation in this matter and would welcome further regulatory oversight in the field. Increased regulation could afford scientists a greater level of protection.
34. The development of techniques to create human-like gametes and embryos is likely to create significant public discomfort as these models become very similar to 'actual' human embryos. Public discussion should consider the future possibilities these new developments may offer. It seems plausible that regulating this field would increase public trust.
35. These developments are likely to raise issues regarding scientific definitions and acceptable uses. There is as ever a balance to be struck between the benefits of certainty and transparency that regulation would bring and the possible curbs that over-regulation might place on innovation.
36. Additionally, there will be times at which the entity in question should be regulated by the HFEA, or when it will be considered under the remit of non-HFE Act regulations. Therefore, one aspect of this

work may need to consider how to establish *when* such cells are considered either germ line cells, or derivatives and therefore under the regulation of the HFE Act.

37. Any changes to the Act in this matter would of course need to consider key ethical questions including the moral significance of embryo-like models.

3. Use of human embryos in research: 'alternative' models

The current situation

38. The Act (schedule 2, section 3A(1)(c)) requires embryo research to be “necessary or desirable” for defined purposes. As ‘alternative’ models of human embryos increase in quality and accuracy, some may hope that (due to practical or ethical issues), this may reduce the need for the use of human embryos in research. Nonetheless, many scientists see the developments in alternative models as an adjunct to their work using human embryos, rather than as a replacement.

Issues

39. If alternative methods of deriving human embryo-like models, are successfully developed and became widely available to researchers, it may be suggested whether it is less ‘necessary’ for research groups to use human embryos in their research. Indeed, some have argued such a development might resolve some of key issues that currently exist within embryo research could be resolved by the use of such ‘alternative models’, including funding limitations and ethical concerns regarding the moral status of the embryo.
40. However, if future scientists feel that notwithstanding the availability of synthetic models, viable human embryos are still necessary to use in their work, it may become harder for the HFEA to confidently define ‘necessary’ in licensing - when presently that can be interpreted as ‘there is no available alternative’ to using embryos.
41. Consideration will therefore need to be given to circumstances where alternatives to human embryos could be used but where human embryos are still required (i.e., where they are ‘desirable’) to answer or validate scientific questions.
42. Currently, the HFEA’s Scientific and Clinical Advances Advisory Committee (SCAAC) keeps developments regarding these alternative methods under review so that the HFEA Licence Committee can bear them in mind when considering future research licence applications in line with the Act.

Options for change

43. **Status quo** – as *bona fide* human embryos are likely to always be necessary in some forms of research due to the scientific benefits and accuracy of using them, the current legislation could continue to encourage their use only when truly necessary.
44. **‘Desirable’ rather than ‘necessary or desirable’** - consideration should be given to future-proofing the Act to take account of the likely development of ‘alternatives’ to research with embryos to ensure that there are not unnecessary restrictions on embryo research.

4. Embryo selection based on Polygenic risk scores

The current situation

45. Under the Act embryo testing is limited only to conditions that are considered “serious”. At present, the use of Preimplantation genetic testing for polygenic disorders (‘PGT-P’) is not in line with the requirements of the Act.

Issues

46. PGT-P provides a polygenic risk ‘score’, which summarises the combined effects of many genetic variants on an individual’s trait. PGT-P aims to provide the probability that an individual will have a certain clinical or non-clinical trait, condition, or disease. These scores represent individualised predictions of health and other outcomes (including cognitive ability or intelligence) derived from genome-wide association studies in adults to partially predict these outcomes.⁵
47. These scores, provided by online commercial companies (but not used in routine clinical care), have been used in adults to identify the risk of diseases such as type 2 diabetes and breast cancer. These tests are now taking place in some countries, such as the US, alongside IVF to assist in embryo selection.
48. The predictions are only probabilistic as it is not possible to establish exactly how genes will influence any given trait. An individual with a high polygenic risk score (PRS) for a condition might never develop it, while someone who scores a low PRS might do so and vice versa. Advocates for the use of PGT-P argue that we make choices based on probabilities all the time, including around parenting.
49. However, other commentators point to potential unintended consequences of using these PRS, including selecting for some adverse traits when avoiding embryos with a higher score for other adverse traits, altering population demographics, exacerbating inequalities in society, and socially ‘devaluing’ certain traits.
50. Practical objections (when considering consumer protection) includes that the vast majority of genetic research used to predict risk has been done in individuals with European ancestry, which makes risk assessments better at predicting outcomes in those with that ancestry. This is an issue, for example, when considering risks that differ between ethnicities. This can include conditions such as hypertension and type 2 diabetes. Additionally, the interactions between genes and their environment may also influence an individual’s risk of a disease or certain trait.
51. We note that if PGT-P was ever to be licensable that it would need to be on a per-condition basis in line with the Act, for regulation to take place similarly to PGT-M.
52. At present, PGT-P technologies are likely to be self-limiting both due to the high cost of the technology and the low number of embryos that would be available for transfer when being highly selective.

Options for change

53. **Status quo** – the current restrictions in the Act that currently limit the use of PGT-P should remain unchanged.
54. **Prohibition** - even *if* PGT-P were considered to be safe and effective, it may be appropriate to reach a view that its use is never acceptable. If so, it would be advisable to set out an explicit prohibition in the Act against the use of PGT-P. This may be considered necessary, for example, to ensure that clinicians are not promoting the technology as a form of risk reduction, when that may not apply to a significant percentage of patients.

⁵ For further, optional, information please see [this paper](#) presented to SCAAC in 2021.

55. **Selective use** - on the other hand, if PGT-P were considered beneficial for enhancing reproductive autonomy, it may be necessary to consider clearer regulation regarding when it *could* be used alongside IVF.

5. Germline genome editing

The current situation

56. The Act does not permit interventions in the nuclear DNA of gametes or zygotes/germline genome editing, regardless of whether at some point in future it were shown to be safe and effective.⁶

Issues

57. Scientific work in the field of genome editing continues to advance,⁷ and it is possible that in future years or decades, clinical promise might be shown for reproductive applications in humans.
58. In theory, this is the only technique that some patients would be able to use for avoiding passing on a heritable condition, since PGT-M cannot be used in certain circumstances, such as when, for example, one parent is homozygous for a dominantly-acting disease gene variant.
59. It is possible that genome germline editing technology combined with PGT-M may eventually be more efficient than use of PGT-M alone.
60. At present, there are significant safety and efficacy issues in the application of genome editing. Additionally, there are of course serious ethical considerations given the long term impact of altering the germline.
61. Since the First International Summit on Human Genome Editing of 2015, there has been significant legal and ethical debate, resulting in many reports and papers from international bodies and national ethics committees. Most reports consider that heritable applications of human genome editing may be acceptable in the future in certain circumstances.

Options for change

62. **Status quo** – leaving the ethics aside, the uncertain state of the science suggests that now is not the time to open up the Act to permit genome editing. The issue could be reconsidered in the future as the evidence develops further.
63. **Potential change later** - to ensure that patient benefit would not be unnecessarily delayed (NB. only *if* scientific, legal, and ethical questions were resolved) it could be proposed that the Act is revised to allow for the possibility of a review of the prohibition against nuclear germline genome editing following Parliamentary debate. This could be done in a similar manner to the 2008 amendments for the regulation of mitochondrial donation. Regulations could eventually allow permitted egg, sperm, or embryos to include those with modified nuclear DNA. Such regulations should only be triggered at such time as efficacy and safety is demonstrated and regulatory structures are in place. In addition, a further restriction on the use could sanction genome editing only when established alternative techniques for avoiding passing on heritable conditions were not appropriate.

⁶ Set out in 3ZA of the Act 1990 (as amended 2008).

⁷ For further, optional, information on the topic see the [Horizon Scanning Prioritisation of Issues](#) paper presented to SCAAC in 2022.

6. Summary

The Legislative Reform Advisory Group is asked to consider:

- The options for change presented for scientific developments
- Whether the regulatory powers of the Act should be extended to new developments
- The issues and impacts on patients and researchers of possible amendments to the Act
- Preferred models to allow the Act to remain 'in-date' for the foreseeable