The regulation of scientific developments – part 1

Introduction

1. The HFE Act 1990 (as amended in 2008) (hereafter 'the Act') has provided a robust but flexible framework in which bioscience and clinical expertise in the UK can flourish. Many leading-edge developments have followed, including in 2015, the world-first decision by the UK Parliament to make lawful treatments to avoid the inheritance of serious mitochondrial DNA diseases for the first time, under the regulatory oversight of the HFEA. Also in 2015, in another regulatory world first, the HFEA licensed the Francis Crick Institute in London to undertake research in human embryos involving the new gene editing technique CRISPR-Cas9, the first time that this work had been done outside of China.
2. These ground-breaking developments in scientific knowledge and treatment capability over the past 30 years have been supported by the UK's strong democratic framework of regulation. In a contested area of scientific and clinical endeavour, the oversight of a robust and flexible regulatory framework has helped to generate public trust, which in turn has created conditions where innovation can more easily flourish.
3. However, research in these areas globally continues at pace and is now in places pushing against, or going beyond, the boundaries of what is permissible in the UK. That alone does not mean that the Act should be changed, but it does require us to consider options for change. In summary, the Act risks being overtaken by both developments in the practice of regulation and developments in scientific research.
4. Two overarching questions arise: *how* research is regulated and *what* areas of research are regulated. This discussion paper considers the way in which the Act regulates scientific research; a companion paper ('The regulation of scientific developments – part 2') considers new developments in research that do not currently fit within the framework of the Act.

1. Regulatory processes

The Act is overly prescriptive in terms of process

5. There is always a balance to be struck between what is written on the face of any Act and what is left to the discretion of the regulator. In recent years in other regulated sectors, that balance has tended towards setting broad principles in primary legislation, allowing the detail to be filled in by regulations or guidance.

The current situation: Specifying techniques

6. The Act is over 30 years old and can be overly prescriptive in terms of process in various places. This means what may be more effectively dealt with by processes specified by the regulator, is set out in the face of the Act (or in Regulations).

Issue

7. For example, the Act regulates mitochondrial donation by specifying a particular technique:

"Regulations may provide that— (a) an egg can be a permitted egg, or (b) an embryo can be a permitted embryo, even though the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease."

8. The Regulations that allow mitochondrial donation set out two permissible techniques for avoidance of transmission of mitochondrial DNA disorders. Should further techniques be developed (e.g. polar body transfer), these would not be permissible, even if clinically more effective.

Option for change

9. **Principles rather than process** – we believe the Act should be revised to give a clear emphasis on the principles to be used, and that it should be explicitly provided on the face of the Act, that that the regulator can implement processes to eg specify licensable techniques, in line with those principles as determined by the regulator. This would allow new research or treatments to be considered and approved or rejected in a more timely way, particularly where a treatment or technique is not specified in the Act.

Supporting innovation

The current situation: Novel treatment processes

10. The Act (Schedule 2, paragraph 1(3)) sets out activities for which treatment licences may be granted, and states that "A licence … cannot authorise any activity unless it appears to the Authority to be *necessary or desirable* for the purpose of providing treatment services". The HFEA has developed a system for authorising applications for licences for novel processes for use in treatment, based on this principle.

11. HFEA's SAC and SCAAC committees decide whether the novel process is suitable for carrying out the licensed activity, by considering whether the treatment process is safe and effective. Once approved by the Authority, a list of the authorised treatment processes is made available on the HFEA Clinic Portal. Any HFEA-licenced clinic can then undertake the appropriate authorised processes, in accordance with their licence, as part of their clinical practice.

12. Once approved, HFEA policy requires that a process goes through an initial review period of two years. Centres using the recently-approved process must inform HFEA that they are doing so, and must return data at the end of the two years to HFEA, to help to add to the existing evidence around safety and effectiveness. Patients are informed about the nature of any treatment they are offered, including likely consequences and risks. Clinics must record the justification for offering each patient a particular treatment alongside relevant clinical and laboratory data.

13. If reports at the end of the two-year window show new evidence that the recently-authorised process is no longer safe or effective enough to be used in treatment, SCAAC can advise on this and SAC can decide de-authorise the process.

14. There is no requirement in the Act, for clinics to carry out long term follow-up studies after treatment has been provided. The HFEA's central register of treatment data could be used as an important tool to facilitate such studies.

Issue

15. The Act has provided helpful principles to guide the HFEA as to whether or not *to* licence treatments, but it lacks explicit principles to guide *how* HFEA should undertake its approval controls over new treatments (or innovation in general) within the principles determined by Parliament.

16. An issue is that SAC and SCAAC consider evidence for safety and efficacy of a novel process available *prior* to authorisation and use in treatment. However, the Act comes with very few explicit regulatory levers for HFEA to use *after* authorisation has been granted, beyond the HFEA's policy requiring the collection of data during the first two years of use.
17. HFEA's powers for requiring evidence-gathering about use of the newly-approved processes in treatment are not set out explicitly in the Act. The Act does not provide HFEA with levers to set standards on the type or quality of evidence that is acceptable for clinics to submit to HFEA around e.g., outcomes of recently-approved treatments. This can lead to the two-year 'recently-approved' window being extended while more information is gathered, allowing for continued use by licensed clinics while the HFEA remains relatively unsighted on the outcomes.
18. The Act also lacks clarity on proportionate actions that the HFEA could take, should evidence of concerns emerge from evidence after initial licensing for treatment use. The Act does not explicitly enable HFEA to use regulatory options between 'authorised for treatment', and 'not authorised', for example by using 'regulatory sandboxes' or formally regulated research.
19. The Act does not give HFEA powers to insist that a novel process application can only be provided as part of research. The HFEA could only refuse to licence such an application for use in treatment if there were sufficient concerns around its safety and effectiveness.
20. A 'regulatory sandbox' is a flexible approach increasingly being used by regulators to encourage innovation, while minimising risks. The 'sandbox' allows a regulator to place conditions on those conducting an approved process, to ensure that it is only used in a limited, specific, monitored setting. The sandbox rules usually involve working within what are effectively research principles, but as determined by the regulator, rather than being formally regulated as research.
21. Sandboxes have been described as 'controlled experiments in which new products, services, or ways of doing things can be placed into a real-world environment. They have the explicit aim of learning about what happens subsequently to inform the development of future regulatory approaches.' This means that a policy 'can manifest and develop through stages, with review-points to judge how likely a risk is to crystalise, and this can be an iterative process'. Sandboxes can provide valuable learning direct to regulators in real time. Some sandboxes are organised such that the licensed provider would be immune from certain sanctions if there were to be specified adverse incidents – as long as their risk communication is excellent and any incidents are communicated to the regulator as soon as they happen.[1]
22. Sandboxes will not be appropriate for all innovations, e.g., those presenting safety risks to patients, some of which may be justified for trial only within formally regulated research. The principles to determine tolerable risk for sandbox approaches within licensed fertility treatment would have to be defined in the Act.

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[1] The **Financial Conduct Authority's Regulatory sandbox** offers an open-ended service as part of their remit to encourage innovation. The propositions must be genuinely innovative, show clear consumer benefit and meet all of FCA's criteria. This version of a sandbox is resource-intensive, because applications are to an extent pre-assessed individually, with a series of checks applied before the application is even accepted for consideration, plus the evaluative task at the end of the pilot. The **Information Commissioner's Office regulatory sandbox** is more directed by the regulator, with the ICO inviting their sector to rounds of sandbox trials invited on specific themes, which ICO define.

23. A sandbox approach might also provide the flexibility to allow HFEA build a long-term dialogue with manufacturers and a model in which to encourage the disclosure of the precise composition of, for example, **culture media**. Although generally considered to be safe, based on past and present experience, composition of culture media can vary, potentially affecting the safety of embryos and likely the clinical outcomes of children born. Currently the HFEA cannot legally require detailed information from companies about composition and safety, as it falls outside our remit. This lack of information also makes comparison of outcomes difficult in research trials. However, in a sandbox approach, which could take into account commercial and competitive sensitivities, HFEA may be able to develop new ways to agree long term information-gathering approaches about issues such as this one. These might be adapted from the MHRA's model whereby the manufacturer can share product details to support defined purposes with the regulator, but for commercial reasons, these details are not made more widely available.
24. Left unchanged, innovation may in effect be stifled by setting a very high bar for any initial approval for a novel treatment process by HFEA. If a greater number of relatively low-risk recently-approved processes could be offered in the clinic under closer, real-time regulatory oversight, this could allow more patients to be offered new clinical developments, while generating more evidence that could better support treatment effectiveness and patient safety.
25. A new approach would be more resource-intensive for HFEA, because greater flexibility for HFEA to determine evidence standards at the initial approval stage, could mean that some applications require more regulatory time. It may also be that under new system, greater numbers of novel processes may be put forward for consideration. An expansion in numbers approved could introduce a more widespread element of increased clinical risk for patients (above the acceptable baseline of evidenced safety and efficacy), than the current approach to novel treatment process applications does.

Options for change

26. **Status quo, with loopholes closed** – it could be decided that currently the HFEA (with scientific input from SCAAC and SAC) already provides sufficient assurance in its approval process that the risks of any novel processes are minimised, primarily based on the evidence on safety and effectiveness available from the outset of the application. The weaknesses in the HFEA's powers around requiring evidence-gathering for newly-approved processes could be specifically addressed in the Act without requiring any new substantive principle to be added into the Act around authorisation processes overall.
27. **Greater post authorisation control via a 'regulatory sandbox'**- The Act could be amended to provide new substantive principles to guide authorisation approaches for novel processes in treatment. For example, to make explicit that the regulator can determine the acceptable standard of evidence that is needed to be submitted by clinics for it to make licensing decisions. This would enable HFEA to require the information that it needs from clinics to authorise novel treatment process applications and to de-authorise authorised processes.
28. This could in turn support e.g., after the HFEA has given a new authorisation for limited treatment use where there is no evidence that a technique is unsafe but where there is limited evidence of its effectiveness, HFEA to put in place more flexible options around prototyping and ongoing testing, evidence-gathering and/or longer-term follow-up. This would help effectiveness to be determined before widespread roll out of the technique in the sector. This could help HFEA to ensure that in the wider sector, patients are only offered treatments that have sufficient evidence to determine whether they are both effective and safe.

29. If the legislation is amended to include principles to allow for a 'regulatory sandbox' approach then consideration should be given to how this kind of regulatory mechanism could be designed to, as far as possible, also support and enable clinics to carry out regulated research where this is the more appropriate approach, including randomised controlled trials for novel processes and treatment add-ons.
30. **Duty to support innovation.** The Act lacks any explicit duty for the regulator to encourage or support innovation in general. This duty could be carried out through treatment approvals or involvement in research/clinical trial approvals, and in many other regulatory activities.

The current situation: Authorising processes

31. As discussed, HFEA is required to have a procedure for licensing only activities that are necessary and desirable for the purpose of providing treatment services, by paragraph 1(3) of Schedule 2 of the HFE Act. Since 2007, the Act has also incorporated Article 6(2) of Directive 2004/23/EC (the European Union Tissues and Cells Directive), which requires that "The competent authority or authorities, … shall accredit, designate, authorise or license the tissue establishment and indicate which activities it may undertake and which conditions apply. It or they shall authorise the tissue and cell preparation processes which the tissue establishment may carry out...'
32. The HFEA is the competent authority under the EUTCD to authorise most of the processes falling under various licensable activities in the Act. HFEA has developed licensing systems to do this work, however it is open to interpretation as to what form authorisation procedures should take. The Act itself doesn't refer directly to how it expects HFEA to authorise such activities or processes.

Issue

33. Because the HFE Act currently relies significantly on interpreting EU legislation, this can cause at times, a lack of clarity. It might be clearer if Parliament established on the face of the Act where it feels that interpreting EU legislation is the optimal approach, or where the UK expects to have areas covered in the Act in its own right. This consideration may also offer a further opportunity for Parliament to delegate more of the detail of regulating licensed activities to the HFEA to determine.

Option for change

34. That the Act is amended to explicitly add principles and legal expectations about how HFEA should authorise processes.

The current situation: Encouraging fertility clinics to be active in research

The Act does not require licensed fertility clinics to be active in research nor to facilitate research at the clinic.

Issue

35. We believe that the sector and patients would benefit from more licensed embryo research being conducted in UK fertility clinics, as well as more legal/ethical/social research. Clinics being research-active is shown to improve standards of clinical care. However, despite the benefits for patients and for research more generally that would come about from more clinics participating in such research, it is difficult to see how such requirements could be mandated in legislation.

36. An achievable minimum might be for the Act to build in a duty to facilitate embryo donation to research conversations into clinic licences. Clinics must already complete paperwork around embryo destruction, or reproductive donation, depending on patients' consent, so offering patients this option would not add significant burden, would enhance patient choice, and support licensed embryo research. Practical issues could arise without a broader consent to embryo donation system in place. Clinics should not pressure patients to donate embryos, (and there is no evidence of this happening) but we are concerned that there is also little evidence of the conversations about donation to research consistently taking place, where we know that other alternative options are being discussed with patients.

Option for change

37. Consideration should be given to amending the Act to require clinics to discuss embryo donation with patients, in order to benefit research more broadly and to support patient autonomy in this area.

2. Artificial intelligence

The current situation

38. The use of AI in reproductive medicine could touch most aspects of a patient's treatment cycle, from patient management and clinical decision-making to gamete and embryo grading.[2] The HFEA has been monitoring AI as a priority topic for our Scientific and Clinical Advances Advisory Committee (SCAAC) since 2019 and we continue to monitor both the research in this area and the use of AI within clinics so that we are ready to either take a policy position, process any applications or produce patient information, where relevant. We also have a new Authority/SCAAC member with expertise in AI and data-driven technology.

39. The following identifies the key issues raised by the use (and regulation) of AI in reproductive medicine.

Issues

40. There is a lack of high-quality research into the effectiveness of many of these algorithms, with few high-quality studies having taken place. There are potential conflicts of interest with commercial companies funding research into their own products or as the named authors.

41. There are concerns about a lack of transparency over AI's decision-making, a risk of unintended bias in the training data, a lack of legal accountability over each element of the model's output, and a lack of skills within the fertility sector workforce to manage the rapid introduction and development of AI.

42. At present, many regulators lack the capabilities to be able to understand AI and identify whether or how to exercise regulatory powers. It would change the dynamic considerably between an inspector and a clinic if the inspector needs to interact with and understand a machine, as opposed to an embryologist or a doctor.

43. The use of AI in the fertility treatment also raises questions about how the Authority would inspect their suitability and appropriate use in centres, as well in quality assurance systems. It is likely that

[2] For further, optional, information on AI please see the **Horizon Scanning Prioritisation of Issues** paper presented to SCAAC in 2022.

regulators as currently resourced, will need significant external support and guidance from government and professional expert bodies to be able to regulate these technologies effectively.

Options for change

44. The HFEA and other regulators are already taking steps to share innovation and good practice so far as is possible within the resources and legal powers that we currently have. Despite concerns and regulatory questions, the use of AI in reproductive medicine is developing rapidly with new technologies frequently being introduced to the sector for commercial use, raising questions of prioritisation and resources for HFEA.
45. The question is whether changes to the Act could support the responsible implementation of AI and data-driver technologies in the sector. If so, what is needed? And should the regulation of AI be specified at a macro or sector specific level? If the latter, then the Act may need to provide that HFEA should define what AI and machine learning is, within assisted reproduction. It should also specify that medical-relevant AI governance applies to research as well as treatment.
46. If the former approach is taken, then the regulation of AI may not need to fall under the remit of the Act and any amendments to the HFE Act should only build in mechanisms to ensure that the use of AI within the fertility sector are keeping in line with the most up-to-date relevant work and regulation in AI.
47. These questions can probably only be answered in light of the National AI Strategy, and the government White Paper which is due to be published in 2022.
48. The HFEA believes that any regulations introduced should be proportionate and risk-based and would welcome LRAG views more generally on this issue.

3. Summary

49. LRAG is asked to consider:
    - What possible amendments to the Act would bring the Act in line with more modern legislation to permit increased flexibility to support research
    - The possible changes to the novel processes authorising, and opening the Act to permit involvement in clinical trial licencing by the HFEA
    - Options for the Act to be ‘future proofed’ via amendment for rapid changes within the field, including AI