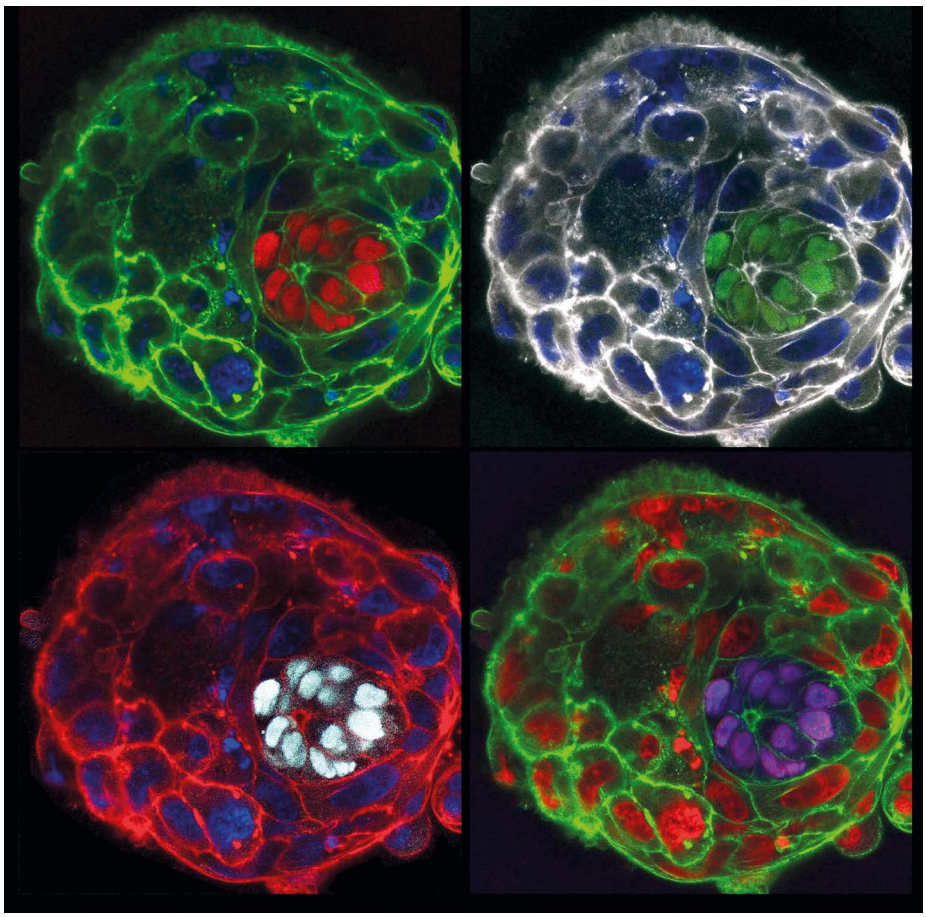

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Research on human embryos is governed by a patchwork of guidelines and rules.

HOW TO REGULATE HUMAN-EMBRYO SCIENCE

Research in genome editing and other biotechnologies is moving too fast for regulators to keep up. **By Philip Ball**

Outside the Third International Summit on Human Genome Editing, protesters held banners that read "Stop designer babies" and "Never again to eugenics", calling for a ban on human genome editing. It was a reminder of the ethical quandaries that embryo science and genome editing can present.

Inside the meeting, held at the Francis Crick Institute in London in March, it was clear that the pace of the science prompting such concerns is quickening. Scientists reported, for example, that they had grown mice using eggs engineered from cells from male mice[1]. The following month, researchers in China reported[2] pregnancies in monkeys after transferring artificial embryos, made from stem cells, into monkey wombs, although the pregnancies did not progress beyond a very early stage.

The conference also hosted a talk by a woman whose sickle-cell disease had been successfully treated by editing the genetic code in her body's blood-producing cells.

Regulators — whose job it is to establish the bounds of what is permissible — are struggling to keep up. "Regulatory approval cannot happen at the same speed as scientific development," says Peter Thompson, chief executive of the UK Human Fertilisation and Embryology Authority (HFEA), a government body seen as a trailblazer in regulating this branch of science and medicine.

The problem was starkly demonstrated five years ago, when Chinese researcher He Jiankui announced, at the Second International Summit on Human Genome Editing in Hong Kong, that he had altered the genomes of twin girls born by *in vitro* fertilization (IVF), with the aim of giving them resistance to infection by HIV. He's work was widely condemned by researchers as irresponsible, and after a Chinese court judged it to involve 'illegal medical practice', he was given a three-year prison sentence.

The World Health Organization currently recommends against the use of heritable (or germline) human genome editing, but has no powers of enforcement — and neither does any other international body. Some national bodies, such as the HFEA, can create rules to govern research and its outputs, but such centralized oversight is relatively rare. Most scientists comply with guidelines formulated by professional bodies such as the International Society for Stem Cell Research (ISSCR), but these principles have neither legal force nor a mandate from wider society.

The ideal rulebook would be agile and able to evolve with the science, and it would include public and expert opinions. But it's not clear that existing procedures can do that job, so the HFEA is considering changing how it works to accommodate the pace of research. In February, it launched a public consultation on ideas to "future-proof" the Human Fertilisation and Embryology Act — the law that governs UK embryo and fertility research.

But will such changes be enough to keep up?

Delicate decisions

Rules and laws governing embryo science have often emerged slowly and piecemeal. After the first IVF births in the 1970s, the UK government convened an expert panel to consider how embryo research should be regulated — for example, how long human embryos could be cultured and studied in the laboratory for. In 1984, the panel recommended a limit of 14 days from fertilization, a restriction that finally became law in the United Kingdom in 1990 and was adopted by several other countries. The ISSCR also adopted this limit in its guidelines — until 2021, when it proposed relaxing the restriction in some circumstances, in response to researchers' newfound ability to grow embryos right up to the limit and taking into account the potentially useful knowledge that could be gleaned from going beyond it.

At the same time, the ISSCR advised against using methods such as CRISPR, a technique that cuts the DNA sequence at specific points, or potentially more accurate 'base' and 'prime' editing techniques, to alter the genome in human embryos, until the safety issues are better understood.

At the London summit, most scientists seemed to agree that somatic-cell editing, which creates changes that are not heritable, is warranted to treat conditions such as sickle-cell disease, provided that safety and efficacy are demonstrated.

The consensus is that germline editing requires much more cautious handling, because the changes are passed on to future generations. But if some of the new precision-editing methods are shown to be safe in human embryos, says Crick developmental

and stem-cell biologist Robin Lovell-Badge, one of the organizers of the summit, the whole field "could accelerate very fast" and demand for germline editing could increase.

Nimbler rulemaking

Science moves fast — but regulation often cannot. For the HFEA, altering regulations would typically require a change in law. "The issue is the inevitable mismatch between a fixed legal framework, which is slow to change, and the constant development of the science," says Thompson.

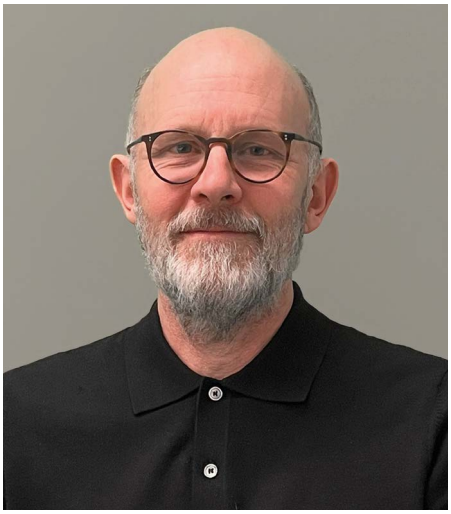
One way to get around this, Thompson says, is to design 'primary' legislation such that it can be more easily amended by 'secondary' legislation, which does not require the same degree of parliamentary scrutiny or approval. That approach was successfully used by the HFEA to grant approval for a technique known as mitochondrial replacement therapy in 2016.

Another approach being explored by the HFEA is a 'regulatory sandbox': a kind of controlled experiment in which fresh ways of doing things are trialled in a small-scale real-world environment. This process was first developed in the finance sector for testing new and unproven investment tools. The HFEA's latest public consultation is a first step towards gauging people's appetite for such approaches.

Some scientific innovations might still fall between the cracks. Take embryo models: synthetic constructs, generally made from embryonic stem cells or stem cells derived from adult somatic cells, known as induced pluripotent stem cells (iPS cells), that recapitulate embryo development. There is no consensus on whether they should be regarded as genuine embryonic organisms or as types of tissue culture. Already, researchers have grown such embryo models *in vitro* until organs begin to develop[3], and the latest study on monkeys indicates that scientists can implant them and initiate pregnancies. Yet this is happening without clear regulations about what is permissible: they "are not regulated at all", says Lovell-Badge.

The HFEA has clear legal powers over some of these technologies, but in other countries regulation evolves more organically. In the United States, the government cannot regulate purely on moral grounds, but it has effectively barred research that creates or destroys human embryos, by restricting federal funding for it. Germline human genome editing is also blocked by an indirect bureaucratic gambit: clinical trials cannot happen without approval from the US Food and Drug Administration (FDA), but the FDA is prohibited from even considering such requests.

Meanwhile, US states can pass their own legislation controlling research and medical procedures, creating a patchwork. But bioethicist Alta Charo at the University of Wisconsin–Madison thinks there are advantages to such an ad hoc system. "We have a 'laboratory of the states'," she says. "It's very messy and inefficient, but it allows for exploration of options."



HFEA

Peter Thompson is head of the UK Human Fertilisation and Embryology Authority.

In Japan, bioethicist Tetsuya Ishii at Hokkaido University in Japan says that such technologies are constrained mostly just by guidelines that are "effective to some extent" but not legally enforceable, particularly for therapies using adult stem cells. By contrast, research and therapies based on iPS cells or embryonic stem cells get "a lot of oversight and regulation in Japan", says developmental biologist Cantas Alev at Kyoto University.

> "Regulatory approval cannot happen at the same speed as scientific development."

Public opinion

When science moves fast, policymakers might respond reactively, says Bartha Knoppers, a specialist in the ethical and legal aspects of genomics and biotechnologies at McGill University in Montreal, Canada. This mindset could unduly constrain science that has possible health benefits, she says. Asking those who might stand to benefit should be a key part of the decision-making. But "whether patients think regulation is going too fast or not fast enough depends on what condition you have", says Bettina Ryll, a founder of the Melanoma Patient Network Europe, who spoke at the genome-editing summit. People with a serious, progressive disease will be more willing to accept risks, she says.

Consultations with stakeholders and the wider public can be difficult, costly — and slow. But without this input, there is the danger of mismatch between policy and public opinion. For instance, some existing restrictions, such as the US ban on federal funding for human-embryo research, have not been assessed in consultation with the public. "Does this [situation] represent public opinion?" says Charo. "No one knows."

Some researchers, however, question why time should be of the essence anyway. Sheila Jasanoff at Harvard University in Cambridge, Massachusetts, a specialist in the social and policy impacts of science and technology, pushes back against the idea that regulations must be changed to keep pace with a fast-moving field. "Why is the slow, deliberative process always seen as the problematic one?" she asks. With this philosophy in mind, in 2020, she and bioethicist Benjamin Hurlbut at Arizona State University in Tempe launched the Global Observatory for Genome Editing, which aims to foster dialogue on this and related biotechnological developments between diverse groups of people.

Whatever the position about regulation, it pays to know what developments are coming. Some international and national organizations already conduct such 'horizon scanning' for fast-moving technologies — although it is not clear that any has yet considered embryo science. For example, the Organisation for Economic Co-operation and Development (OECD) runs an Observatory of Public Sector Innovation, which seeks to develop guidance for governments and the public sector on the opportunities and risks of emerging technologies such as artificial intelligence (another area in which advances are outpacing regulatory oversight).

Hank Greely at Stanford University in California, who researches the legalities of bioethics, has called for the wider establishment of such horizon-scanning groups, as well as auditing bodies that would keep tabs on whether regulations are being followed and remain fit for purpose[4]. The question is who would fund and oversee such projects, he adds; industries, governments and scientific institutions might all be considered to have vested interests.

In the end, making sure that fast-moving science is regulated in a timely and effective manner is about maintaining a robust social contract between science and society. "Are we continually asking ourselves, is this where we want to go? Who will it serve?" says Knoppers. "It's about keeping vigil."

Philip Ball is a science writer based in London.

1. Murakami, K. *et al. Nature* **615**, 900–906 (2023).
2. Li, J. *et al. Cell Stem Cell* **30**, 362–377 (2023).
3. Amadei, G. *et al. Nature* **610**, 143–153 (2022).
4. Greely, H. T. *Glob. Public Pol. Gov.* **2**, 266–282 (2022).