

# World view



By Robin  
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## Why stem-cell guidelines needed an update

**New criteria aim to reassure the public to permit progress in contentious research.**

Over the past five years, researchers have kept human embryos alive in culture longer than once thought possible and cultured stem cells into structures that model embryos and organs with unprecedented sophistication. Perhaps most striking is the creation of animal-human chimaeras by injecting cells from one species into an early-stage embryo from another species. This might enable, for example, a pig to produce a human heart. Other techniques include making eggs and sperm from stem cells, editing genomes and replacing organelles. These approaches could one day help to treat or avoid human disease, and are already improving biological understanding.

Some find these scientific advances scary and uncomfortable. They raise complicated questions around ethics, beliefs, norms and values. Most scientists want clear boundaries delineating which experiments are acceptable, both legally and to society. And the public wants reassurance. That is why the International Society for Stem Cell Research (ISSCR) has updated its guidelines to reflect current science. These guidelines set standards that are consulted by researchers, policymakers, and funders, journals and others who review research.

The updated guidelines, published this week, are the product of a task force, which I chaired. It comprised 45 international experts, including scientists, clinicians, ethicists, lawyers and policy specialists. We deliberated over 18 months and more than 100 Zoom calls. We consulted relevant polls and public-engagement projects. The guidelines were then peer reviewed by a similar set of experts.

What changes did we recommend? Perhaps the most striking is relaxing the '14-day rule', the limit to culturing intact human embryos in the laboratory, which has been written into law by some dozen countries, including the United Kingdom and Australia. Beyond this point, embryos must be destroyed. Fourteen days is shortly before the stage at which the first signs of the central nervous system appear (the first neurons appear at day 42).

When the limit was proposed some 40 years ago, no one could culture human embryos much beyond 5 days, the time of implantation. Now, it prevents study of a critical period, between 14 and 28 days, when the beginnings of tissues are established. Processes that go awry during this time are thought to cause recurring miscarriages and congenital abnormalities, for example those of the heart and spine.

Researchers can also use stem cells to grow structures that are startlingly like embryos. These 'embryo models' almost certainly would not develop normally if implanted in a uterus;

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indeed, our guidelines ban doing so. Still, embryo models could inform us about the 14–28-day period. Comparing them with actual human embryos is the best way to assess their relevance and use them for experiments that might otherwise require embryos. Insights gained – for example, derivation of gametes *in vitro* – might address miscarriage and infertility and could be used to assess techniques, such as heritable genome editing, to avoid genetic disease.

Up to now, the 14-day rule has served science well. It has allowed research that is essential for many assisted-conception techniques to proceed in the face of strong opposition, notably from religious groups. Even scientists who saw value in experiments beyond 14 days, and viewed the time limit as arbitrary, were reluctant to discard a workable compromise made with public input.

The ISSCR's solution is to require review and approval of proposals to study embryos beyond 14 days. (The approval process, whether by institution or national body, varies by country; all should have representation from specialists and lay members.) Importantly, each proposal should be judged individually, on whether the research is justifiable in terms of the value of the information obtained, whether there are alternative ways to obtain the information and so on. The more embryos that would be used, or the longer they would be kept in culture, the higher the bar.

Before approval could be given, it would require sufficient public support. This should be assessed quantitatively (using tools such as opinion polls) and qualitatively (using, for instance, citizen panels). Applying the guidelines will demand extensive public engagement, including consideration of social justice and whether experiments are an appropriate use of limited resources.

In past guidelines, the ISSCR recognized three broad categories of experiment: banned; permitted with dedicated review and oversight; and permitted generally. Now we have added nuance to these categories. We suggest that certain types of research, such as allowing animals with human gametes to breed, should not be permitted at all because they are ethically concerning, lack compelling scientific rationale or both. Other kinds (such as heritable genome editing) are not permitted now, but might be one day – with evidence about safety and efficacy, and public support.

The guidelines discourage premature commercialization of stem-cell-based interventions, and propose ways to curtail the activities of rogue clinics that offer untested, unsafe interventions with no basis in science.

Such oversight is more complicated but more valuable. Blanket bans enshrined in law appeal in their simplicity, yet leave the public worse off, and are more vulnerable to dogma or instinct rather than evidence. Guidelines from international scientific societies can offer leadership in reassuring scientists and the public.