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AUTHOR(S):

Sawai, Tsutomu; Okui, Go; Akatsuka, Kyoko; Minakawa, Tomohiro

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**TITLE: Promises and Rules****SUBTITLE: The implications of rethinking the 14-day rule for research on human embryos**

By Tsutomu Sawai<sup>1†</sup>, Go Okui<sup>1</sup>, Kyoko Akatsuka<sup>2</sup>, Tomohiro Minakawa<sup>3</sup>

- 1) Institute for the Advanced Study of Human Biology (WPI-ASHBi), KUIAS Kyoto University, Japan
- 2) Uehiro Research Division for iPS Cell Ethics, Center for iPS Cell Research and Application, Kyoto University, Japan
- 3) Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application, Kyoto University, Japan

† Corresponding author: Dr Tsutomu Sawai ([sawai.tsutomu.4s@kyoto-u.ac.jp](mailto:sawai.tsutomu.4s@kyoto-u.ac.jp))

In *On Revolution*, Hannah Arendt, one of the great political thinkers of the 20th century, stated that “promises and agreements deal with the future and provide stability in the ocean of future uncertainty where the unpredictable may break in from all sides”.<sup>1</sup> She cited the Mayflower Compact, which was “drawn up on the ship and signed upon landing” on the uncharted territory of the American continent, as such an example of promise in Western history. Human beings are born with the capacity to act freely amid the vast ocean of uncertainty, but this capacity also creates unpredictable and irreversible consequences. Thus, in society and in politics, moral virtues can only persist through “making promises and keeping them”.<sup>2</sup>

**The 14-day rule as a promise**

Arendt also commented that modern science and technology were opening up such “uncharted territory” and correctly foresaw the advent of *in vitro* cultured human embryos – which became reality in the 1970s. This technology and the new territory it opened, came with a promise – in the sense of Arendt’s words – to respect moral views about the

sanctity of human life and to advance research in a responsible way. Starting with the UK and the USA, more than 20 countries adopted the “14-day rule,” which stipulates that human embryos cannot be grown *in vitro* longer than 14 days after post-fertilization or beyond the appearance of a primitive streak, whichever comes first.<sup>3</sup>

There are two main reasons why the limit was set at 14 days. The first is that the embryo is not yet an individual. Some people would argue that a person’s identity is determined at the moment of fertilization, but since the embryo can divide into twins until the formation of the primitive streak, which begins around 13 days after fertilization and signals the onset of gastrulation, it is not yet an individual with a determined identity. The second reason is that the embryo does not begin to develop a nervous system – that will ultimately enable sentience – until 14 days post-fertilization or the appearance of the primitive streak.

If the presence of a nervous system is what matters morally, it could be argued that the limit could be set later than 14 days. However, the guidelines in the UK established in the 1980s reaffirmed that the formation of the nervous system does begin with the formation of the primitive streak. Thus, if the embryo is prevented from developing beyond that stage, no sentience problems can arise.

Critics of the 14-day rule often point out that it was a compromise, yet the etymological sense of the word (com-promise) conversely reminds of the fact that it is an enactment of mutual promise. Similar “promises” were implemented by many countries in the form of laws or guidelines as their researchers ventured into the uncharted territory of research with human embryos. These promises and agreements have helped to create and maintain public trust in biomedical research.<sup>4</sup>

### **New ISSCR guidelines**

At the end of May 2021, the International Society for Stem Cell Research (ISSCR), the largest and most influential academic society specifically dedicated to research on stem cells and embryos, published its renewed guidelines with some major revisions.<sup>5</sup> Among

the most controversial changes was removing the previous (2016) 14-day limit for embryos cultured *in vitro* and embryo-like structures generated from stem cells. “Embryos cultured *in vitro*” include surplus IVF embryos donated to research and embryos specifically created for research – the ISSCR makes no distinction between these two.

There are three main reasons for the ISSCR’s decision to remove this internationally accepted rule from its guidelines. First, advances in technology now make it possible to culture embryos *in vitro* beyond 14 days, which was technically impossible in the 1980s when the 14-day rule was first adopted. Second, since it is now possible to generate embryo-like structures from human pluripotent stem cells – which means that fertilization is no longer necessary – the 14 day rule is no longer a significant criterion, at least for research using embryo-like structures. Third, as very little is known about embryonic development after fertilization and after the formation of the primitive streak,<sup>6</sup> it will provide valuable knowledge that may help to elucidate the causes of diseases that occur early in development.<sup>7</sup> The significance of the third point was already discussed when the 14-day rule was formulated, but the first and second points have only recently been subject to debate in light of technological advances. What should be noted here in regard to the first and second point is the distinction between fact and value. Generally, in ethics, the value judgment of “ought” cannot be derived solely from the fact of “is.” In other words, the fact that technological advances have made it possible to do something that was impossible before does not imply the ethical validity of that action.

The updated guidelines stipulate that it is permissible to culture embryos *in vitro* until 14 days after fertilization or the formation of the primitive streak and to culture stem cell-based structures that mimic the complete embryo (“stem cell-based embryo models that represent the integrated development of the entire embryo, including its extra-embryonic membranes”) for the minimum period necessary to achieve scientific objectives “only after review and approval through a specialized scientific and ethics review process.”<sup>5</sup>

The guidelines also prohibit the implantation of human embryo-like structures from stem cells into a human or animal uterus. In regard to *in vitro* embryo culture beyond the

primitive streak, the ISSCR recommends that “national academies of sciences, academic societies, funders, and regulators should lead public conversations on the scientific significance as well as the societal, moral, and ethical issues of allowing such research.” They would accept the decision of countries to extend the 14-day rule only “[i]f such conversations do lead to broad public support for the research within a jurisdiction, and if local policies and regulations permit.” Moreover, “embryo culture beyond 14 days and into primitive streak formation and gastrulation could be considered in those jurisdictions for review by the specialized oversight process” on the condition that the minimum number of human embryos necessary to achieve the research objectives is used.<sup>7</sup>

### Concerns about the ISSCR’s Decision

Some objections and concerns have been raised about the ISSCR’s new guidelines. For example, while the society calls for public debate on whether to extend the 14-day rule, the ISSCR has been criticized for making this decision without sufficient public debate.<sup>8</sup> ISSCR has argued for the legitimacy of the deliberative procedures that led to this decision.<sup>9</sup> Moreover, guidelines are just recommendations by an academic society that do not and should not trump national laws or guidelines.

There is also concern that the ISSCR did not set a new endpoint until which *in vitro* culture embryos could be cultured.<sup>10</sup> Indeed, the society emphasized the significance of research on embryos beyond 14 days post-fertilization, but there is neither mention of other timelines nor developmental landmarks, such as the appearance of a neural tube or nerve cells, at or with which embryos would become subject to moral and legal rights. One could argue that the ISSCR’s intention is to generally encourage debate on the merits of embryo research – including a review of the 14-day rule – based on the scientific significance of research on embryos versus the moral concerns associated with that research. Nevertheless, we get the impression that the ISSCR’s justification does not give enough consideration to moral concerns vis-à-vis scientific merits.

## An International Perspective

In any case, the revised guidelines could indeed prompt countries to adapt their legal and regulatory framework for research on human embryos. Optimistically, countries without sufficient regulations or countries that have only reluctantly adopted the 14-day rule may now organize the public debates the ISSCR is asking for prior to changing any laws or regulations. However, it might be too optimistic to expect that countries with a progressive or even aggressive research agenda or those that do not consider human fetuses as subjects of moral rights before 120 days after fertilization will fully engage in such discussions.<sup>11</sup> Other countries may also decide that the benefits of research on human embryos after 14 days of fertilization outweigh the foregone opportunity costs without an adequate public discussion.

This raises other questions of how the international community should react to individual countries' decision to abandon the 14-day rule, how long *in vitro* culture of human embryos and embryo-like structures should be permitted, and how to distinguish between intact embryos and stem cell-based embryo-like structure that fully or partially mimic the embryo. It may also start discussions about the need for international standards in research using human embryos and embryo-like structures or even an international treaty to maintain such standards – something that the research community has so far avoided by wide adoption of the 14-day rule.

If individual countries abandoned the 14-day rule, it could jeopardize international cooperation in research when, for instance, funding agencies in one country with stricter regulation would require scientists in another country to adhere to their rules, as is already the case when using animals in research. To further enable and manage such collaboration may therefore require some form of international oversight to replace the 14-day rule. This could be achieved for instance by an international registry for *in vitro* research on human embryos.

This registry could be established by a specialized agency, such as the WHO, which already manages a similar registry for human genome editing after it made

recommendations for a framework for the governance of human genome editing<sup>12,13</sup>. These recommendations encapsulate nine discrete areas, including registries; international research and ‘medical tourism’; illegal, unregistered, unethical or unsafe research; intellectual property; and education, engagement and empowerment. A major advantage is that the framework covers broader topics in the context of human genome editing, not only basic research or clinical application. A similar registry for creating and using human embryos and embryo-like structures may also cover both basic research and clinical applications. *Nature* journals have already announced that they will adopt ISSCR guidelines.<sup>18,19</sup> If the WHO established a registry, scientific journals could ‘enforce’ wide use of such a registry by requiring that authors register their research projects before submission.

### **How can Japan Decide?**

To ensure transparency and accountability in civil society, it will be crucial to start and support public discussions on the governance of research that uses human embryo and embryo-like structures. In Japan, which adopted the 14-day rule, the ISSCR guidelines may indeed rekindle such discussions. Japan’s policy is based on a 2004 report *The Fundamental Way of Thinking in Treating the Human Embryo*, which defines human embryos up to 14 days post-fertilization as “buds of human life”, that is, potential human beings, while the development of “human life” starts only after the formation of the primitive streak and subsequent organ differentiation. Japan allows the experimental use of embryos before 14 days of fertilization on an exceptional basis, depending on the purpose, such as generation of embryonic stem cells or research to improve assisted reproductive technologies. Based on previous discussions, it is unlikely that a decision will be made to allow experimental use of human embryos beyond 14 days.

If the 14-day rule were to be relaxed without sufficient deliberation and participation of civil society, it would mean that what was once promised by the scientific community is now discarded unilaterally. If that were to happen, the credibility of the scientific community would be in jeopardy. The ISSCR’s guidelines are therefore only a starting point for a wider deliberative process, and should not and need not to be adopted without

adequate discussion. In the face of an uncertain future, each country must make thoughtful decisions reflecting on past promise-making experiences.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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