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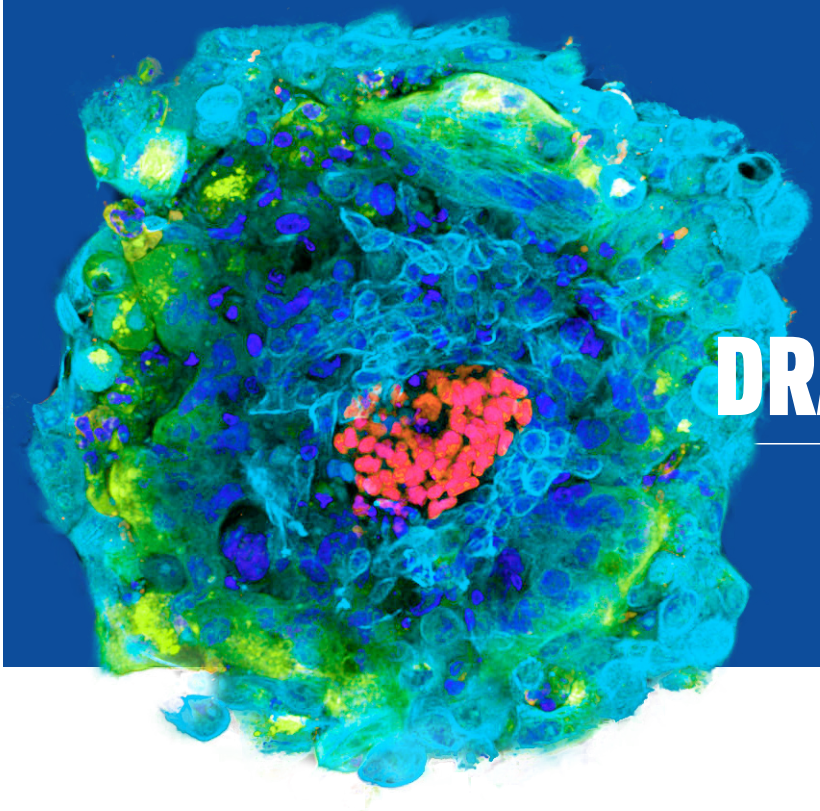

DRAWING THE LINE

ETHICAL, POLICY, AND SCIENTIFIC PERSPECTIVES ON U.S. EMBRYO RESEARCH

MOVING THE LINE? FINDINGS AND RECOMMENDATIONS FOR HUMAN EMBRYO RESEARCH

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Introduction

The guideline limiting human embryo research *in vitro* to 14 days post fertilization (dpf)—generally known as the 14-day rule—is widely accepted by many governments, foundations, and nongovernmental organizations (NGOs) interested in human embryo research. In several countries such as the United Kingdom, research on embryos beyond 14 dpf is illegal (Matthews and Gallego Marquez 2019). However, in the United States where human embryo research with federal funds is banned, there are no laws prohibiting scientists from conducting research on embryos beyond 14 dpf using nonfederal funding. This deadline is thus not a legal rule but a voluntary guideline recommended by scientific and medical societies, including the International Society for Stem Cell Research (ISSCR 2016), the National Academies of Science, Engineering, and Medicine (NASEM 2010), and the Association for Reproductive Medicine (ASRM 1986). In practice, however, U.S. scientists are reluctant to violate the 14-day guideline.

Until recently, concerns about the deadline were simply theoretical because the technical capacity to conduct research on embryos beyond the 14-day limit did not exist. That changed in 2016 when two research groups were able to culture embryos *in vitro* up to 14 days, at which point they ended experiments to avoid violating the 14-day rule (Shahbazi 2016; Deglincerti et al. 2016). This newly developed technical capacity has led some commentators to contemplate the pros and cons of a possible extension of the 14-day guideline (Harris 2016; Hyun, Wilkerson, and Johnston 2016; Pera 2017; Warnock 2017). Two new questions have thus arisen: Should the guideline be changed? If so, what should replace it? These questions have scientific, policy, and ethical dimensions.

Recommendations

Over the past 18 months, we have studied the scientific, political, and ethical considerations associated with the question of whether the 14-day rule should be changed. We assessed the scientific literature to determine what is known about early human development, what remains to be known, and what expanding human embryo research could elucidate if it were allowed (Wagner and Matthews 2019). We reviewed current U.S. human embryo research policies, the history of how those policies were developed, and how they impacted research (Matthews and Yang 2019). We surveyed the top national research and development (R&D) countries and compared their human embryo research policies to U.S. policy—with special emphasis on the U.K. Warnock Report and the U.K. Human Fertilisation and Embryology Act of 1990 (Matthews and Gallego Marquez 2019).
We also conducted a comprehensive survey and analysis of the ethical and moral concerns associated with human embryo research and how these concerns impact changes to the 14-day limit (Iltis et al. 2019). Finally, we assessed emerging technologies to replicate early human embryo development—what we refer to as human cell culture models of early development (hCCMEDs) but are also known as “embryoids” or “synthetic embryos.” Our assessment describes hCCMEDs, how the 14-day limit impacts research using them, and how they affect our views of the 14-day limit (Matthews et al. 2019).

Further, we talked with scientists, ethicists, and policy scholars for additional feedback on this project. We hosted two workshops in 2018 to explore opinions, options, and views of the 14-day limit. The first workshop, at Rice University's Baker Institute for Public Policy in Houston, focused on U.S. policy options and concerns, which allowed us to understand the diversity of thoughts on the subject. This workshop also included an open public session to allow community members to engage with the research and research team. The second workshop, at the Brocher Foundation in Geneva, Switzerland, brought experts from Europe to discuss transnational policies and our preliminary recommendations. Finally, we interviewed additional experts and representatives of funding agencies and NGOs for their perspectives on the 14-day rule and our preliminary recommendations.

Based on this work, we developed a series of final recommendations that highlight the ethical and policy issues related to human embryo research. In addition, we address the questions: should the 14-day guideline be changed? And if so, what should replace it? These recommendations focus primarily on the U.S. context but can also be applied to other national policies and international guidelines.

Respecting the Special Status of Human Embryos

Recommendation 1: Embryo research should be conducted only when other, less controversial means of answering important research questions are unavailable. When it is conducted, scientists must be aware of public perceptions of the work and engage with the public in a thoughtful manner.

Discussions of the special status of embryos and the concept of respect when using embryos are not new. These notions were discussed in both the 1979 Department of Health, Education, and Welfare report and the 1984 U.K. Warnock report. Furthermore, most jurisdictions also require that scientists use human embryos only when other means are unavailable. Respect for the human embryo was prevalent in previous recommendations for human embryo research, and it should be clearly emphasized when approaching the work.

Human embryo research is a sensitive and controversial area, especially in the United States (Matthews and Yang 2019). No consensus exists on the permissibility of such research (Iltis et al. 2019). At this time, the scientific literature does not indicate the availability of alternative techniques that could completely replace human embryo research (Wagner and Matthews 2019). Therefore, scientists are likely to continue to find human embryo research essential to understanding human embryo development.

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Even so, scientists pursuing human embryo research should be aware of, and sensitive to, the wide range of public perceptions of their work. They should endeavor to engage in thoughtful and open discussion with the public to justify their work, to demonstrate the inadequacy of alternatives, and to explain why their work is compelling and should be pursued for the public good. Transparency involves not only sharing information but subjecting research to public scrutiny and oversight mechanisms as described in Recommendation 3.

Different Guidelines for Different Entities

Recommendation 2: Given the biological, political, and ethical differences between human embryonic stem cells, hCCMEDs, and human embryos, guidelines for research involving each of these entities should be created individually.

For human embryonic stem cell (hESC) research, U.S. scientists predominantly follow guidelines from the NIH (2009), NASEM (2010), and ISSCR (2016). The NIH guidelines address hESC research, but the NIH does not fund research using human embryos and therefore does not have any guidelines for it. In contrast, the ISSCR and NASEM both point to the 14 day-limit, both with regard to hESC research and the creation of hESCs. Neither the ISSCR nor NASEM have discussed or deliberated on the limitations to human embryo research directly. The perceived risks, ethical concerns, and knowledge obtainable from human embryo research are different enough from hESCs that they warrant separate guidelines, regulations, and review (Iltis et al. 2019).

In addition, emerging technologies now allow scientists to manipulate hESCs and other pluripotent cells to create entities—called hCCMEDs, "embryoids," or "synthetic embryos"—that organize themselves similarly to different stages of early embryo development (Matthews et al. 2019). Current technology is unable to recreate much more than an incomplete representation of the early embryo, and these entities lack the potential to develop into a human at this point. This might change in the future. Guidelines for hCCMED research should consider the possibility that technological advances will allow for the development of features that precisely resemble human development but also keep in mind their utility as an alternative to using human embryos.

Need for Improved Research Oversight

Recommendation 3: Human embryo, hESC, and hCCMED research should undergo a scientific and ethical review process that has adequate support to allow for a consistent review of proposals across institutions.

Public trust in scientific institutions requires not only public justification of scientific pursuits but also evidence that such pursuits will respect the limits imposed on them, including oversight processes. For human embryo research, this concept is even more important since there is no national consensus on what research, if any, should be conducted. Even if we maintain the status quo—leaving the 14-day limit—the systems in place for reviewing and overseeing human embryo research up to 14 dpf should be refined

and applied consistently. It is important to have a trustworthy system in place before anyone should expect the public to trust in the oversight of human embryo research.

Unfortunately, not all human embryo research currently is being reviewed by an oversight committee. In 2016, the ISSCR recommended that embryo research be reviewed by the same institutional scientific and ethical oversight groups as stem cell research—Stem Cell Research Oversight (SCRO) committees. SCRO committees were originally developed based on recommendations from the ISSCR and NASEM. They are based at one or a set of universities and tasked with reviewing proposals that culture human embryos for hESC derivation, as well as proposed research that examines early human embryo development modeled using hESCs (such as hCCMEDs) or induced pluripotent stem (iPS) cells (ISSCR 2016; NASEM 2010). The ISSCR recommends that SCRO committees also review human embryo research proposals in a new embryo research oversight (EMRO) process (Daley et al. 2016; Kimmelman et al. 2016). Although this might not be occurring at many institutions right now, this oversight would help respect the sensitive nature of human embryo research and allow research to be vetted for scientific, ethical, and policy considerations. It would provide a level of ethical oversight the research might not have otherwise, and it would maximize the possibility that the research is scientifically sound and appropriate. Since the SCRO committees' areas of expertise overlap with the expertise needed to review broader human embryo research, it seems like a good match. In addition, the EMRO process described by ISSCR is consistent with embryo research policy statements by the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) (Daley et al. 2016).

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Unlike other research oversight committees such as institutional review boards (IRBs) for human subjects review and institutional animal care and use committees (IACUCs), SCRO committees are not mandated by federal regulations. Therefore, these committees are not subject to oversight and there is currently no accreditation for them. Ultimately, SCRO committees are not accountable to anyone beyond the institutions that create and authorize them, and those institutions are not accountable to anyone regarding their SCRO policies and practices. This impacts the authority that SCROs have within academia, especially when making controversial decisions such as rejecting a research proposal for ethical reasons. This breeds inconsistent practices and can erode public confidence in the oversight function of these committees and the research they review.

Furthermore, many SCRO committees may lack the knowledge or confidence to review all proposals using human embryos, hESCs, or hCCMEDs due to the specialized nature of this research. This is especially true in emerging areas of research including hCCMEDs and early human embryo development. Additional resources and training are needed to help

SCRO committees address complicated and challenging issues associated with human embryo, hCCMED, and other novel and emerging areas of embryo research.

The lack of accountability and access to resources and training for SCRO committees could be filled by professional societies such as the ISSCR. Professional societies could provide additional resources for SCRO committees to help them review human embryo research proposals, similar to guidance available for IRBs through the NIH Office for Human Research Protections or other sources (Bankert and Amdur 2011). This should include training of SCRO members to highlight emerging and controversial research topics. As is the case already at some large universities, creating consulting and auditing services for SCRO committees could give the committees access to outside experts for specific questions and project reviews. This would allow human embryo research proposals, as well as sensitive research on hESC and hCCMEDs, to undergo comprehensive, thoughtful reviews through a process validated by an external accrediting body at all research institutions.

Maintaining the Status Quo

Recommendation 4: The 14-day limit should be maintained unless additional arguments are sufficiently robust to address the current political and social objections to allowing embryo research beyond 14 dpf.

When considering if the 14-day guideline should be changed, there are two primary options for policymakers to consider: 1) keep the 14-day limit or 2) change it (Figure 1). For scientific, political, and ethical reasons, we recommend keeping the 14-day limit and maintaining the status quo at this time.

Maintaining the status quo would allow scientists to increase our knowledge regarding human embryos up to 14 dpf.

Scientifically, there is considerable knowledge to be acquired from research up to 14 dpf, as it only recently became possible to approach this limit (Wagner and Matthews 2019). Although the Dickey-Wicker Amendment prevents the use of federal funding for human embryo research, there are no federal restrictions on human embryo research in the U.S., and only voluntary guidelines prevent research beyond 14 dpf. Maintaining the status quo would allow scientists to increase our knowledge regarding human embryos up to 14 dpf. While maintaining the status quo will limit new research beyond 14 dpf, we found that there is limited scientific justification to extend the limit at this point in time, although this could change as knowledge increases about early human development prior to 14 dpf (Wagner and Matthews 2019).

Politically, keeping the status quo—leaving the 14-day guideline in place and conducting research only prior to this point—would be the most feasible option in the U.S., especially under the current federal administration. It is a politically pragmatic decision that considers the fact that the public has not shown substantial resistance to the current

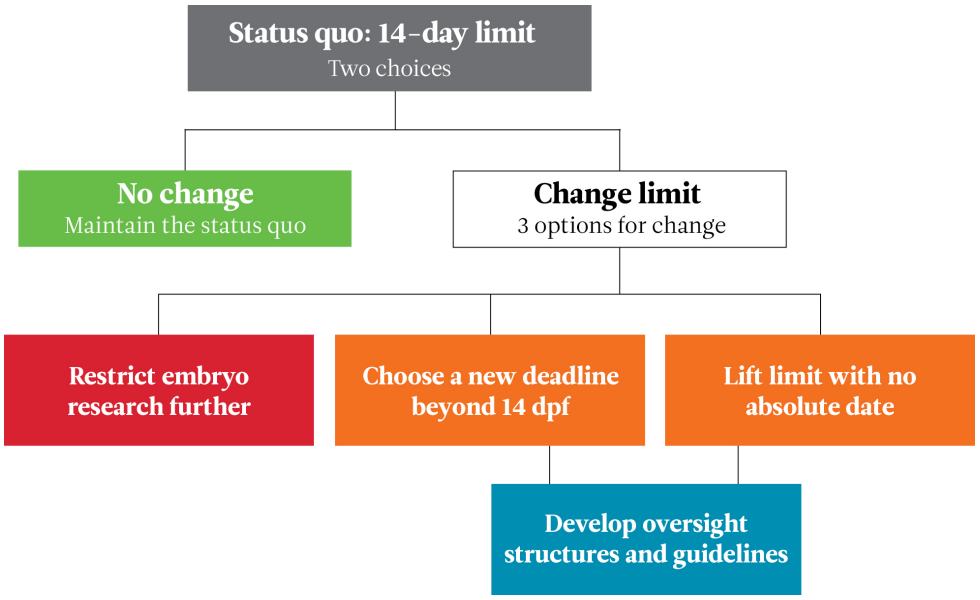
political compromise, which allows privately funded human embryo research but bans federal funding for it via the Dickey-Wicker Amendment (Matthews and Yang 2019).

Ethically, changing the 14-day guideline would seem premature. The 14-day guideline has been in place for more than 30 years and only now can be appropriately characterized as a compromise among competing ethical positions (Iltis et al. 2019). Before 2016, growing a human embryo *in vitro* beyond 14 dpf was not technically possible. The limits were imposed by technology and not by policy. Therefore, advocates supporting human embryo research lost nothing in agreeing to a 14-day guideline in the 1980s. Adopting the 14-day guideline was a compromise only for those who opposed all research on embryos. They conceded what they wanted, which was to prohibit the destruction of human embryos. Furthermore, we know what type of research the policy limits and what it allows, thus preventing possible conflicts between researchers and regulators, anxieties in the public about the scope of research allowed, mistakes by researchers who might circumvent the regulations, and public mistrust of the scientific community.

Other Options: Changing the 14-day Guideline

While we recommend maintaining the status quo and keeping the 14-day limit on human embryo research in the United States at this time, other countries, NGOs, or individuals might believe that the guideline needs to be replaced now or in the future. If the decision to change the guideline is made, there are three policy options for what should replace it: 1) restricting research, 2) replacing the deadline with a new one, or 3) removing it entirely (Figure 1).

Figure 1. Policy options for the 14-day limit on human embryo research. Policymakers must engage in a series of decisions regarding human embryo research, including whether to change the 14-day limit as well as what that change would involve.



First, it is conceivable that policymakers might restrict human embryo research, such as banning it or restricting it to an early time point. Policymakers could cite the moral status of the embryo or even the availability of alternative technologies, such as hCCMEDs, as a replacement for human embryos (see Matthews et al. 2019) as justifications. However, as mentioned earlier, the scientific literature does not reveal any genuine alternatives to human embryo research at this time; at the very least, research using hCCMEDS requires comparing them with human embryos to validate results (Wagner and Matthews 2019). The ethics literature also does not offer new arguments related to the impermissibility of early human embryo research (Iltis et al. 2019). However, this does not necessarily mean that U.S. policymakers will not act without new data or arguments to justify restricting human embryo research.

A second option is that policymakers could choose to extend the research deadline to a different time point, such as 17, 21, or 28 dpf or anchor it to a morphological feature such as neural tube closure, initiation of a heart beat and blood circulation, or the emergence of limb buds. Option three is that policymakers could remove the deadline altogether. If chosen, these latter two options also would require the development of new guidelines with appropriate justifications and oversight.

<u>Recommendation *5*</u>: Any commission or advisory body that reviews the 14-day limit should include broad stakeholder participation.

Past U.S. federal commissions and advisory bodies charged with making recommendations for human embryo research policies have been criticized for poor representation and not including a full range of perspectives (Matthews and Yang 2019). For example, these commissions often do not have religious perspectives represented, despite the large population in the United States that affiliates with a religion (Iltis et al. 2019). Any request for a review of proposed changes to human embryo policy, even when conducted within a scientific society or nongovernmental agency such as the ISSCR or NASEM, must involve transparent, meaningful, and inclusive public engagement and dialogues. Engagement with the lay public and explaining the possible benefits of human embryo research are especially important. Scientist should also be prepared to listen to public' and stakeholder objections and concerns. Additionally, evidence regarding the most appropriate methods for obtaining and incorporating stakeholder input should inform how stakeholders should be engaged in this process.

Any request for a review of proposed changes to human embryo policy must involve transparent, meaningful, and inclusive public engagement and dialogues.

<u>Recommendation 6</u>: Any proposal to change the 14-day limit must offer well-reasoned and compelling ethical and scientific arguments regarding the need to change it. The proposal should also include justifications for what should replace it.

Public trust in scientific institutions is necessary for science to achieve its social aims; therefore, there must be sufficient scientific, ethical, and public justification for changing the current limit on human embryo research (Iltis et al. 2019). The 14-day guideline is a widely implemented restriction that was the product of years of study and discussion. Changing it hastily could undermine public trust in scientists and policymakers. Furthermore, changing it risks giving the impression that technological capacity alone dictates which policies to maintain or modify. That something can be done is not a reason to believe that it should be done.

Public trust in scientific institutions is necessary for science to achieve its social aims; therefore, there must be sufficient scientific, ethical, and public justification for changing the current limit on human embryo research

Even if a change to the 14-day guideline is deemed appropriate, there is no consensus on how to define a new limit or whether there should be a limit at all. After discussions during the two project workshops and interviews with scholars on the subject, we found that there is no consensus on a new deadline. Some scholars have suggested 17 or 18 dpf (when the neural tube closes), while others suggest 28 dpf (doubling the current deadline) or later points when abortive fetal tissues are available through donation. Others suggest that the new guideline should rely on physical characteristics and cellular functions rather than a specific post-fertilization date. In addition, some scholars recommend that no specific time should be identified; instead, research should be judged on its individual merit and the potential value of the knowledge to be gained.

To lead change, a scientific consensus would be required from one or more scientific or medical societies at a minimum. Without a broad agreement within the scientific community on a change, it would be politically challenging to expand the limit (Matthews and Yang 2019). This is especially significant in the United States since scientists do not have federal regulations restricting embryo research to 14 dpf, but instead follow guidelines from the ISSCR and NASEM. Without their consensus, for example, private funders are unlikely to change their policies, as many are linked to NASEM guidelines (Matthews and Yang 2019).

To lead change, a scientific consensus would be required from one or more scientific or medical societies at a minimum.

Conclusions

These recommendations offer avenues for additional discussions and conversations about the 14-day guideline among interested stakeholders (Box 1). Regardless of whether scientists or others choose to promote changing human embryo research policies or accept existing limitations, engagement with the public will help us all understand the nature of human embryo research, the obtained and obtainable knowledge, and the possible medical advances. Furthermore, engagement will help scientists understand public concerns more fully. Overall, public dialogues will help advance science as a public good worthy of public support. Finally, by continuing to engage the public regularly, scientists can help alleviate concerns that science is moving too fast and without regard to public opinion and ethical concerns.

Box 1. Recommendations

1. Embryo research should be conducted only when other, less controversial means of answering important research questions are unavailable. When it is conducted, scientists must be aware of public perceptions of the work and engage with the public in a thoughtful manner.
2. Given the biological, political, and ethical differences between human embryonic stem cells, hCCMEDs, and human embryos, guidelines for research involving each of these entities should be created individually.
3. Human embryo, hESC, and hCCMED research should undergo a scientific and ethical review process that has adequate support to allow for a consistent review of proposals across institutions.
4. The 14-day limit should be maintained unless and until additional arguments are sufficiently robust to address the current political and social objections to allowing embryo research beyond 14 dpf.
5. Any commission or advisory body that reviews the 14-day limit should include broad stakeholder participation.
6. Any proposal to change the 14-day limit must offer well-reasoned and compelling ethical and scientific arguments regarding the need to change it. The proposal should also include justifications for what should replace it.

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