新興人體胚胎研究技術、十四天規則和胚胎的特殊地位

Emerging Human Embryo Research Technologies, the 14-day Rule, and the Special Status of the Embryo

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摘要 Abstract

胚胎研究的“十四天規則”已經在國際上實施了幾十年。當前，很多科學家正在挑戰這一限制，因為技術進步使得人類胚胎和胚胎的細胞模型可以培養到其早期發育階段的後期。一些學者質疑人們長期以來持有的胚胎研究應該受到限制的信念，即超過十四天的胚胎研究是不道德的，他們開始提出替代性指導方針。本文通過回顧“十四天規則”的歷史和受這一規則影響的新興研究領域的情況，審查一項新的關於人類胚胎和類胚胎的指南。我們表明社會和政治哲學、形而上學和倫理學所關注的問題對於解釋和應用新的建議或開發替代方案具有核心作用。至關重要的是，科學家在突破十四天的限制去做任何研究之前，應該制訂明確的、深思熟慮的、且有文化敏感性的指導方針，包括具體限制和監督程式，以確保科學能夠適當地回應社會的需求和價值判斷。

After 40 years of abiding by an international guideline that barred human embryo research beyond day 14 of embryonic development, many scientists are now challenging this limit due to technological advances suggesting that embryos and cell-based models of embryos can be cultured to later points in early development. Some scholars have questioned the long-held belief that research beyond 14 days is unethical and have begun proposing alternative guidelines for research. In this paper, we examine a proposal for new human embryo and embryoid guidelines by reviewing the history of the 14-day limit and emerging areas of research that are impacted by these guidelines. We then show how social and political philosophy, metaphysics, and ethics are central to interpreting and applying these new recommendations or developing alternatives. Before conducting any research beyond day 14, scientists must develop clear, thoughtful, and culturally sensitive guidelines that include limitations and oversight procedures to ensure that science responds to societal needs and values.

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I. Emerging Technologies, Guideline Changes, and the Status of Human Embryo

Recent scientific developments in human embryo research highlight the importance of fundamental philosophical questions that concern metaphysics, ethics, and political philosophy in assessing biomedical technologies.[1] Questions have re-emerged about the nature and status of human embryos and stem cell-based embryo models (or embryoids). Human embryos were traditionally noted as being 'special' entities and treated with "some added measure of respect beyond that accorded to other animal subjects" (Warnock 1984).

Recently, scientists have challenged this classification, leading to renewed questions related to how human embryos ought to be treated, whether and when they may be destroyed, and the role of the public in science governance and policy. They have suggested that policymakers create new guidelines for research and expand research using human embryos and embryoids. There are also renewed calls for "public conversations" regarding conducting human embryo research after 14 days after fertilization, a limit that has been widely endorsed and followed for more than 40 years.

Here, we examine scientists' proposals for human embryo and embryoid regulation to illustrate the significance and inescapable importance of fundamental philosophical questions to interpreting and implementing the human embryo research guidelines. First, we situate these proposed recommendations in its historical context and describe the critical changes made from previous guidelines. Then we identify emerging areas of research related to or involving embryo research where these matters once again will be central to assessing new biomedical technologies and describe some of the new questions these will generate. Finally, we demonstrate some of the ways in which issues in social and political philosophy, metaphysics, and ethics are central to interpreting and applying these new recommendations.

(1) For the purposes of this paper, we define an embryo as the time from fertilization to eight week post fertilization, at which point it is considered a fetus until birth.

Developing thoughtful and culturally sensitive guidelines related to human embryo research should be a goal for all countries considering expanding research in this area. These guidelines should also include limitations and oversight procedures to ensure that science responds to societal needs and values rather than functions unilaterally.

II. The Origin of the 14-day Limit

Over the past four decades, research using human embryos has been permitted up to day 14 in most locales. This 14-day limit was established and endorsed by scientific and professional societies as well as incorporated into laws and guidelines in many countries (Matthews and Morali 2020). The limit of 14 days was first recommended in a 1979 US report related to *in vitro* fertilization (IVF) (US DHEW 1979a). It was confirmed as the consensus limit when a 1984 UK report on IVF suggested the same time (Warnock 1984). Subsequently, scientists, based on national regulation or voluntarily, adopted the 14-day limit as a compromise with the public and as a show of good faith that they would respect the human embryo's special status, which is less than the full rights of a human, but more than an animal or cell line.

While some scholars suggest that the 14-day limit is arbitrary with no philosophical significance, both the US and UK commissions chose this point for several reasons (Hyun et al. 2016 and 2021; Matthews et al. 2021a). Fourteen days post-fertilization corresponds to the development of the primitive streak, which is easily visible under a microscope and one of the first significant signs of embryo organization (US DHEW 1979a; Warnock 1984). It is also toward the end of the process of implantation, prior to which the embryo spontaneously dies in an estimated 50 percent of cases (US DHEW 1979b). It is believed to be the last point at which twinning can occur and is thus seen by some people, especially religious members of the commissions, as the point of true individuation (US DHEW 1979b; Warnock 1984). As a result, the majority of research intensive countries have a 14-day limit (Matthews and Morali 2020).

Ethicist LeRoy Walters, who was involved in the preparation of the 1979 US report, believed that the 14-day date was also a safe choice, because it was far beyond researchers' ability to grow human embryos in 1978, such that the limit did not restrict research in actuality (Webster and McEwen 2016; Matthews et al. 2021a). Scientists' ability to study early human embryo development *in vitro* has, until recently, been limited to the time the implantation stage begins (between days five and seven), which is also when an IVF egg would be implanted.

It is also important to note that not all national policies have a 14-day limit, even in research intensive countries. The United States only has limits on research that is federally funded; it prohibits federal funding of human embryo research but not research that uses non-federal sources. The US National Institutes of Health (NIH) also seems to ban portions of embryoid research, choosing to review and evaluate embryoid research on a case-by-case basis, although there is no officially listed policy for what embryoid research can and cannot be conducted using NIH funds (Matthews and Morali 2020). Other countries, including Russia and Germany, ban human embryo research. Switzerland has an alternative policy, limiting research to seven days or less, implying it only allows IVF and embryonic stem cell (ESC) research, which is a product of embryos that are 5-6 days after fertilization. The diversity and plurality of societal views within and between countries highlights challenges finding a new scientific consensus for human embryo research. This plurality also suggests that public and stakeholder engagement would be necessary in developing new policies (Matthews et al. 2021a). For examples on how public and stakeholder engagement could look, one only needs to look at how the US and UK reports on IVF were developed.

(1) US Department of Health, Education and Welfare Report

The US report was created by the Department of Health, Education and Welfare (DHEW) Ethics Advisory Board (EAB) during President Jimmy Carter's Administration. The EAB was chaired by a lawyer, James C. Gaither, with a doctor as the vice chair, David A. Hamburg (who was also the president of the Institute of Medicine, now the National Academy of Medicine). The board included 13 doctors, legal experts and ethicists (Bonnicksen 2002; US DHEW 1979a). During their deliberative process, they requested written and oral comments from scholars in the fields of reproductive medicine, ethics, theology, law, and social sciences and received more than 2,000 documents from these experts and the public (US DHEW 1979a). They also hosted 11 public hearings in nine cities across the US in Atlanta, Bethesda, Boston, Dallas, Denver, Detroit, Kansas City, Philadelphia, and Seattle.

In their 1979 report, the EAB asserted that human embryo research was "acceptable from an ethical standpoint," but mandated that "no embryos will be sustained *in vitro* beyond the stage normally associated with the completion of implantation (14 days after fertilization)" (US DHEW 1979a). This 14-day limit was a compromise developed to gain unanimous approval within the committee and to respect differing views. Both Gaither and Hamburg acknowledge the plurality of views within society and within their

committee. However, Gaither believed that it was important for the report to be unanimous and Hamburg noted "we are restricting the grounds for ethical acceptability; and in so doing, are trying to some extent to accommodate the different values that enter into this picture" (Hurlbut 2017). The EAB members also recognized the importance of a limit for political and pragmatic reasons. Furthermore, the EAB concluded that "the human embryo is entitled to profound respect; but this respect does not necessarily encompass the full legal and moral rights attributed to persons" (US DHEW 1979a).

(2) The UK Warnock Report

The UK report was developed by the Committee of Inquiry into Human Fertilisation and Embryology, more commonly known as the Warnock Committee after the philosopher Dame Mary Warnock who chaired the committee (Warnock 1984). The committee included 16 participants with seven doctors and scientists from different religious backgrounds, two lawyers, a court recorder, two social workers, two managers of a healthcare trust, a theologian, and the vice president of the U.K. Immigrants Advice service (Wilson 2014). The committee held public and private meetings and obtained oral and written comments from approximately 300 organizations and individuals in reproductive biology and associated fields and 695 submissions from the public (Hammond-Browning 2015).

The 1984 report included 64 recommendations, including Recommendation 44: "It shall be a criminal offense to handle or to use as a research subject any live human embryo derived from IVF beyond that limit (i.e. 14 days after fertilization)" (Warnock 1984). The majority of the committee agreed that "though the human embryo is entitled to some added measure of respect beyond that accorded to other animal subjects, that respect cannot be absolute, and may be weighed against the benefits arising from research" and concluded that "research conducted on human *in vitro* embryos and the handling of such embryos should be permitted only under license" (Warnock 1984).

However, in contrast to the US report, not all the members of the UK committee agreed that human embryo research should be permitted. Three dissenters believed it was "wrong to create something with the potential for becoming a human person and then deliberately to destroy it" (Warnock 1984). Another four individuals disagreed with the recommendation of allowing human embryos to be created solely for research. Warnock later indicated that this divided committee more accurately reflected the public: "if our Committee had been undivided it would inevitably also have been unrepresentative, perhaps seen as biased" (Warnock 1985).

Warnock felt that it was not the committee's job to define when life begins, doing so would have delayed and perhaps even prevented the report from being completed (Hurlbut et al. 2017; Hammond-Browning 2015). Instead the committee bypassed the question of embryos' rights, focusing on "how ought we to treat them? What protection ought they to be offered by the law, so that, in the end, they may have some rights created for them by new laws, if this is what we want?" (Warnock 1987).

The decision to create a limit was based on the desire to have a clear definitive law. However, Warnock acknowledged that the specific date might be arbitrary:

> We were criticized because [14 days] was an arbitrary figure, and in a way it was, it could have been other than 14. But to block a slippery slope, what is essential is one unchangeable, definite figure, and this is what I insisted on...The one thing we could be sure of was that before this time an embryo could suffer no pain or discomfort, having no vestige of a nervous system. (Hurlbut et al. 2017)

However, Warnock was adamant regarding the importance of research oversight and of maintaining the limit as part of the law. The limit was indeed passed as the Human Fertilisation and Embryology Act of 1990 (Matthews and Rowland 2011). Passing a law and creating boundaries for research was necessary and desirable to "show that research can be regulated without being banned, [and] that knowledge can be pursued without being put to morally intolerable uses" (Warnock 1988). Prior to her death in 2019, Warnock was not swayed to change the limit, despite research advances:

> I was determined that this figure of 14 should be seen as written in stone, a matter of legislation, not mere guidelines, and so we recommended that to keep an embryo alive longer should be a criminal offence, subject to up to 10 years' imprisonment if it were committed. It is my belief that the bill would never have got through Parliament if it had not contained this clause, which has indeed been incorporated in legislation by other countries. I am personally rather unwilling to see the limit changed, at least until a good deal of research has taken place in the additional days [of embryo culture *in vitro*] now available. This is not because I doubt the scientists who say that there is a huge amount to be learned from the study of embryos *in vitro* up to, say, 21 days, but simply because I fear that those who oppose research using human embryos would triumphantly marshal their forces, and say

> that the limit has been adhered to only because technically it had proved impossible to do otherwise. (Hurlbut et al. 2017)

Given the deliberative process and public and stakeholder engagement conducted by the two initial groups from US and UK prior to recommending that human embryo research be permitted up to the 14-day limit, and considering the new communication technologies we have that allow for easier discussion and collaboration, it's surprising that the limit was set aside with arguably no public engagement. Scientists and scholars wrote commentaries on for and against the rule should be changed, predominantly in the academic literature. A scientific society removed the limit from their research guidelines. And without public discussion, scientists are beginning to propose and conduct research on human embryos beyond day 14 (Powell 2021; Svoboda 2021).

III. Lifting the 14-day Limit

For almost four decades, the 14-day limit was relatively unchallenged and accepted by scientists as the norm. This changed in 2016 after two research groups (one based in the United States that chose to follow existing international guidelines and the other in the United Kingdom, which was bound by UK law restricting embryo research) reported culturing human embryos *in vitro* up to the 14-day limit, then destroying their cultures due to the limit (Deglincerti et al. 2016; Shahbazi et al. 2016). When these studies were published, discussions renewed around the 14-day limit, with some scholars suggesting moving the limit to a later time point in development to allow for additional research (Appleby and Bredenoord 2018; Chan 2018; Hyun et al. 2016 and 2021).

Prior to 2016, the 14-day rule functioned more as a theoretical boundary than as a practical limitation on research; even the most promising culture conditions could only maintain a human embryo through nine days of development (Matthews et al. 2021a). Beyond the initial 2016 publications research on human embryos that reached 14 days in culture, research in 2019 and 2021 described the *in vitro* culture of monkey embryos up to 20 days post-fertilization and the development of an *ex utero* culture system capable of supporting mouse embryos through organ development (Niu et al. 2019; Aguilera-Castejon et al. 2021). These advancements suggested the possibility of maintaining human embryos in culture past 14 days of development.

While scientists acknowledged the value of the 14-day rule as a compromise amongst varied beliefs on the moral status of human

embryos, some believe the proscription blocks valuable areas of research and that now that it seems possible to do research beyond 14 days, such research such be allowed (Clark et al. 2021; Hyun et al. 2021). By extending research beyond 14 days, additional scientific knowledge and therapeutic possibilities could arise. Some have even suggested that "the 14-day limit fails to uphold the human right to benefit from science" and it is unethical not to do research at later stages (Master et al. 2021; Stein 2021). Many proponents also suggest that since the date was a policy decision and not a rigid moral principle, the limit should be moved or removed (Hyun et al. 2021).

Adding complexity to this issue is research using embryoids. Embryoids (also known as stem cell-based embryo models) are organized pluripotent stem cells (e.g. ESCs or induced pluripotent stem cells) that model aspects of early human development (Matthews et al. 2021b).[2] It is unclear how these models should be regulated since some models had the 'potential' to be a human embryo (although this potential was limited) and others did not, depending on things such as what cell-types are present and how the embryoid is cultured (2D versus 3D). These issues heightened discussions around the 14-day limit and alternatives (Hyun et al. 2020; Rivron et al 2018).

Since 2016, several science organizations have been re-evaluating guidelines for human embryo research. The most public change came from the International Society for Stem Cell Research (ISSCR) in 2021. ISSCR is a scientific society that represents more than 4,000 stem cell researchers from around the world (www.isscr.org). The society is known for developing and promoting guidelines that outline permissible forms of stem cell and related areas of research activities. Although ISSCR guidelines lack a formal enforcement mechanism, they set standards which inform public policy, guide institutional practices, and influence investment in research (Lovell-Badge 2021; Turner 2021). In countries that lack a comprehensive national policy on human embryo research, such as the United States, professional societies serve a key role in delineating acceptable conduct for research institutions (Matthews and Morali 2020). As such, revisions to ISSCR guidelines both respond to and enable advancements in scientific research. First issued in 2006, the most recent update in 2021

(2) Embryoids are known by several names in the literature including general names like embryo models, artificial embryos or the acronym SHEEFs (synthetic human entities with embryo-like features). There are also names associated with specific models of developmental timepoints, such as gastruloids or blastoids, as well as those which describe the cells used. These names and others are explored in Matthews et al. 2021b. For this manuscript, we use the name 'embryoid' to describe all models developed from pluripotent stem cells, regardless of the source or developmental time point being modeled.

modifies ISSCR guidelines from 2016 (ISSCR 2021; Lovell-Badge et al. 2021).

The ISSCR guidelines changed from banning all research, both embryo and embryoid, past day 14 to a more complex set of guidelines (Table 1) (ISSCR 2021). The recommended research oversight switched from having only three categories (permitted, permitted with review, and prohibited) to five categories (Table 2). Category 1 has two subcategories: permitted (1A) and permitted with review (1B). While research activities can be conducted without oversight, some must be reported to the entity managing the oversight process. Similarly, category 3 now distinguishes between entirely prohibited activities (3B), such as human reproductive cloning, and those with the possibility of acceptance in the future (3A), such as germline editing. Perhaps most significantly, the 2021 ISSCR guidelines removed the 14-day limit for the *in vitro* culture of human embryos impacting this work as well as embryoid research (ISSCR 2021). Instead of a date limit, scientists suggest reviewing human embryo research on a case-by-case basis. (Table 1)

The scientists justified removing the 14-day limit primarily on the basis of knowledge to be gained by allowing research on more developed, older embryos (Clark et al. 2021). In particular, expanding human embryo research offers the possibility of illuminating early embryogenesis, which encompasses the abnormal developmental patterning responsible for many early pregnancy losses, neural tube defects, and other congenital diseases (Appleby and Bredenoord 2018; Hurlbut et al. 2017; McCully 2020). This move reflected what scientists believe was "evolving attitude to what might be permissible" and is based on a utilitarian view of embryo research, with the good research outweighing the pains caused by embryo research (Lovell-Badge et al. 2021).

Table 1: ISSCR Recommendations for Human Embryo and Embryoid Research

Year	Entity	Recommendation
2016	Embryo, Embryoid	**Prohibited Research Activities (Category 3):** *In vitro* culture of any intact human preimplantation embryo or organized embryo-like cellular structure with human organismal potential, regardless of derivation method, beyond 14 days or formation of the primitive streak, whichever occurs first.

2021	Embryo, Embryoid	**Recommendation 2.1.1:** All research that (a) involves preimplantation stages of human development, *in vitro* human embryo culture, derivation of new embryo-derived cells or lines, integrated stem cell-based embryo models, or (b) entails the production of human gametes *in vitro* when such gametes are tested by fertilization or used for the creation of embryos, shall be subject to review, approval, and ongoing monitoring, as appropriate, through a specialized oversight process capable of evaluating the unique aspects of the science and the associated ethical issues (see below).
2021	Embryo	**Recommendation 2.2.2.1:** Given advancements in human embryo culture, and the potential for such research to yield beneficial knowledge that promotes human health and well-being, the ISSCR calls for national academies of science, academic societies, funders, and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research. Should broad public support be achieved within a jurisdiction, and if local policies and regulations permit, a specialized scientific and ethical oversight process could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives.

Sources: ISSCR 2016 and 2021

While the pain to the embryo is likely minimal or non-existent, these calculations do not take into account the outrage from those who believe it is morally wrong to destroy human embryos for research at all (Warnock 1987). The removal of the 14-day limit is also substantive change from the intent and ethical framework proposed in the original 2006 and 2016 guidelines, which noted research beyond day 14 “should not be pursued at this time because of broad international consensus that such experiments lack a compelling scientific rationale or raise strong ethical concerns” (ISSCR 2016).

Despite the existence of the same "strong ethical concerns" in 2021 as were in 2006 and 2016, the new guidelines prioritize the opinions of scientific experts regarding what is ethically permissible. This decision also comes at the expense of engaging and respecting wide-ranging, pluralistic views on when an embryo possesses moral rights and without extensive public engagement raises serious concerns (Johnston et al. 2021; Matthews et al. 2021a).

Table 2: ISSCR 2021 Recommended Categories for Research Oversight

Category	Description
1A	Exempt from review by specialized oversight process: most *in vitro* pluripotent stem cell research, most *in vitro* organoid research, and transfer of human stem cells into postnatal animal hosts.
1B	Reportable to the entity responsible for specialized oversight: non-integrated stem cell-based embryo models, *in vitro* culture of chimeric embryos, and *in vitro* gametogenesis (without fertilization or generation of embryos).
2	Reviewed by a specialized oversight process: acquiring human embryos for *in vitro* research, derivation of cell lines from human embryos, genetic alteration of embryos or gametes, *in vitro* culture of human embryos until 14 days post-fertilization/primitive streak formation, transplanting human cells into non-human embryos for gestation in a non-human uterus, integrated stem cell-based embryo models, and transferring human embryos into a human uterus following mitochondrial replacement.
3A	Currently prohibited due to safety concerns: heritable genome editing, transferring human embryos with edited mitochondrial DNA into a human uterus (not including MRT), and using gametes derived from human stem cells for reproduction.
3B	Prohibited due to ethical concerns: gestating human stem cell-based embryo models, human reproductive cloning, breeding human-animal chimeras that have the potential

	to form human gametes, transferring a human-animal chimeric embryo to a human or ape uterus, and transferring human embryos to an animal uterus.

Sources: ISSCR 2021

The 2021 guidelines also revise how embryoid research is reviewed. Previously embryoids were grouped under the 14-day limit on the basis of their "organismal potential," precluding them from being cultured beyond 14 days (Hyun et al. 2020). Given the experiments required to prove an embyroid might develop into a viable human embryo require growing an embryoid to see if it can, which is prohibited by ethical standards, organismal potential was a difficult label to apply to these models (Anthony et al. 2021). As a result, the 2021 guidelines removed the term "potential" and instead organized embryoids into two different oversight categories—non-integrated (1B) and integrated (2) —without a time limit on cell culture (Clark et al. 2021). Integrated models contain all cell-types needed to mirror a human embryo, including embryonic and extra-embryonic cells. In contrast, non-integrated models replicate specific features of peri-implantation embryos but lack some aspect—usually a cell-type—seen in the complete embryo (ISSCR 2021). Predominantly, many embryoids placed in category 1B lack extra-embryonic cell-types, those cells which are involved in the development of the placenta and yolk sac. The guidelines suggest scientists minimize the culture period for integrated embryoids, but otherwise they permit them to research any developmental time point approved by specialized review (ISSCR 2021). To safeguard against the possibility of pregnancies originating from embryoids, the guidelines ban the transfer of human embryoids into a human or animal uterus (Table 2).

While this classification system does not directly address potentiality, the justification the scientists used in separating the two groups notes the non-integrated models have "no reasonable expectation of achieving substantial development" and ultimately classifies them based on potentiality (Lovell-Badge et al. 2021). This suggests that, should research advance to the point that non-integrated models could achieve substantial development, they might be treated differently.

Many scholars argued for removing an absolute time limit on embryoid culture for practical reasons. Most embryoids diverge from the developmental progression of human embryos and bypass milestones used to set ethical bounds (Aach 2017; Matthews et al. 2021a). For example, they can skip the primitive streak stage or

progress to gastrulation (approximately day 17) in less than 14 days (Rossant and Tam 2021).

Transitioning away from applying the 14-day limit to embryoids also would, in theory, promote research using these models instead of using embryos (Clark et al. 2021; Matthews et al. 2021a). Embryoid models possess numerous advantages over human embryos including ease of acquisition and opportunity for genetic manipulation. As such, they can be used to test hypotheses prior to or in place of human embryo research. Researchers have already generated integrated models of the human blastocyst using pluripotent stem cells, but stopped their experiments due to the 14-day limit (Yu et al. 2021; Liu et al. 2021). Given the new guidelines without the limit, the techniques pioneered by Yu *et al.* and Liu *et al.* may enable modelling of the post-implantation period and beyond (Powell 2021; Svoboda 2021).

Scientists justify increasing research on embryoids as being less ethically contentious than research on embryos because they "are not bona fide embryos" (Lovell-Badge et al. 2021). Nevertheless, many believe that an evaluation of the moral status of embryoids will be necessary as these entities become more sophisticated and better approximate true embryos (Aach 2017; Hengstschläger and Rosner 2021; Denker 2021). Relevant neurological features such as the ability to feel pain or development of brain activity, constitute distinguishing markers that could confer greater moral status on an embryoid (Aach et al. 2017; Denker 2021; Pereira Daoud et al. 2020; Piotrowska 2021). However, the choice of which features are relevant to moral status is controversial in itself and involves disputed moral or ethical claims. As discussed below, scientists generally have avoided addressing these issues with respect to embryos and there is no reason to believe they will seek to explore these claims about the moral status of embryoids in the future.

IV. New and Existing Philosophical Questions

Proposals to expand embryo research beyond 14 days raise a host of questions where ethics, philosophy of science, social and political philosophy, and science and technology studies intersect with emerging biotechnologies. Many of these questions are similar to ones posed by and to the US and UK committees, discussed above, more than 40 years ago. To develop embryo research recommendations, these previous committees consulted a wide range of invested stakeholders, such as scientists and doctors, as well as members of the public to understand their concerns and expectations. As a result, they both recommended what is widely characterized as a compromise to allow research on human embryos, but only for the first 14 days.

There are two main clusters of philosophical questions related to recent initiatives to change or remove the 14-day limit. The first cluster concerns the meaning and significance of public conversations and broad public support ISSCR refers to in its 2021 guidelines. The second cluster revolves around the status of or respect owed to human embryos, the significance of advancing scientific knowledge, and the role judgments about these matters are poised to play in assessing embryo research based on the new guidelines.

(1) What is the Meaning and Significance of Public Conversations and Broad Public Support?

Guidelines from science societies and other non-governmental organizations hold no true weight in and of themselves. Their significance derives from the importance their members and others attribute to them. Membership can be revoked for non-adherence, although this may not impact a researchers' ability to conduct, present or publish research. Nonetheless, most scientists tend to hold them in high esteem and follow them as a sign that they conduct ethical research. For the ISSCR guidelines, many aspects are already present in national laws and guidelines regulating research, making it more likely that scientists in those jurisdictions will honor them (Matthews and Morali 2020). However, in jurisdictions in which there is neither a ban on human embryo research nor a legal prohibition on research beyond 14 days, such as the United States, voluntary implicit agreements among scientists to honor the 14-day limit set forth in ISSCR's previous guidelines (ISSCR 2016) and other guidelines, such as those developed by the National Academies of Science, Engineering and Medicine (NASEM 2010), were the basis of limiting embryo research.

The scientists who conducted human embryo research reported the 14-day limit as the reason for ending their experiments in the two 2016 papers: Deglincerti et al. and Shahbazi et al. Deglincerti et al. noted: "We concluded our experiments at [day] 14, in accordance with internationally recognized bioethical guidelines." The UK researchers had a similar statement, but were also guided by UK law, the Human Fertilisation and Embryology Act of 1990 (Matthews and Morali 2020). Furthermore, multiple groups have created blastoids, integrated embryoids that mimic the human blastocyst and contain both embryonic and extraembryonic cell types. In 2021, US and Australian research groups cultured blastoids *in vitro*, but stopped prior to day 14 due to the ISSCR 2016 guidelines (Liu et al. 2021; Yu et al. 2021). The Australian group specifically stated "the 2016 ISSCR Guidelines do not permit research that cultures human embryos or embryo-like

structures beyond 14 days post-fertilization and/or formation of the primitive streak, whichever occurs first" (Liu et al. 2021).

In issuing guidelines that place no time or developmental limit on such research (embryo or embryoid), ISSCR opened the door to research beyond 14 days *in the absence* of "public conversations" and evidence of "broad public support" despite calling for these within their guidelines (see Recommendation 2.2.2.1). Since ISSCR's announcement in May 2021 that the 14-day limit was removed, it has been reported that US researchers were already proposing projects to culture human embryos beyond day 14. Brivanalou (the principal investigator for the Deglincerti et al. 2016 research) applied to his institution for permission to culture embryos to day 21 (Powell 2021; Svoboda 2021). Zernicka-Goetz (in whose lab the Shahbazi et al. 2016 research was conducted) now has a lab in the United States and has indicated similar plans to pursue research after 14 days. In addition, a third Israel-based group, with no legal 14-day limit, is looking into converting protocols it used to grow mice embryos to use on human embryos in an effort to culture them beyond 14 days (Svoboda 2021). Others working on integrated embryoids are likely to follow suit, growing the entities beyond day 14 where permissible legally.

Scientists are asking for less oversight and expanded permission to do their own area of research, which some might consider a conflict of interest. For example, Brivanlou was a member of the ISSCR committee which removed the 14-day limit, along with several co-authors on integrated embryoids papers and ethicists who serve on advisory boards of companies exploring these technologies. None of these conflicts were noted in the reports or supplemental manuscripts describing the recommendations (Anthony et al. 2021; Clark et al. 2021; Lovell-Badge et al. 2021). Further, the case-by-case review in locations without a national law or oversight committee entrusts decision-making to local institutional review boards or similar committees that can be easily pressured to advance cutting-edge research for high profile scientists. These committees are also under no obligation to conduct the suggested public engagement.

Public discourse allows for a fair negotiation of boundaries for human embryo research which balance scientific expertise and moral concerns (Chan 2017; Matthews et al. 2021a). In the development of the 2021 guidelines, the ISSCR reported that they consulted polls and public engagement projects; however, unlike their 2016 guidelines, the review and redrafting stages excluded direct public outreach and a public comment period (Subbaraman 2021; Lovell-Badge 2021). Essentially, scientists unilaterally abandoned the 14-day rule. Scientists developed the guidelines independently, pushing forward with research absent meaningful public engagement. This decision

could undermine their credibility and the legitimacy of resulting regulatory frameworks. Compromise was a key factor for members of the Warnock Committee—respecting both the knowledge that can be gained as well as the concerns of those opposed to all human embryo research (Warnock 1987). By going back on the 14-day limit compromise, especially without any clear new limit, scientists are also risking public trust that they can conduct this research ethically or be trusted to honor commitments (Green et al. 2021; Johnston et al. 2021; Matthews et al. 2021a).

The absence of public discussion prior to effectively lifting the limit in many jurisdictions stands in stark contrast to the activities that led up to the 14-day limit (described above). Nevertheless, ISSCR's recommendations suggest that public conversations and broad public support are important (though not necessary or essential) for expanding research beyond 14 days. The first cluster of questions, therefore, concerns the understanding and significance of 'public conversations' and 'broad public support' in expanding embryo research beyond 14 days.

The call for "public conversations," we assume, is a call for what is often called public engagement. As such, it could have a variety of goals (Iltis, Hoover, Matthews 2021). First, on an instrumentalist account of public engagement, these conversations would be aimed at garnering support for expanding embryo research and reducing the likelihood of public discontent or controversy. They would, in a sense, be aimed at convincing the public to accept and support research on embryos beyond day 14. Alternatively, the call for "public conversations" could be grounded in principles of democratic governance, such as a commitment to including parties affected by decisions in decision-making processes. These views inform the democratic deliberation literature, which often treats such deliberations as a condition for justifiable laws and policy (Habermas 1996; Cohen 1989; Gutmann and Thompson 2004; Fishkin 2011). A third account of the purpose of "public conversations" is based on a view of science as a social enterprise and public good, according to which public engagement contributes to excellent science that responds to public interests (Barbosa et al. 2020; Jasanoff 2004; Jones 2014).

The purpose or goals of public conversations shapes their character. Although in the ISSCR guidelines it does not specify the purpose of the public conversations, the reference to achieving rather than assessing public support in Recommendation 2.2.2.1 (Table 1) suggests that the guidelines reflect an instrumentalist understanding of public engagement. If the goal is to "achieve" broad public support, then public conversations are more likely to be modeled on "outreach"

or “science communication,” which involve primarily delivering information to inform and shape public opinion (Iltis, Hoover, Matthews 2021).

Activities aimed at achieving broad public support would be less likely to openly engage a broad segment of the population in meaningful dialogue, which would include an openness to incorporating new information, suggestions, and perspectives in developing recommendations (Pieczka and Escobar 2013). Ideals for public and stakeholder engagement, previously articulated from a literature review, call for such efforts to be comprehensive (begin early/upstream), transparent, inclusive, methodologically sound (conducted using methods demonstrated to be effective for engagement), and accountable (Iltis, Hoover, Matthews 2021). In calling for public conversations regarding the 14-day limit after issuing guidelines that lift the limit indicates that ISSCR might not recognize the importance of public conversations that meet the criteria for effective public engagement.

A clear account of the purpose of public conversations is important to establish the goals and hence determine the methods that would satisfy the guidelines. An additional question is whether ISSCR’s apparently limited appreciation for effective public engagement is appropriate. Much of the literature on science policy and science and technology studies would demand rigorous public engagement prior to changing a long-established policy that was developed subsequent to significant public conversations.

In addition to the questions surrounding the nature and goals of “public conversations” are questions about what would constitute “broad public support” and the significance of broad public support for justifying or legitimating embryo research. The term ‘broad public support’ used in Recommendation 2.2.2.1 remains undefined (Table 1), and it is unclear what ISSCR would recognize as “broad public support” or why ISSCR holds that such support might be significant in justifying embryo research beyond 14 days. Interestingly, ISSCR does not use the term ‘consensus,’ which has its roots in de Tocqueville’s work in political philosophy and which has been the focus of sustained analysis in the bioethics and social and political philosophy literature. Numerous commissions, committees, and working groups exploring controversial issues within and beyond bioethics have aimed at consensus-building (Veatch and Moreno 1991; Kelly 2003). Nevertheless, the term “broad public support” is sufficiently close to the idea of consensus that the latter can help elucidate some of the different possible understandings of broad public support and under what circumstances it would be justifiable to claim that it exists. The literature generally distinguishes between consensus and unanimity.

(Beatty and Moore 2010; King 1997; Gutmann and Thompson 1990) Some even have argued that we should have more confidence in decisions made by consensus that are not the objects of unanimous agreement because dissenting voices can challenge deliberators to consider alternatives and refine their judgements, thereby improving the quality of decisions (Beatty and Moore 2010; Elster 1986). Indeed, the Warnock report followed this principle, with regard to the recommendation to permit human embryo research, although the US report was presented as unanimous (US DHEW 1979a; Warnock 1984).

After rejecting the idea that consensus necessarily requires unanimity, McCloskey holds that consensus refers:

> to a measurable state of concurrence around values that can be specified. Consensus exists in degree and can be expressed in quantitative form. No one, of course, can say how close one must come to unanimity before consensus is achieved, for the cutting point, as with any continuous variable, is arbitrary. Still, the term in ordinary usage has been reserved for fairly substantial measures of correspondence …. (McCloskey p. 363).

Given that consensus requires a reasonably high level of agreement, it comes as no surprise that claims regarding the existence of consensus on bioethics topics have been challenged as factually inaccurate (Schüklenk 2004; Cherry 2010).

Other studies of consensus in bioethics demonstrate that the term 'consensus' refers to different states of affairs (Trotter 2002; Kelly 2003; Engelhardt 2002). Trotter distinguishes "strong consensus" and "weak consensus" (Trotter 2002). Strong consensus, he says, "occurs when an opinion is shared widely throughout an entire population" (p. 37). In contrast, weak consensus refers to situations where "there is fundamental agreement among designated authorities but only passive acceptance (without concurrence) in those outside the elite group" (p. 37). The latter, Trotter demonstrates, is prevalent in bioethics. In other words, often claims that consensus exists on a matter are claims to (merely) weak consensus, which Trotter argues is inadequate for conferring the authority often thought to derive from consensus.[3]

Kelly (2003) examines consensus claims emerging from bioethics commissions and other public bioethics bodies and finds two distinct uses of the term as well. While consensus-building can refer to processes in which the relevant publics participate in processes

(3) On the role consensus in justifying legitimate political authority see, for example, Moreno 1988; Kucaewski 2007; and Jennings 1991.

through which public bioethics bodies "identify and contribute to society consensus concerning controversial science" (p. 356), the term often refers to something rather different. The consensus-building work of public bioethics bodies often refers to "a pragmatic, policy-facilitating relationship in which [public bioethics bodies] negotiate policy alternatives for policy makers that are acceptable to scientists and their patrons and accord with some 'sense' of a common moral view" (p. 356). The latter hardly can be said to reflect societal or public consensus, yet invoking the term 'consensus' and at least appearing to include the public can confer a sense of moral authority and legitimacy on a group's recommendations.

In addition to various understandings of consensus itself, there are different accounts of the processes or conditions that must be followed to make a justifiable claim that consensus exists. Consensus that is secured through the exclusion of dissenting voices, manipulation, or criticism of dissenters is suspect (Snead 2009). Many scholars have criticized the new guidelines noting that the scientists called for public engagement while creating guidelines in the absence of public engagement (Soni and Baylis 2021; Sawai et al. 2021). In addition, many of the scientists promoting efforts to remove the 14-day limit are individuals conducting human embryo and embryoid research, which were previously restricted by the limit. While some nonscientists participated in the process, the majority held long-standing affiliations with ISSCR. There appears to have been limited to no engagement with others outside the society as ISSCR developed its new guidelines, nor did the society present evidence that the guidelines received support of the majority of the membership. Therefore, any claim to consensus on the new guidelines even among scientists would be suspect.

What ISSCR means by broad public support matters and the concept itself raises numerous philosophical questions. Answers to these questions alter the character and implications of ISSCR's guidelines. At stake is whether and when it would be reasonable to assert that there is broad public support for research on embryos beyond day 14. While the new guidelines suggest that it would be important to secure such support, ISSCR has, in effect, already authorized research on embryos beyond day 14 without "public conversations" and in the absence of evidence of "broad public support."

(2) Special Status of the Embryo

ISCCR's 2021 guidelines recommend an oversight and review process for human embryo and embryoid research (Table 2). Some of this oversight is similar to what they outlined in the 2016

recommendations, while some is new to address research on embryos beyond 14 days (Table 1). These recommendations highlight several contested ethical issues that are central to the review process. Unspoken are the questions and judgments about the moral status of human embryos, the respect owed to embryos, the significance of deep disagreement in many pluralistic societies regarding embryo destruction, the respect owed to those individuals who morally oppose any embryo research, how embryos may be used and for what purposes, the value or significance of particular scientific advances or areas of knowledge generation, and how competing goods or potential benefits are judged against various harms or risks.

Recommendation 2.1.2 pertains broad to various types of research, including research on human embryos and embryoids. It specifies that the "oversight process must include an assessment of the scientific rationale and merit of research proposals, the relevant expertise of the researchers, and the ethical permissibility and justification for the research." They describe the assessment of ethical permissibility and justification in Recommendation 2.2.2.1:

> Research goals must be assessed within an ethical framework to ensure that research proceeds in a transparent and responsible manner. The project proposal should include a discussion of alternative methods and provide a rationale for performing the experiments in a human rather than animal model system, for the proposed methodology, and if the studies involve preimplantation human embryos, a justification for the anticipated number to be used. (ISSCR 2021)

For the newly-allowed category of research on embryos beyond 14 days, ISSCR's 2021 guidelines state that the oversight process "could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives" (Table 1). Taken together, the recommendations indicate that the oversight process is supposed to assess the justifiability of at least three major decisions, all of which depend on an understanding of the moral status of or respect owed to embryos. First is the justification to use human rather than animal models, which we read as at least in part a justification for using human embryos at all. Second is the justification for using the specified number of embryos and using only as many as necessary. Third is a justification for culturing embryos for the specified time beyond 14 days and subsequently destroying them based on whether the "scientific objectives necessitate and justify" that time (Recommendation 2.2.2.1). However, as they specifically use the

"could" instead of "should" in the wording of the recommendation, they make this justification optional for oversight committees, not required.

Questions about the moral status or respect owed to embryos or permissible uses of embryos are relevant to assessing research both before and beyond 14 days. It seems that thus far in overseeing embryo research, oversight committees typically have not grappled extensively with these issues in assessing the justifiability of using human embryos and using the proposed number of embryos. As Jones observes, the UK's Human Fertilisation and Embryology Authority (HFEA), the authority created by the Human Fertilisation and Embryology Act of 1990 that regulates fertility treatments and research involving human embryos, is permissive to research where human embryos are destroyed. By 2008, an estimated 1.2 million embryos were destroyed or discarded, and all but one research proposal was granted, with the rejected proposal granted after an appeal (Hansard 2008; Jones 2011). Jones notes, "The apparent profligacy in the use of human embryos and the extraordinary record of never ultimately refusing a research license makes it difficult to substantiate the claim that research is subject to stringent controls and monitoring" (Jones 2011). An oversight body that never says "no" to scientists gives the appearance of one that assumes that the destruction of embryos is routinely permissible rather than of one that assesses whether it is permissible. Jones offers additional evidence for the view that the embryo research oversight process in the UK does not engage the full range of ethical issues before it in noting that,

> In 2005 the chair of the HFEA [Suzi Leather] told parliament that she thought that 'you must subscribe to the acceptability of embryo research' (House of Commons 2005: Vol. 1, para. 202) in order to be a member of the HFEA. This seems to exclude from membership those who would show too high a regard for the status of the embryo. However, there was no suggestion that having too little respect for the embryo was an obstacle to membership. (Jones 2011, p. 69)

The same HFEA Chair made similar remarks to the US President's Council on Bioethics (Jones 2011). In other words, only people who already assume that embryo destruction is justified may be part of the process that allegedly is designed to assess the justifiability of embryo destruction. And, there appears to be no concern that including people who hold that embryos may be destroyed for any purpose at all because they are not "special" and are not "owed respect" might undermine the oversight process.

Despite the possibility that questions about the moral status of the embryo or respect owed to the embryo appear to be ignored in at least some oversight processes, assumptions about these matters play a role in every single assessment of embryo research in the recommended oversight process. These judgments are at work even when they are assumed and not discussed or disclosed.

The removal of the 14-day limit in the 2021 guidelines introduces the third consideration regarding the moral status of embryos: the respect owed to embryos or the permissible use of embryos at more advanced ages/developmental stages. In exploring this third area for assessment, the importance of the first two areas becomes evident. Assessing whether human embryo use is justifiable, whether the number of embryos to be used is justified, and whether the time in culture beyond 14 days is justified involves a comparison of various possible right- and wrong-making conditions, such as goods and harms, interests, rights, duties, or risks and potential benefits. The question of what we are comparing, therefore, is central to the process of justification. All three areas that require justification in the recommended oversight process require an account of what is being compared, how to assign moral significance to what is being compared, a clear account of what is at stake, and how to assign value to the potential gains in various types of scientific knowledge.

Notice, for instance, how one's account of the moral status of the embryo can affect one's description of what is at stake in embryo research. Moral status refers to being "morally considerable, or to have moral standing" and "to be an entity toward which moral agents have, or can have, moral obligations" (Warren 1997, p. 3). The "needs, interests or well-being" of entities with moral status must be considered in deliberating about how to treat them (Warren 1997). For example, does a proposed study that involves use and destruction of human embryos involve killing a human being or destroying a clump of morally insignificant cells or something in between?

Different views about the moral status of human embryos also affect how we assess all three justification questions. First is the justification for using human embryos at all. If one holds that embryos have full moral status equivalent to a born human being (and we assume that it is not permissible to kill human beings for the purpose of generating even important new knowledge), then one is much more likely to reject embryo-destructive research. Only individuals willing to authorize the killing of an adult child or human for the purpose of knowledge generation would approve it. However, if one holds that embryos have less-than-full moral status, one might, at least sometimes, hold that embryo-destructive research is permissible.

Judgments here will vary greatly depending on one's precise account of their moral status and of the value of new knowledge.[4]

Moral status judgments also might influence assessments of embryoid research. One might ask when they become 'embryo-like' enough to be viewed as embryos and regulated as such. ISSCR guidelines indicate that this point occurs when scientists believe the entity has the capacity to grow *in utero*. However, without studies to determine when embryoids could grow *in utero*, it would not be possible to reliably determine their status. Furthermore, the questions become more complicated when one looks at research on developing the artificial womb, including previously mentioned work on mouse embryos, where it is unnecessary to implant the embryo or embryoid into a uterus to promote growth to later stages of development.

Second, moral status views also might affect how we assess the permissibility of using any given number of embryos. Again, if embryos have moral status equivalent to a born human being, the answer likely will be zero. Other moral status accounts will be more flexible, but we should expect to find differences between those who hold that embryos have greater rather than lesser degrees of moral status. If embryos have a significant degree of moral status, someone might hold that a particular goal would justify destroying 10 embryos but not 50 embryos. If embryos have very little moral status, then the same goal (or even a less "worthy" goal) might justify destroying hundreds or even thousands of embryos. The account of what is at stake relative to the same potential outcome (new knowledge) varies. That variation translates into different assessments of whether the action is justified.

Some people might limit the number of embryos that may be used out of concerns for commodifying or harming women in order to obtain embryos and not because of concerns that it is wrong to destroy the embryos themselves. This concern can be mitigated when using embryoids, which can be produced in larger numbers without requiring donations of embryos (although many embryoids were a result of embryo donations to create the pluripotent stem cells they are developed from).

Third is the justification of time in culture beyond 14 days and subsequent destruction of those older embryos. One's understanding not only of the moral status of the embryo but of the basis for it will have special significance in assessing research on embryos older than

(4) Some people will draw a further distinction here between embryos that are created for the purposes of being destroyed in research and embryos that are "left over" after *in vitro* fertilization procedures and donated for research. For discussion of this point, see Iltis, de Melo-Martín, and Robert 2019.

14 days. Commonly cited bases for assessing the moral status of an entity include species membership, possessing particular physical characteristics, or having particular cognitive capacities. Among those who ground moral status in particular physical characteristics or cognitive capacities, some hold that merely having the potential to develop those characteristics or capacities suffices or that having the potential for them confers at least some moral status, while others require that an entity already possess those features. In addition, in embryo research the notion of individuality sometimes plays a significant role. Some hold that being a unique individual is necessary (though not sufficient) for having moral status, such that embryos earlier than 14 days or in whom the primitive streak has not yet emerged could twin and thus are not unique individuals.[5] Although species membership should not change one's judgments, people who hold other accounts of the basis for moral status might assess the permissibility of research on embryos at various time points beyond 14 days differently depending on when the requisite physical or cognitive capacities emerge. For instance, if the beginning of neural development matters as some hold because it is essential for "the possibility of sentience and most other qualities considered relevant to the moral status of persons" (US NIH 1994), then research beyond 14 days might be impermissible or require a much greater likelihood of yielding highly important new knowledge to be justified. On the other hand, if sentience is at least a necessary condition for having moral status, then research on embryos far beyond 14 days might be deemed permissible.

If one holds that moral status begins at the point at which one can live outside the womb —viability—then research on embryos of any age might be justifiable as well as on fetuses up to approximately 26 weeks or perhaps as low as 20 weeks if periviability is sufficient. In that case, the limits of permissible research would change as medicine advances and is able to support younger fetuses and perhaps eventually embryos outside the womb, including through the development of artificial womb technology. Those who hold that embryos' moral status increases as they develop, sometimes referred to as emerging moral status, might assess the permissibility of research at different time points differently (Koplin and Gyngell 2020). Here, again, the specific considerations they deem relevant at different points in time will affect their judgments.

These questions become even more complicated with addressing the status of an embryoid. Per ISSCR guidelines, the embryoid is

(5) For an overview of each of these views and examples of where they can be found in the literature, see Iltis, de Melo-Martín, and Robert 2019.

treated like a cell culture line or model with no special status granted. Integrated models that claim capacity to develop to later stages get research oversight, while other models without extra-embryonic cells are allowed to proceed unregulated. No regard is given to when they will obtain 'special status' or become embryo-like enough to be regulated, instead the assumption is that despite best effort by scientists to more accurately recapitulate the embryo, they will never achieve success in truly mimicking it.

At the same time, different accounts of the value of potentially generating various types of knowledge inform assessments of proposed embryo research. Although space limitations prevent us from exploring this further here, it is important to recognize the complexity of value judgments pertinent to the justification of research as described in the ISSCR guidelines. These guidelines call on oversight bodies to consider and compare not only the permissibility of using embryos but the value of proposed research.[6]

An additional consideration in comparing the destruction of human embryos and potential knowledge to be gained will be the likelihood of generating significant knowledge from any particular proposed project. For instance, if one holds embryos in high moral regard, one might insist that scientists demonstrate a much greater likelihood of generating significant new knowledge whereas someone who holds that embryos are owed little or no moral consideration might accept less well-defined research projects.

ISSCR does not refer to embryos as having "special status" or as being "special" or warranting respect, terms that various groups have used in writing recommendations and guidelines regarding embryo research in the past. For instance, the EAB concluded that "the human embryo is entitled to profound respect; but this respect does not necessarily encompass the full legal and moral rights attributed to persons" (US DHEW 1979a). Similarly, the Warnock Report referred to the "special status" of the embryo.

Despite omitting such language, ISSCR's guidelines indicate that even for research on embryos up to 14 days, a rationale for using human embryos and for using the proposed number of embryos requires justification. Yet, ISSCR offers no explanation for why this is the case. Why does the destruction of embryos for research purposes need to be justified and why must the number of embryos used be minimized? What about the embryo matters such that ISSCR guidelines call on scientists to justify their destruction and minimize the number of embryos they destroy? In comparison, embryoids

(6) For further discussion of competing accounts of the value of scientific knowledge generation, see Iltis, de Melo-Martín, and Robert 2019.

research does not require any justification on the manipulations done, the number of embryoids created or how long they are allowed to develop. Does the reason to limit the number used have something to do with the embryos themselves, or is it to minimize offense to those who recognize embryo destruction as a form of killing a human being? Or, are embryos considered a scarce resource to be used sparingly because of their relative scarcity? Understanding the reasons behind ISSCR's requirements might tell us something about how they understand the embryo, yet there is nothing in the guidelines to answer these questions, which are relevant to embryo research at any developmental point/age, including before 14 days.

It is possible that ISSCR guidelines presume that embryos in fact are not special and do not merit particular respect. Instead, oversight is necessary to avoid public backlash. This, Jones has suggested, was the rationale behind the Warnock Report's recommendations for limiting embryo research and requiring strict oversight. He notes that the Warnock Report refers to embryos as having "special status" but does not offer an account of the nature of that status (Jones 2011). Indeed the Warnock report seems to hint it is the widespread anxiety of the public not the research itself that warrants oversight:

> Nevertheless, because of the special status that we accord to the human embryo, such research must be subject to stringent controls and monitoring…We see these controls as essential to safeguard the public interest and to allay widespread anxiety. (Warnock 1984)

As a result, Jones notes that:

> 'Special status' thus stands as a cipher for public feelings. This explains why consultations of the HFEA have the strategic function of managing public reactions, for on this account the function of the whole regulatory structure is not to grant actual protection to the embryo, but rather to maintain public support for policies decided primarily on utilitarian grounds. (Jones 2011, p. 76)

It is possible that ISSCR similarly does not recognize embryos as having special status in themselves but instead seeks to set up structures that will protect science from public concern, scrutiny, and objections. In reviewing literature produced by the committee prior to and soon following the release of the guidelines this seems to be the case (Clark et al 2021; Hyun et al 2021). Yet, if we take the guidelines seriously, an account of the moral status of the embryo, of the kind of

respect (if any) owed to embryos, and the permissible uses of embryos are relevant to assessing the permissibility of research before and after 14 days. These are fundamental philosophical questions that are at the heart of assessing embryo research whether or not they are discussed openly.

V. Conclusion

The impact of changes to human embryo and embryoid research guidelines varies depending on where the work is conducted. In jurisdictions where a 14-day limit is embedded in law, like the United Kingdom, any expansion would require passing new legislation (Matthews and Morali 2020). In countries with complete or partial bans on human embryo research, the suggested changes will not likely impact the status quo. However, for countries without national laws or policies, non-binding guidelines from scientific societies play an important role in how science is conducted and governed. For such countries, the recent changes are quite significant. For example, the new guidelines permit researchers in the United States to pursue research on human embryos beyond day 14 as long as their designated research oversight committees approve the procedures.

ISSCR developed their 2021 recommendations, which included expanded human embryo and embryoid research, without public consultation. The justifications for allowing more research was based on possible scientific knowledge to be obtained, despite previous notes in their 2006 and 2016 that the work was considered unethical. In support of reviewing the 14-day limit, Hyun et al. 2016 noted that the 14-day limit "is a public policy tool designed to carve out a space for scientific inquiry and simultaneously show respect for the diverse views on human embryo research" rather than a bright moral line designating the onset of moral status. It is unclear how the new guidelines demonstrate "respect for the diverse views on human embryo research."

After 40 years of compromise, it seems odd to change the 14-day policy without public engagement. By avoiding public dialogues, scientists dismissed previous concerns about the use of human embryos in research that existed in 1979 when the 14-day limit was conceived. Perhaps they believe these concerns are no longer valid or that the public no longer ascribes 'special status' to embryos, as they did decades ago. Without extensive public and stakeholder engagement, there is not sufficient evidence to support such a position. Existing literature suggests that while many accept human embryo research and note embryos should not be given the full rights of an adult human, many still honor the ideals found the Warnock report,

that "the human embryo is entitled to some added measure of respect beyond that accorded to other animal subjects" (Warnock 1984).

In its 2021 report on human genome editing, the World Health Organization (WHO) defined governance and good governance as:

> The norms, values and rules of the processes through which public affairs are managed, so as to ensure transparency, participation, inclusivity and responsiveness. Good governance is value-based and principle-driven. Good governance is an iterative, proactive, ongoing process that includes mechanisms for regular revisions. Good governance promotes public confidence. It requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical, and healthcare communities as well as the public. (WHO Human Genome Editing Report 2021)

We encourage scientists to view human embryo and embryoids research policies in light of promoting good governance as defined by the WHO. Science policies should not be developed solely by scientists, but instead policy development should reflect the reality that science is a public endeavor. When jurisdictions consider whether or how to integrate new guidelines with their local guidelines, they should first institute robust public and stakeholder engagement. Moreover, they should recognize that changing policies in ways that suggest to the public that scientists will not respect limits could seriously undermine public confidence, especially at a time when challenges to the scientific process are prevalent. This possibility warrants significant caution. As we learned from the 2019 incident when researchers genetically-manipulated human embryos, public backlash for research they deem unethical and unacceptable is quick and vicious. It impacts the research, research institutions, and even points toward deficiencies in national policies.

Additionally, the omission of guidance on what research would be warranted or providing any limit based on age or developmental markers discarded a key benefit of the 14-day rule: clarity (Green et al. 2021). Both scientists and the public understood what was and was not allowed. While scientists claim that there will be oversight, it is no longer clear where those limits will be, or whether there will be any limits at all. A definitive and objective timeline for *in vitro* culture reassured the general public that scientists "accept limits" (Johnston et al. 2021). Such assurance is no longer available.

Finally, overseeing embryo research to determine when human embryos may be destroyed in research, how many embryos may be used, and for how long embryos may be grown in culture before being

destroyed depends on unresolved metaphysical and ethical questions about the status of or respect owed to human embryos and the significance of advancing scientific knowledge. Even when not explicitly addressed, assumptions about such matters are central to our understanding of and response to human embryo research. In the end, public engagement is vital for the purpose of getting various perspectives to help develop a new human embryo compromise policy, if one is needed. Without this engagement, scientists might find it challenging in a pluralistic society to gain approval for new research using embryos and embryoids.

參考文獻 References

Aach J., Lunshof J., Iyer E., Church G.M. "Addressing the ethical issues raised by synthetic human entities with embryo-like features," *eLife* 6, 2017, pp. e20674.

Aguilera-Castrejon A., Oldak B., Shani T., et al. "Ex Utero Mouse Embryogenesis From Pre-gastrulation too Late Organogenesis," *Nature* 593, 2021, pp. 119-124.

Anthony E., Lovell-Badge R., Morrison S.J. "New Guidelines for Stem Cell and Embryo Research from ISSCR," *Cell Stem Cell* 28(6), 2021, pp. 991-992.

Appleby J.B., Bredenoord A.L. "Should the 14-day rule for embryo research become the 28-day rule?" *EMBO Molecular Medicine* 10(9), 2018, e9437.

Barbosa S., Toe L.P., Thizy D., et al. "Engagement and social acceptance in genome editing for human benefit: Reflections on research and practice in a global context," *Wellcome Open Res* 5, 2020, pp. 244.

Beatty J., Moore A. "Should We Aim for Consensus?" *Episteme* 7(3), 2010, pp. 198-214.

Bonnicksen A.L. "Oversight Through Federal Research Funding," In *Crafting a Cloning Policy: From Dolly to Stem Cells* (Georgetown University Press, 2002).

Chan S. "How and Why to Replace the 14-Day Rule," *Current Stem Cell Reports* 4(3), 2018, pp. 228-234.

Chan S. "How to Rethink the Fourteen-Day Rule," *Hastings Center Report* 47, 2017, pp. 5-6.

Cherry M.J. "The Illusion of Consensus: Harvesting Human Organs from Prisoners Convicted of Capital Crimes," *The Journal of Medicine and Philosophy* 35(2), 2010, 220-222.

Clark A.T., Brivanlou A., Fu J., et al. "Human embryo research, stem cell-derived embryo models and in vitro gametogenesis: Considerations

leading to the revised ISSCR guidelines," *Stem Cell Reports* 16(6), 2021, pp. 1416-1424.

Cohen, J. "Deliberative democracy and democratic legitimacy", in A. Halmin and P. Petiti (eds.), *The Good Polity*, Oxford, Blackwell, 1989, p. 17-34.

Deglincerti A., Croft G.F., Pietila L.N., et al. "Self-organization of the in vitro Attached Human Embryo," *Nature* 533(7602), 2016, pp. 251-254.

Denker H. "Autonomy in the Development of Stem Cell-derived Embryoids: Sprouting Blastocyst-like Cysts, and Ethical Implications," *Cells* 10(6), 2021, pp. 1461.

De Tocqueville A. *Democracy in America* (London: Saunders and Otley, 1838).

Engelhardt H.T. "Consensus Formation: The Creation of an Ideology," *Cambridge Quarterly of Healthcare Ethics* 11(1), 2002, pp. 7-16.

Elster J. The market and the forum: three varieties of political theory, in J Bohman and W Rehg (Eds.), *Deliberative Democracy* (Cambridge: MIT Press, 1986).

Fishkin J. *When the People Speak: Deliberative Democracy and Public Consultation* (Oxford: Oxford University Press, 2011).

Green R.M., West M.D., Hayflick L. "Don't Abandon 14-day Limit on Embryo Research, It Makes Sense," *Nature* 594, 2021, pp. 333.

Gutmann A., Thompson D. "Moral Conflict and Political Consensus," *Ethics* 101(1), 1990, pp. 64-88.

Gutmann A., Thompson D. *Why Deliberative Democracy?* (Princeton University Press, 2004).

Habermas J. *Between Facts and Norms: Contributions to a Discourse Theory of Law and Democracy*, trans. William Rehg (Cambridge: MIT Press, 1996).

Hammond-Browning N. "Ethics, Embryos, and Evidence: A Look Back at Warnock," *Medical Law Review* 23 (4), 2015, pp. 588-619.

Hansard. 2008. House of Commons Written Answers to Questions. Human Embryo Experiments: Licensing. Volume 471 Part 40. Column 342W. 29 January.

Hengstschläger M., Rosner M. "Embryoid Research Calls for Reassessment of Legal Regulations" *Stem Cell Research & Therapy* 12, 2021, article 356.

Hurlbut J.B. *Experiments in Democracy: Human Embryo Research and the Politics of Bioethics* (Columbia University Press, 2017).

Hurlbut J.B., Hyun I., Levine A.D., et al. "Revisiting the Warnock Rule," *Nature Biotechnology* 35(11), 2017, pp. 1029-1042.

Hyun I., Wilkerson A., Johnston J. "Embryology policy: Revisit the 14-day rule," *Nature* 533, 2016, pp. 169-171.

Hyun I., Munsie M., Pera M.F., et al. "Towards Guidelines for Research on Human Embryo Models Formed from Stem Cells," *Stem Cell Reports* 14(2), 2020, pp. 169-174.

Hyun I., Bredenoorden A.L., Briscoe J., et al. "Human embryo research beyond the primitive streak," *Science* 371(6533), 2021, pp. 998-1000.

Itlis A.S., de Melo-Martin I., Robert J.S. "Human Embryo Research Beyond Day 14: Ethical Questions and Considerations," Baker Report, 2019

https://www.bakerinstitute.org/media/files/files/20b9e242/chb-pub-greenwall-ethics-021219.pdf

Iltis A.S., Hoover S., Matthews K.R.W. “Public and Stakeholder Engagement in Developing Human Genome Editing Policies: What does it mean and what should it mean?” *Frontiers in Political Science* 3, 2021, e730869.

International Society for Stem Cell Research (ISSCR). “Guidelines for the Field of Stem Cell Research and Regenerative Medicine,” May 2021 https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation.

ISSCR. “Guidelines for Stem Cell Research and Clinical Translation,” May 2016 https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation/guidelines-archive.

ISSCR. “Guidelines for the Conduct of Human Embryonic Stem Cell Research,” December 2006 https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation/guidelines-archive.

Jasanoff S. “A mirror for science,” *Public Underst Sci* 23(1), 2014, pp. 21-26.

Jasanoff S. (ed). *States of Knowledge: The Co-Production of Science and the Social Order*. London: Routledge. 2004.

Jennings, B. “Possibilities of consensus: Toward democratic moral discourse,” *Journal of Medicine and Philosophy*, 16(4), 1991, 447-463.

Jones R.A. “Reflecting on public engagement and science policy,” *Public Underst Sci* 23(1), 2014, pp. 27-31.

Jones R.A. “The ‘special status’ of the human embryo in the United Kingdom: an exploration of the use of language in public policy,” *Human Reproduction and Genetic Ethics* 16, 2011.

Johnston J., Baylis F., Greely H.T. “ISSCR: Grave Omission of Age Limit for Embryo Research,” *Nature* 594, 2021, pp. 495.

Kelly S.E. “Public Bioethics and Publics: Consensus, Boundaries, and Participation in Biomedical Science Policy,” *Science, Technology, & Human Values* 28(3), 2003, pp. 339-364.

King P.A. “Embryo research: the challenge for public policy,” *J Med Philos* 22(5), 1997, pp. 441-455.

Koplin, J.J., Gyngell, C. Emerging moral status issues. Monash Bioeth. Rev. 38, 95–104 (2020).

Kuczewski M. Democratic ideals and bioethics commissions, in LA Eckenwiler and F Cohen (Eds.), *The Ethics of Bioethics: Mapping the Moral Landscape* (Baltimore: Johns Hopkins University Press, 2007).

Liu et al. Modeling Human Blastocysts by Reprogramming Fibroblasts into iBlastoids *Nature* 591, 2021, pp. 627-632.

Lovell-Badge R. “Stem-cell guidelines: why it was time for an update” *Nature* 593, 2021, pp. 479.

Lovell-Badge R., Anthony E., Barker R.A., et al. “ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update,” *Stem Cell Reports* 16(6), 2021, pp. 1398-1408.

Master Z., Lovell-Badge R., Knoppers B. “ISSCR Guidelines Uphold Human Right to Science for Benefit of All,” *Nature* 595, 2021, pp. 494

Matthews K.R.W., Iltis A.S., Gallego Marquez N., et al. Rethinking Human Embryo Research Policies, *Hasting Center Report* 51(1), 2021a, pp. 47-51.

Matthews K.R.W., Wagner D.S., Warmflash A. "Stem Cell-Based Models of Embryos: The Need for Improved Naming Conventions," *Stem Cell Reports* 16(5), 2021b, pp.1014-1020.

Matthews K.R.W., Morali D. "National human embryo and embryoid research policies: A survey of 22 top research-intensive countries," *Regenerative Medicine* 15(7), 2020, pp. 1905-1917.

Matthews K.R.W., Rowland M. "Stem cell policy in the Obama age: U.K. and U.S. perspectives," *Regenerative Medicine* 6(1), 2011, pp. 125-132.

McCloskey H. "Consensus and Ideology in American Politics," *Am Polit Sci Rev* 58(2), 1964, pp. 361-382.

McCully S. "The Time has Come to Extend the 14-day Rule," *Journal of Medical Ethics* epub, 2021.

Moreno J.D. "Ethics by Committee: The Moral Authority of Consensus," *J Med Philos* 13(4), 1988, pp. 411-432.

National Academies of Science, Engineering and Medicine (NASEM). *Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research*. (The National Academies Press, 2010).

Niu Y., Nianqin S., Tan T., et al. "Dissecting Primate Early Post-implantation Development using Long-term In Vitro Embryo Culture," *Science* 366(6467), 2019, p. eaaw5754.

Pereira Daoud A.M., Popovic M., Dondorp W.J., et al. "Modelling Human Embryogenesis: Embryo-like Structures Spark Ethical and Policy Debate," *Human Reproduction Update* 26(6), 2020, pp. 779-798.

Pieczka M., Escobar O. "Dialogue and science: Innovation in policy-making and the discourse of public engagement in the UK," *Sci Publ Policy* 40(1), 2013, pp. 113-126.

Piotrowska M. "Research Guidelines for Embryoids," *Journal of Medical Ethics* 2021, epub.

Powell K. "What's Next for Lab-grown Human Embryos?" *Nature* 597, 2021, pp.22-24.

Rivron R., Pera M., Rossant J., et al. "Debate Ethics of Embryo Models from Stem Cells," *Nature* 564, 2018, pp. 183-185.

Rossant J., Tam P.P.L. "Opportunities and Challenges with Stem Cell-based Embryo Models," *Stem Cell Reports* 16(5), 2021, pp. 1031-1038.

Sawai T., Okui G., Akatsuka K., Minakawa T. "Promises and Rules" EMBO Reports 22, 2021, pp. e53726.

Schüklenk U. "The Standard of Care Debate: Against the Myth of An 'International Consensus Opinion'," *Journal of Medical Ethics* 30(2), 2004, pp. 194-197.

Shahbazi M.N., Jedrusik A., Vuoristo S., et al. "Self-organization of the Human Embryo in the Absence of Maternal Tissues," *Nature Cell Biology* 18(6), 2016, pp. 700-708.

Snead O.C. "Bioethics and Self-Governance: The Lessons of the Universal

Declaration on Bioethics and Human Rights," The Journal of Medicine & Philosophy 34(3), 2009, pp. 204-222.

Soni S., Baylis F. "Human Embryo Research Beyond 14 Days? International Perspectives," *The Hastings Center Bioethics Forum* 7-June-2021 https://www.thehastingscenter.org/human-embryo-research-beyond-14-days-international-perspectives/.

Stein R. "Controversial New Guidelines Would Allow Experiments on More Mature Human Embryos," *NPR* 26-May-2021 https://www.npr.org/sections/health-shots/2021/05/26/1000126212/new-guidelines-would-allow-experiments-on-more-mature-human-embryos.

Subbaraman N. "Limit on Lab-grown Human Embryos Dropped by Stem-cell Body," *Nature* 594, 2021, pp. 18-19.

Svoboda E. "The Next Frontier for Human Embryo Research," *Nature Outlook* 29-Sept-2021 https://www.nature.com/articles/d41586-021-02625-0.

Trotter G. "Bioethics and Healthcare Reform: A Whig Response to Weak Consensus," Cambridge Quarterly of Healthcare Ethics 11(3), 2002, pp. 37-51.

Turner L. "ISSCR's Guidelines for Stem Cell Research and Clinical Translation: Supporting Development of Safe and Efficacious Stem Cell-Based Interventions," *Stem Cell Reports* 16(6), 2021, pp.1394-1397.

US Department of Health, Education, and Welfare Ethics Advisory Board (DHEW). *Report and Conclusions: HEW Support of Research Involving Human in vitro Fertilization and Embryo Transfer* (US Government Office of Printing, 1979a).

US DHEW. *Appendix: HEW Support of Research Involving Human in vitro Fertilization and Embryo Transfer* (US Government Office of Printing, 1979b).

US National Institutes of Health (NIH). *Report of the Human Embryo Research Panel, Volume 1* (NIH, 1994).

Veatch R.M., Moreno J.D. "Consensus in Panels and Committees: Conceptual and Ethical Issues" *The Journal of Medicine and Philosophy* 16(4), 1991, pp. 371-373.

Warnock M. *Report of the Committee of Inquiry into Human Fertilisation and Embryology* (Her Majesty's Stationery Office, 1984).

Warnock M. "Moral Thinking and Government Policy: The Warnock Committee on Human Embryology." *The Milbank Memorial Fund Quarterly Health and Society* 63(3), 1985, pp. 504-522.

Warnock M. "Do Human Cells Have Rights?" *Bioethics* 1(1), 1987, pp. 1-14.

Warnock M. "A National Ethics Committee?" *British Medical Journal* 297(6664), 1988, pp. 1626-1627.

Warren M.A. *Moral Status: Obligations to Persons and Other Living Things* (Oxford University Press, 2000)

Webster M, McEwen A. "The Primitive Streak," *Radiolab* 26-Sept-2016 https://www.wnycstudios.org/story/primitive-streak.

WHO Expert Advisory Committee on Developing Global Standards for

Governance and Oversight of Human Genome Editing. *Human Genome Editing: a Framework for Governance* (Geneva: World Health Organization, 2021).

Wilson D. "'Where to Draw the Line?' Mary Warnock, Embryos and Moral Expertise." In *The Making of British Bioethics* (Manchester University Press, 2014), pp. 140-186.

Yu L., Wei Y., Duan J., et al. "Blastocyst-like Structures Generated from Human Pluripotent Stem Cells," *Nature* 591, 2021, pp. 620-625.