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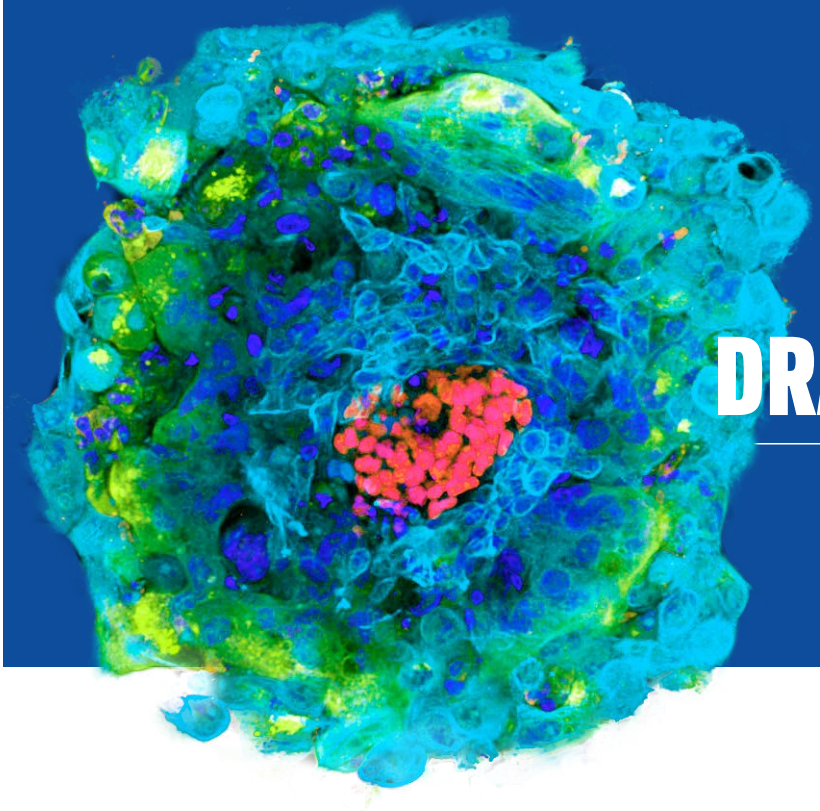

DRAWING THE LINE

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

THE WARNOCK REPORT AND INTERNATIONAL HUMAN EMBRYO RESEARCH POLICIES

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"The Warnock Report and International Human Embryo Research Policies"

Introduction

Human embryo research guidelines are not found in any international rule or code. Instead they are developed by each nation and aim to serve their internal interests and goals. What is allowed or prohibited varies by country, but many countries, especially in North America and Europe, were influenced by or chose to replicate a variation of the 14-day limit.

The 14-day limit originates in the 1979 U.S. Department of Health, Education, and Welfare (DHEW) report related to *in vitro* fertilization (IVF) (DHEW 1979). This report suggested that the United States should allow human embryo research up to the 14th day of development, although this rule was never codified into U.S. law. However, scientists still use the 14-day limit as a guide for their work. The 14-day rule is more often associated with the 1984 U.K. report authored by the Committee of Inquiry into Human Fertilisation and Embryology (Warnock 1984). Referred to as the Warnock report after the committee's chair Dame Mary Warnock, the report also recommended restricting human embryo research to the 14th day post fertilization (dpf). Unlike the U.S. report, these recommendations led to the U.K. government passing the Human Fertilisation and Embryology Act of 1990 (HFE Act), which set the 14-day rule into law.

In this paper, we provide a detailed history and analysis of the U.K.'s Warnock report—one of the seminal policy and philosophical reviews of human embryo research—and its impact on policy and public discussions. We also survey other national policies associated with IVF and human embryo and human embryonic stem cell (hESC) research. While each nation determined their own policy for human embryo research, many, but not all, were guided by the Warnock report and the 14-day rule. Some chose similar limits while others imposed more restrictions. A few others—similar to the United States—never passed explicit regulations but their scientists abide by the limit as part of an international consensus that is promoted by scientific societies including the International Society for Stem Cell Research (ISSCR).

The Warnock Report and Human Embryo Regulation in the United Kingdom

The Committee of Inquiry into Human Fertilisation and Embryology

In 1978, the first baby was born as a result of IVF. The procedure was conducted in the United Kingdom by two scientists—Robert Edwards and Patrick Steptoe (Tauer et al. 2014). While this procedure was a great step forward in improving medical interventions for infertility, it also generated public discomfort and anxiety. In the U.K., the public was "divided between pride in technological achievement, pleasure at the new-found means to relieve, at least for some, the unhappiness of infertility, and unease at the apparently uncontrolled advance of science, bringing with it new possibilities for manipulating the early stages of human development" (Warnock 1984). With the development of IVF, scientists could also study the developing embryo in culture for research purposes alone. These developments "inevitably led to an examination of the moral right of the embryo" (Warnock 1984).

As a result, the U.K. government assembled a group of distinguished scholars to review and assess both IVF and human embryo research. This group included 16 participants—nine men and seven women. While officially known as the "Committee of Inquiry into Human Fertilisation and Embryology," it is better known as the "Warnock Committee." The committee consisted of seven doctors and scientists from different religious backgrounds, none of whom were directly involved with IVF, and eight individuals from other professions, including two solicitors, a court recorder, two social workers, two managers of a health care trust, a theologian, and the vice president of the U.K. Immigrants Advice service (Wilson 2014).

The committee was announced in July 1982. Their goal was to examine the emerging field of human assisted reproduction technologies. More specifically, the charge stated that they were "to consider recent and potential developments in medicine and science related to human fertilisation and embryology; to consider what policies and safeguards should be applied, including consideration of the social, ethical, and legal implications of these developments; and to make recommendations" (Warnock 1984).

For the first year, the committee held public and private meetings. They also collected evidence and opinions to gather different perspectives on IVF (Warnock 1984). The committee obtained oral and written submissions from approximately 300 organizations and individuals in reproductive biology and associated fields (Hammond-Browning 2015). They received an additional 695 submissions from the public. Moreover, the committee devoted their second meeting to learning about developmental biology from committee member Dame Anne McLaren, a developmental biologist and director of the Medical Research Council Mammalian Development Unit. They decided to have a seminar because they wanted the committee to "make an informed decision as to when the barrier should be erected" for human embryo research, which required understanding the early embryology (Warnock 2017).

During the committee's second year, the group focused on writing the final report, which was released in July 1984. Warnock saw the report as foundational for future policy, noting "it is no good making recommendations for legislation which could never in any conceivable circumstances be carried through Parliament, nor recommendations which, if eventually they became law, would be unenforceable" (Warnock 1985). In later writings, Warnock described their approach as bypassing the question of the embryo's rights, focusing instead 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" (Warnock 1987).

The Warnock Report and Recommendations for Human Embryo Research

The Warnock report made 64 recommendations that focused predominantly on regulating IVF. The principal part of the report outlined provisions for a regulatory body, which would later become the Human Fertilisation and Embryology Authority (HFEA). Its main purpose is to license and oversee IVF and human embryo research. The committee recommended that this "new statutory licensing authority be established to regulate both research and those infertility services which we have recommended should be subject to control" (Warnock 1984). The report also had a series of recommendation for IVF. In addition, there were nine recommendations related to human embryo research (Table 1).

Table 1. Warnock Report Recommendations for Human Embryo Research.
The Warnock report made 64 recommendations related to IVF and human embryo research. Part D, "Legal limits on research," listed nine recommendations (#42-50) for human embryo research.

#	Recommendation
42	We recommend that the embryo of the human species should be afforded some protection in law.
43	Any unauthorised use of an *in vitro* embryo would in itself constitute a criminal offence.
44	Legislation should provide that research may be carried out on any embryo resulting from IVF, whatever its provenance, up to the end of the 14th day after fertilization, but subject to all other restrictions as may be imposed by the licensing body.
45	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).
46	No embryo which has been used for research should be transferred to a woman.
47	Any unlicensed use of trans-species fertilization involving human gametes should be a criminal offense.
48	The placing of a human embryo in the uterus of another species for gestation should be a criminal offense.
49	The proposed licensing body promulgates guidance on what types of research, apart from those precluded by law, would be unlikely to be considered ethically acceptable in any circumstances and therefore would not be licenced.
50	Unauthorised sale or purchase of human gametes or embryos should be made a criminal offence.

Source: Warnock 1984, 84-85.

The committee listened to a variety of opinions regarding the rights of human embryos. One of the main arguments against using human embryos for research was that it "is morally wrong because of the very fact that they are human" (Warnock 1984). However, for others like IVF researcher Robert Edwards, it was important to balance future benefits, such as a baby for an infertile couple and medical knowledge, against pain and harm to the embryo (Warnock 1984, 1985).

Despite these differing opinions, the committee was able to develop a unanimous consensus that "the embryo of human species should be afforded some protections in

law" (Warnock 1984). Furthermore, based on a majority—although not unanimous—opinion, the committee recommended 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" (Warnock 1984). Therefore, a majority concluded that "research conducted on human *in vitro* embryos and the handling of such embryos should be permitted only under license" (Warnock 1984). After the report was published, Warnock remarked that research oversight is necessary and desirable, as it "show[s] that research can be regulated without being banned, [and] that knowledge can be pursued without being put to morally intolerable uses" (Warnock 1988).

The decision to limit human embryo research to 14 days was based on recommendations from both the majority of scientific organizations that contributed evidence and scientists on the committee, especially McLaren. Later, referring to the 14-day deadline, McLaren stated that, "If I had to point to a stage and say 'This is where I began being me,' I would think it would have to be here" (Cavaliere 2017). McLaren's view was that at this point in development embryos form the primitive streak, an easily observable early sign of embryo organization. McLaren argued that scientists could experiment on embryos before this stage in development because it preceded neural differentiation and thus the possibility of human embryos experiencing pain. She also believed that 14 days was the last possible point of twinning, where one cell can split into two identical embryos, and that this time point could be viewed as the beginning of individuality (Wilson 2014). In addition, McLaren proposed the use of the term 'pre-embryo' when referring to the product of fertilization prior to the formation of the primitive streak (Wilson 2014). The Spanish government uses this term in their human embryo policy; however, the scientific community never adopted it (Puca 1995).

The committee received comments from several scientific and medical organizations regarding the limit. The report noted that the "Royal College of Obstetricians and Gynaecologists suggested that embryos should not be allowed to develop *in vitro* beyond a limit of 17 days, as this is the point at which early neural development begins" (Warnock 1984). In contrast, the British Medical Association recommended a limit of 14 days, while the Medical Research Council and the Royal College of Physicians suggested the later end of the implantation stage as the limit.

Although the committee provided strong justification for the 14-day limit, Warnock would later note that the cutoff was not necessarily the only one they could have chosen. However, in spite of recent efforts to move the deadline, she remains firm in her belief that the limit should be maintained at 14 days for now. Addressing this specifically in 2017, she stated:

> Some people have criticised the 14-day limit on the grounds that it is arbitrary and therefore irrational. The charge of arbitrariness is partly justified. We did pick on a number of days, after which we understood that the embryo began to develop more swiftly towards becoming a curled-up fetus with a spinal cord and a central nervous system. The number 14 was not arbitrary in the sense that we

> drew it out of a hat. But it was arbitrary in the sense that it might have been a different number, though not very greatly different. (Warnock 2017)

Not all the members of the committee agreed with the recommendations to allow human embryo research. Three dissenters—Madeline Carriline, John Marshall, and Jean Walker—believed it was "wrong to create something with the potential for becoming a human person and then deliberately to destroy it" (Warnock 1984). As a result, they recommended against experimentation on human embryos. Another four individuals—Scott Baker, A.O. Dyson, N. Edwards, and Wendy Greengross—also dissented (Warnock 1984). While they supported creating human embryos for IVF and conducting research on human embryos left over after IVF treatments, they 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. She noted that "if our Committee had been undivided it would inevitably also have been unrepresentative, perhaps seen as biased" (Warnock 1985). She also noted that it was not their job to define when life begins. She believed that philosophy cannot "come up with definite 'correct' answers, whatever may be expected of it by those who do not practice the subject" (Warnock 1985). If the committee had been required to define the moral status of the embryo, this would have delayed and perhaps even prevented the report from being completed (Hammond-Browning 2015).

After the report was submitted and made public, Warnock and other committee members, especially McLaren, worked to disseminate their findings and recommendations to members of Parliament, scientific organizations, and the general public (Warnock 2002). In addition, the committee collected more than 100 submissions of opinions from individuals and organizations regarding the committee's recommendations (Hammond-Browning 2015). The majority of the submissions had an unclear stance on embryo research. That is not surprising, since only nine out of 64 recommendations were related to embryo research. Of those who did comment, many criticized the 14-day limit as well as the decision to allow embryos to be created for research (Hammond-Browning 2015). Interestingly, several groups, including the Association for Spina Bifida and Hydrocephalus (ASBAH), the British Humanist Society, and the National Association for Family Planning Doctors, suggested that there be no limit or that the limit be more flexible (Hammond-Browning 2015).

One major critique was that the recommendation to limit human embryo research to the first 14 days was not appropriately justified. Philosopher Ronald Green noted that "Dame Warnock and her colleagues opted merely to state the feelings of most members of the committee about the matters under review" (Green 2001). U.K. philosopher Richard Hare argued that Warnock did not have the committee members review the benefits and harms associated with particular moral positions extensively enough (summarized in Wilson 2014). The Chief Rabbi of Great Britain, Immanuel Jakobovits, referred to the 14-day rule as a compromise "splitting the difference at some random point" with "arbitrary lines of demarcation between what is to be morally acceptable and criminally culpable" (Jakobovits 1984). Other broader critiques questioned whether allowing human embryo research for

the first 14 days instituted a slippery slope in which additional ethical boundaries could be moved as time passed (Lockwood 1988).

In spite of the many criticisms, the 14-day limit was passed into law in the U.K. in 1990 and has functioned as a respected guideline in many other countries. Indeed, this limit has remained unchallenged for more than 30 years. Only recently, at a time when scientists have been able to grow human embryos to the 14-day mark for the first time and have been faced with having to stop their research (Shahbazi et al. 2016; Deglincerti et al. 2016), have scientists and other scholars begun to question the limit (Hyun et al. 2016).

The HFE Act of 1990 and the Development of HFEA

It was not until six years after the report was completed that the U.K. passed legislation on IVF and thus on embryo research. Prior to the IVF bill being passed, the Warnock report recommendations were challenged by a bill to regulate IVF by Minister Enoch Powell in 1985 (Evans and McLaren 1985). This bill, called the Unborn Children (Protection) Bill, would have made all research using IVF a criminal offense. It forbade all human embryo research, including studies to understand and improve assisted reproductive technologies (Lockwood 1988; Cannell 1990; Horsey 2015; Yoxen 1988). Interestingly, the conservative Prime Minister Margaret Thatcher favored passing legislation based on the Warnock report's recommendations despite its liberal approach to research (Richardt 2003). Ultimately the Unborn Children (Protection) Bill was never passed.

In the interim, the U.K. Medical Research Council (MRC), which allocated U.K. government funding for biomedical research, created a committee to apply and oversee the Warnock report's recommendations on research (Yoxen 1988). This voluntary licensing authority developed guidelines consistent with the report, including the 14-day limit and informed consent for gamete donations (Horsey 2005). Scientists honored the MRC and the 14-day limit. Several scholars argue that by doing so, they helped shape and push forward the final IVF legislation in the U.K.—the Human Fertilisation and Embryology (HFE) Act.

The 14-day limit was passed into law in the U.K. in 1990 and has functioned as a respected guideline in many other countries.

The HFE Act gained Royal Assent on November 1, 1990 (Horsey 2005). The act followed the report's recommendations on research, allowing human embryo research prior to the 14th day after fertilization and the creation of human embryos for research purposes (Matthews and Rowland 2011). Furthermore, it established a regulatory agency, the Human Fertilisation and Embryology Authority (HFEA), to license and monitor IVF and human embryo research. HFEA reviews applications for research and only permits projects deemed "necessary and desirable" (HFE Act 1990). The HFE Act includes a list of areas considered to be appropriate (Box 1), and it also criminalizes creating human embryos without obtaining the required license.

Box 1. Human Fertilisation and Embryology Act

Licences for research

1. A licence under paragraph 3 cannot authorise any activity unless the activity appears to [HFEA]—
   a) to be necessary or desirable for the purpose specified in sub-paragraph (2) ('the principal purposes'),
   b) to be necessary or desirable for the purpose of providing knowledge that, in the view of [HFEA] may be capable of being applied for the purposes specified in sub-paragraph (2)(a) or (b), or
   c) to be necessary or desirable for such other purposes as may be specified in regulations.
2. The principal purposes are—
   a) increasing knowledge about serious disease or serious medical conditions,
   b) developing treatments for serious disease or serious medical conditions,
   c) increasing knowledge about the causes of congenital disease or congenital medical conditions that does not fall within paragraph (a),
   d) promoting advances in the treatment of infertility,
   e) increasing knowledge about causes of miscarriage,
   f) developing more effective techniques of conception,
   g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryo before implantation, or
   h) increasing knowledge about the development of embryos.

Source: HFE Act of 1990 with 2001 and 2008 Amendments, http://www.legislation.gov.uk/ukpga/2008/22/schedule/2/crossheading/licences-for-research

The HFE Act was amended in 2001 and 2008 (Matthews and Rowland 2011). The 2001 amendment was the result of scientific developments, including research involving human embryonic stem cells (hESCs). This amendment allowed for new lines of research using hESCs and somatic cell nuclear transfer (sometimes referred to as therapeutic cloning, cloning for cells, or tissue engineering) with a license from HFEA, while banning human reproductive cloning (cloning for reproductive purposes). Newly established hESC lines were also required to be placed in a public cell bank (the U.K. Stem Cell Bank) for broad use by researchers (Matthews and Rowland 2011).

The second amendment in 2008 was the result of a scheduled review of the HFE Act (Matthews and Rowland 2011; Horsey 2005). This amendment permitted the generation of human-animal hybrid embryos in exceptional circumstances and with a HFEA license. The revision of the HFE Act was not intended to alter the law, but instead to clarify and consolidate the HFEA's authority over human-animal hybrid work, requiring all such work to obtain a license from HFEA (Horsey 2005; Matthews and Rowland 2011).

Beyond the U.K., the Warnock report and its recommendations informed national policies in other countries as well. Legislation passed in several countries included the limit on research at 14 days and/or at the development of the primitive streak (see next section for more details). However, these countries did not take the extra step of developing a specific regulatory agency to oversee the research. While some countries embraced the 14-day rule for human embryo research from the Warnock report, others disagreed. Scholars point to an Italian law prohibiting any human embryo research to be a result of the Warnock report and the HFE Act's more permissive policies (Puca 1995). With dozens of papers analyzing the report and its recommendations, it has made a significant impact on discussions about human embryo research policies internationally.

National Human Embryo Research Policies

Over the past several decades, nations interested in IVF, human embryo research, and hESC research have negotiated internal state policies that oversee scientific work in these areas. In this section, we describe human embryo research legislation, regulations, and guidelines in selected countries. While this review is not exhaustive, it highlights the similarities and differences between national contexts, focusing on major performers in research and development (R&D). The views of the human embryo as a research tool vary internationally from permissive to completely prohibitive.

Twenty-one countries were selected for this review, including the United States and the United Kingdom (Table 2). These countries were chosen based on their gross expenditures in R&D (GERD) and the percent GERD per gross domestic product (GDP). These countries are the top-ranked performers in the U.S. National Science Board's 2018 Science and Engineering Indicators, with data obtained from the Organisation of Economic Co-operation and Development (OECD) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) Institute for Statistics Data Centre (NSB 2018; OECD 2017; UNESCO 2017). Human embryo research policies for each country were evaluated and categorized into one of four groups: no limit, a ban, a 7-day limit, and a 14-day limit (Table 2).

Beyond the U.K., the Warnock report and its recommendations informed national policies in other countries as well.

One set of countries—Brazil, China, France, India, Israel, and the United States—does not have statutory research restrictions for human embryo research. Several of these countries have guidelines developed from nongovernmental organizations that recommend human embryo research be limited to before 14 days of development or the formation of the primitive streak. Others have no legislation related to the 14-day limit in their research guidelines, but scientists seem to be following guidelines from the International Society for Stem Cell Research (ISSCR) or other international consensus guidelines on research using human embryos (ISSCR 2016). The United States has no federal policy on human embryo research (although it bans federal funding for all embryo-destroying research), but the U.S.

Table 2. Human Embryo Research Policy of Top Performers in Science and Technology R&D based on GERD and GERD/GDP. Top performers spend between $15.3 billion (Spain) and $497 billion (U.S.) on R&D, with GERD/GDP ranging from 0.63% (India) to 4.25% (Israel).

Country	GERD ($billions)	GERD/GDP	Policy
Australia*	$23.134	2.11%	14-day limit
Austria	$13.321	3.12%	Ban
Brazil*	$38.448	1.17%	No limit
Canada	$27.071	1.71%	14-day limit
China	$408.829	2.07%	14-day guideline only
France	$60.819	2.22%	14-day guideline only
Germany	$114.778	2.93%	Ban
India	$50.269	0.63%	14-day guideline only
Israel	$13.024	4.25%	14-day guideline only
Italy	$30.102	1.33%	Ban
Japan	$170.003	3.29%	14-day limit
Netherlands	$16.910	1.99%	14-day limit
Russia	$38.136	1.10%	Ban
South Korea	$74.052	4.23%	14-day limit
Spain	$19.735	1.22%	14-day limit
Sweden	$15.372	3.28%	14-day limit
Switzerland	$17.688	3.42%	7-day limit
Taiwan	$33.564	3.05%	14-day limit
Turkey	$16.605	0.88%	Ban
United Kingdom	$46.260	1.70%	14-day limit
United States	$496.585	2.74%	14-day guideline only

Note: * GERD and GDP data are from 2015 except for Australia (2013) and Brazil (2014).

Source: NSB 2018, Table 4-5.

National Academies of Science, Engineering, and Medicine (NASEM) released nonbinding guidelines on hESC research, which recommend scientists limit human embryo research to 14 days (NASEM 2010). In China, the Chinese Ministry of Science and Technology and Ministry of Health recommended a 14-day limit as part of their hESC guidelines in 2003 (Chinese Ministry of Science and Technology and Ministry of Health 2003). But research directly on human embryos is not addressed outside of this document, which describes their use in developing hESCs. In Brazil, legislation permits the development of hESCs from nonviable embryos and bans "genetic engineering on human germ cells, human zygotes or human embryos," but does not specifically discuss a limit to research on human embryos (Brazilian Civil Cabinet Sub-Office of Legal Affairs 2005; Palma et al. 2015; Pranke et al. 2014). In France, the law permits the use of leftover IVF embryos for scientific research with prior authorization and when no other research options are available or viable (France 2013; Drabiak-Syed 2013). The law requires licensing by the Biomedicine Agency but does not mention a research limit (France Biomedicine Agency 2012). Israel has a 1999 law banning reproductive cloning (Knesset 2016) and a set of guidelines for hESCs from 2001, but does not specifically discuss limiting human embryo research to a date or developmental feature (Israel Academy of Science and Humanities 2001).

A second group of countries has banned all research on human embryos, including Austria, Germany, Italy, Russia, and Turkey. Austria's 1992 law states that "cells capable of development may not be used for purposes other than medically assisted procreation" (Austrian National Council 2002). In Italy, legislation passed in 2004 states that "any experimentation on a human embryo is prohibited." The only research allowed is for "therapeutic and diagnostic purposes" and to protect "the health and development of the embryo" (Parlamento Italiano 2004). Germany banned the creation of supernumerary embryos (embryos created for IVF but stored and not used) and embryos created for nonreproductive purposes (for research), eliminating all potential embryo sources for research (German Federal Ministry of Justice and Consumer Production 1990). Russian law prohibits the creation of "a human embryo for the production of biomedical products" as well as "using biological materials obtained by suspension or interruption of the development of a human embryo or fetus for the development, production and use of biomedical cell products" (Russian Federation 2016). The Turkish policy for human embryos is embedded in their assisted reproduction regulation, which prohibits the creation of human embryos for nonreproductive purposes and the storage of embryos for anything other than medical purposes. The law also requires that embryos be transferred to a uterus for reproductive purposes or destroyed five years after fertilization (Turkey 2005).

Switzerland stands alone in the third group by allowing human embryo research, but only prior to the seventh day of development. Swiss law also prohibits the creation of embryos for research purposes "[modifying] the genetic material in a germ cell" and the use of "embryos for any purpose other than the derivation of embryonic stem cells" (Federal Assembly of the Swiss Confederation 2003). This restriction allows for IVF research as well as the derivations of hESCs (that occur around 5-6 dpf) but limits *in vitro* human embryo research.

The final group of countries limit research to 14-days or the formation of the primitive streak. Nine countries are found in this group: Australia, Canada, Japan, the Netherlands, Spain, South Korea, Sweden, Taiwan, and the United Kingdom. Sweden's policy is most similar to the U.K.'s policy. Others are slightly more restrictive. Furthermore, Japan's, the Netherland's, and Spain's policies require approval of human embryo research.

Sweden's policy on human embryo research, the 2006 "Genetic Integrity Act," is similar to the United Kingdom's HFE Act (Swedish Ministry of Social Affairs 1991). Specifically, it states that "experiments for the purpose of research or treatment on fertilized eggs and eggs used for somatic cell nuclear transfer may be carried out no longer than up to and including the 14th day after fertilization or cell nuclear transfer respectively." Similar to the U.K., Sweden allows the creation of embryos for research purposes.

Spain's law "prohibits the creation of human pre-embryos and embryos exclusively for the purpose of experimentation." This is the first mention of a 'pre-embryo,' which the law defines (similar to McLaren) as "an embryo constituted in vitro that is formed by the group of cells that are the result of progressive division of the egg cell, from the time it is fertilized until 14 days after" (Spain 2007). But as Spain specifically defines the embryo as the fertilization of an egg and sperm, researchers can develop embryos from other techniques including somatic cell nuclear transfer (aka cloning, or inserting nuclear DNA from one source into an unfertilized egg) and pathogenesis (promoting an egg to grow without sperm DNA).

Australia, Canada, Japan, the Netherlands, South Korea, and Taiwan have slightly more restrictive policies than the U.K. These countries allow human embryo research, but only on embryos created for reproductive purposes and donated for research. The Australian 2002 "Research Involving Human Embryo Act" prohibits the intentional development of a "human embryo outside the body of a woman for a period of more than 14 days" (Australian Office of Parliamentary Counsel 2002). Similarly, Canada bans maintaining a human embryo "outside the body of a female person after the fourteenth day of its development following fertilization or creation, excluding any time during which its development has been suspended" (Canada 2004). Guidelines for research on human embryos in Japan come from the Minister of Education, Culture, Sport and Technology and are to be reviewed as science progresses (Japanese Guidelines on the Derivation and Distribution of Human Embryonic Stem Cells 2010).

The Netherlands passed the "Embryo Act" in 2002, which allows research if "a positive opinion has been obtained from the central committee on the research protocol" (Korthals 2002). An earlier law from 1998, "Medical-Scientific Research with People", defines the central committee and its role (Netherland Act Medical-Scientific Research with People 1998). This committee only approves a proposal if it may benefit medicine and no alternative methods to conduct the study are available. The act also forbids "an embryo outside of the human body to develop for more than 14 days."

South Korea and Taiwan do not have a 14-day rule. Instead, their policies only mention the formation of the primitive streak, which could potentially allow researchers to conduct work on human embryos slightly longer than 14 days, since developmental timing is not always consistent. These laws, however, follow the spirit of the limit on research promoted by the Warnock report. Taiwan bans embryos derived from somatic cell nuclear transfer, embryos created for research purposes, hybrid embryos (which have cells or DNA from animals), implanting embryos used in research, and "the *in vitro* culture of embryos with primitive streaks" (Taiwanese Department of Health 2007). South Korea's 2008 law, "Bioethics and Safety Act", bans the creation of embryos for research and requires the embryo be stored for five years before being donated to research (South Korean Minister of Health, Welfare and Family Affairs 2008). After this period, embryos may be used "only until the embryological primitive streak appears in their developmental process."

Conclusion

The 14-day guideline for human embryo research might date back to the U.S. DHEW report in 1979, but the guideline was implemented and promoted as a scientific norm only after the 1984 Warnock report. Scientists have embraced this rule and the main set of recommendations coming from the ISSCR (ISSCR 2016). While many national human embryo research policies in countries with high R&D expenditures have chosen to make the 14-day rule legally binding, the majority of countries, including the United States, have not. Some countries have chosen more restrictive policies, while others have only guidelines or no formal policy.

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