Revisiting the Warnock rule

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Is it time to reassess the 14-day rule for human embryo research?

The seminal 1984 Warnock Report[1] established that research on human embryos should be limited to the first 14 days of development (**Box 1**). Since that time, the rule has been broadly adopted and adhered to across the research community. With the introduction of new methodologies into human embryology, however, our ability to culture human embryos *in vitro* has progressed rapidly, to the point where we now are reaching the 14-day Rubicon. In August 2016, two groups in the UK and in the US reported experiments on human embryos that were sustained in culture for 12–13 days after fertilization[2,3]. To comply with British law, the UK lab destroyed its embryo on the 13th day. In the following article, *Nature Biotechnology* brings together a group of experts to discuss whether, in the light of these advances, it is now time to reassess the 14-day rule.

***Nature Biotechnology*: What technical advances are influencing decisions as to whether embryo research should proceed beyond 14 days?**

Robin Lovell-Badge: It was the appreciation that the use of materials that allow peri-implantation embryos to maintain a relatively normal three-dimensional (3D) structure, and the development of culture systems capable of achieving this, made it possible to grow human embryos to 13 days. These have not yet been grown beyond, to 14 days or beyond (at least, there have been no publications reporting this).

There are probably several limitations of the current methods that are likely to compromise normal development much beyond 13 or 14 days. The 3D structure has to be supported, but flexible to allow growth and changes in shape of the embryo. The trophectoderm derivatives need to be encouraged to grow away from the embryo proper, rather than crowd into it and disrupt embryo patterning; in other words, these systems need to better mimic invasion of the trophoblast into the endometrium. And there needs to be an efficient means of exchange of oxygen and nutrients into the embryo, and of metabolites and waste products out of it. More sophisticated tissue-engineering methods, involving precisely patterned materials and distribution of relevant growth factors, etc., could provide solutions.

I can't see how genome editing would help to extend the period over which embryos could be cultured. However, the techniques would be valuable tools to explore the biology of these embryos.

Jeantine E. Lunshof: *In vitro* attachment platforms that permit ongoing development after 7 days post fertilization (d.p.f.), when the embryo must implant itself or it will perish, are one of the technical advances that have been crucial for growing human embryos up to the 14-day limit. Although the UK researchers halted experiments just before that point, the embryos might well have developed further beyond 14 days.

Alison Murdoch: Notwithstanding the limited availability and very poor genetic quality of most human eggs and sperm, the main technical challenge in embryo culture is to achieve an environment that is as close as possible to the physiological state. This applies to all stages of development starting from egg acquisition. Most fertilized eggs will be genetically abnormal, and very few have the potential to develop to 14 days. The longer that embryos are grown in an artificial environment, the greater the likelihood that they no longer represent the physiological state. Interpretation of the results then becomes a challenge.

Alison Murdoch is a clinician at the Newcastle Fertility Centre, whose first research license from the Human Fertilisation and Embryology Authority (HFEA) was in 1991; since that time, her group has undertaken continuous licensed embryo research projects in the clinic. In addition to research related to understanding the early stages of human embryo development and improving fertility treatment, her group has generated human ESCs and developed mitochondrial replacement procedures.

Martin F. Pera: To date, the modifications to embryo culture that have enabled extended growth approaching the 14-day limit have in fact been fairly simple, if elegantly applied. In future, we can envision more use of engineered three-dimensional culture systems incorporating smart surface modifications, controlled delivery of growth factors and precise control of the physical environment, to mimic the niche of the post-implantation embryo. It will be important, where possible, to achieve normal embryonic development without

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genetic modification, though undoubtedly genetic modification will be useful in studying development.

Magdalena Zernicka-Goetz: As the work in our lab shows, we have only recently been able to devise methods enabling us to culture mouse and human embryos to the equivalent '14-day' stage[2,4,5]. Developing methods to further extend this time will first require research in a model organism, such as the mouse. At some point, the embryo (mouse or human) reaches a stage at which it depends upon the developing placenta for a supply of nutrients and for gas exchange. The challenge, therefore, will be to develop a way of substituting for the placenta or developing an artificial placenta in which the embryo can grow. Then there will be a further challenge of developing a vascular system in the artificial placenta that can interact with the developing vascular system of the embryo.

Qi Zhou: I think that advances are being made both in our understanding of early embryonic development based on model animal studies and in the optimization of embryo culture systems. The main technical challenges to growing embryos for longer periods remain our lack of knowledge about the complex regulatory signals required for further embryonic development and about the maternal–fetal interactions required for embryo growth. Looking forward, I anticipate that tissue-engineering technologies, such as three-dimensional (3D) bioprinting and the stem cell technologies, may help overcome such challenges by enabling the creation of more complex and precisely controlled environments for *in vitro* embryo culture.

Qi Zhou has been studying embryonic development for nearly 30 years; his research group now focuses mainly on work with early human embryos, including the establishment of human ESC lines and in particular parthenogenetic human ESC lines, as well as human ESC-based regenerative medicine.

What can be learned by growing human embryos beyond 14 days?

Insoo Hyun: Growing human embryos in culture for a short time beyond 14 days could allow researchers to gain important insights into early body plan formation and tissue specialization. Improved understanding in these areas could also help advance knowledge of certain types of birth defects and miscarriages and of how to predict which early-stage *in vitro* fertilization (IVF) embryos are most likely to produce a successful pregnancy. In the near future, I believe there may be strong pressures from different areas of biomedical research to extend the 14-day limit. For example, developmental biologists interested in understanding the role of various genes in early embryogenesis might use CRISPR–Cas9 to silence select genes so as to compare the development of gene-edited embryos to that of control embryos. Going beyond the 14-day limit will be most informative in these cases because it is at this point that vast amounts of specialization begin to occur.

Also, for the preclinical evaluation of the safety of mitochondrial replacement techniques, or even the safety and functionality of pluripotent-stem-cell-derived 'artificial' gametes, one would hope that researchers do their due diligence and compare the long-term *in vitro* development and specialization of research embryos those of to 'natural' embryos. This should be done before any modified embryos or embryos created from artificial gametes are used for reproductive purposes. The examination of pluripotent stem cell lines derived from modified embryos will not be as informative as the direct observation of modified embryos at post-implantation stages of development *in vitro*.

J. Benjamin Hurlbut: There is no question that an enormous amount could be learned about human development by studying it the laboratory, both in observing normal development and in using human embryos as experimental resources for studying the developmental effects of induced genetic changes, exposure to exogenous chemicals, simulated or artificial uterine environments, etc. Yet the 'importance' of such research can only be properly evaluated in a larger social and ethical context. One can imagine many experiments that some researchers would consider important but that would transgress important social and ethical boundaries—for example, creating viruses with pandemic potential, or subjecting human beings to serious risk without their permission in the name of advancing medical knowledge. There is already substantial disagreement about whether human embryo research at earlier stages of development is ethically acceptable. One important effect of the 14-day rule has been to limit the range of social and ethical uncertainty. Although the 14-day limit is law only in some countries, it has been nearly universally affirmed by the international scientific community, for instance by the International Society for Stem Cell Research (ISSCR) and the US National Academies. It has stood for a kind of scientific consensus that this sort of research requires definitive ethical limits. Thus, the 14-day rule is seen as reflecting scientists' commitments to respecting human integrity and to restraint in the face of widespread ethical uncertainty. It reflects a commitment to society to treat the limit as inviolable, no matter how enticing an experiment might be, and to take ethical responsibility as more important than whatever scientific answers might be produced.

J. Benjamin Hurlbut is an historian of science who looks at how democratic societies develop ways of addressing morally and technically complex problems in the biosciences and biomedicine. His recent book, *Experiments in Democracy: Human Embryo Research and the Politics of Bioethics*, explores US debates over human embryo research.

R.L.-B.: Almost all we know about early post-implantation development of human embryos comes from the 'Carnegie Series', a collection of histological sections of staged post-implantation embryos. (These were obtained many years ago by asking women who were scheduled to have hysterectomies to have sex on a particular day, so that it was known when fertilization was likely to have occurred—giving the age of the embryo found in the uterus after surgery.) These provide a useful description of what the embryos look like at a level of histology, but can't provide any understanding. They don't allow the use of any modern methods of analysis and consequently do not provide any information about dynamics, cell fate relationships, genes that are required for patterning, cell-type specification, etc.

Consequently, we know almost nothing about human embryo development in the period (sometimes referred to as the black box period of human development) between 7 days, when implantation occurs, and about 28 days, which is the earliest stage at which it is possible to obtain embryos after terminations (abortions). (Early terminations are often due to ectopic pregnancies, where the embryo has implanted in the oviduct, which is very painful and can cause serious complications to the woman, and needs to be removed.) So the simple answer to your question is: almost everything.

Most of what we know about the various processes listed below comes from studies in mice. There has some work done in, for example, pigs, which might have some similarities in structure to the human embryo at a particular stage, and also in nonhuman primates, although use of the latter raises ethical issues. Even if there are similarities between human embryos and those of other species, we don't know if these are just superficial—the only way to find out is to do the direct comparison with human embryos.

From 7 to 13 days, the embryo is implanting in the womb and establishing extraembryonic cell types that will form the placenta and yolk sac. The new ability to culture embryos from 7 to about 13 days will be important to allow studies on these processes. It is possible that there is also some early patterning of the epiblast, the disc of pluripotent cells that will go in to form the embryo proper. The patterning may be revealed by looking at gene expression. However, without being able to culture the embryos to later stages, it will not be possible to know what this patterning means because the axes (anterior–posterior, left–right) are not established until gastrulation begins at about 14 days.

From 14 to 28 days, gastrulation occurs to lay down the three primary germ layers: ectoderm, mesoderm, ectoderm. These layers are then further modeled to give all the anlagen (progenitor tissues) for the various organs and tissues of our body. Primordial germ cells (PGCs) and extraembryonic mesoderm are also specified early during gastrulation. PGCs have obvious importance. Extraembryonic mesoderm is critical in many respects: it contributes to the placenta, yolk sac, blood vessels and blood cells, etc., etc. All the different components formed via gastrulation, as well as the extraembryonic tissues that first form before this, interact to help pattern the embryo and the various tissues within it. The extraembryonic tissues are also critical to provide nutrients, some hormones, gas exchange, to remove waste, etc.

J.E.L.: Growing human embryos beyond 14 days will allow the study both of physiological development and of early developmental disorders. Only *in vitro* embryo research can illuminate the development of the nervous system, from the moment of the appearance of the primitive streak on. *In vitro* embryo research is also important for the understanding of early pregnancy loss as well as late pregnancy complications.

A.M.: Theoretically it enables the investigation of developmental events that occur after 14 days, notwithstanding the problems mentioned above. These events mainly relate to implantation and placentation, but there is still a lot to be learned about those before 14 days. For clinical treatment, the embryo should not be kept in an artificial environment longer than absolutely necessary. Currently, I do not foresee benefit beyond the hatching stage (~7 d.p.f.). Any development beyond that should be for research only.

M.F.P.: The most important immediate outcome of the culture of the human embryo to post-implantation stages would be to provide a multi-omics baseline for comparison of normal embryonic human development to that of the nonhuman primate, the mouse and human pluripotent stem cells (hPSCs). Beyond that, long-term embryo cultures—or more likely hPSC cultures that mimic post-implantation embryogenesis—will provide models that enable us to study gene function in early development, to improve technologies for producing cells of medical importance from hPSCs, to understand the origins of developmental disorders, and to understand how the massive epigenetic programming that occurs in these early stages of development affects later stages and indeed health status in childhood and beyond. These are important outcomes of medical consequence that are unlikely to be achieved through any other approach apart from modeling human embryonic development *in vitro*.

M.Z.-G.: After 14 days, we begin to see the first development of what will become the germ layers of the future body. Being able to observe these events will teach us about the signaling involved in the onset of the development of the organ systems. This is a stage at which pregnancies often fail because development goes awry. If we can reveal the principle processes of normal human embryo development, then we can begin to understand how things might go wrong and, in future, how to prevent these abnormalities.

Q.Z.: Going beyond 14 days would enable the study of developmental patterning and its regulation in human embryos, as well as mechanisms of lineage segregation and cell fate. The study of these processes is important for us to gain a better understanding of human development, which is different in many respects from that of model animals.

Laurie Zoloth: Scientists argue persuasively for this concept as a way to better understand the complexities of human development in these early stages. However, an embryo grown in a dish is an approximation, a construct, a model, and may not yield accurate information, for a dish is an environment substantially different from a women's womb, and because of this, it may, in the end, not yield enough information to justify the significant ethical and religious issues it raises.

Laurie Zoloth is a leader in the field of religious studies and Dean of the Divinity School of the University of Chicago. She has done research on the religious traditions and texts that discuss the moral status of human embryos. Throughout her career, she has maintained an interest in ethical questions surrounding human embryo development, mapping the human genome, human ESC research, and heritable human gene editing and oncofertility and the creation of embryos from frozen and stored human oocytes.

If the 14-day rule were to be extended, where should it be extended to and what moral and ethical criteria should be applied in determining the extension?

I.H.: Some people believe in a 'single-criterion' view of moral personhood (i.e., that there exists a single touchstone property that confers full moral status, be it conception, sentience, self-consciousness, or the like). Others hold a 'gradualist' view (i.e., that moral status is not all or nothing but rather increases over time depending on the emergence of a series of significant properties). In either view, there exists, for some people, a morally significant threshold beyond which they believe research on human embryos would not be ethically permissible. Therefore, if the 14-day

limit were to be extended, even more people could become ethically concerned about embryo research than currently may be the case, depending on exactly where the new line is redrawn. Personally, I believe that the 14-day rule was originally intended to serve as a public policy tool to carve out a space for scientifically meritorious human embryo research while at the same time respecting as many diverse views of the beginnings of moral personhood as possible. If this original intent is to be preserved, then I believe the right approach is not to set forth a new uniform limit somewhere else on the developmental trajectory of human embryos. Rather, it would be to take a case-by-case ethical review approach that looks to the scientific merit and rationale of a particular embryo research proposal. It would be better to articulate clear ethical principles and standards for the evaluation of embryo research protocols, rather than relying on new lines in the sand that may end up being crossed in the future anyway for new and compelling scientific reasons. This case-specific approach would be tempered, of course, by what is scientifically possible in terms of embryo culture, and whether there are other methodologies available besides extended cultivation to answer the research question at hand, assuming it is of humanitarian importance to pursue it.

J.B.H.: For many people, moral concerns arise from the very earliest stages of development. Regardless of one's personal ethical views about embryo research, this is a social fact that must be acknowledged. Given this, the questions of what the limit should be and what criteria should be applied are not abstract, ethical questions. They must be asked in ways that acknowledge the moral concerns of the wider social community. Science is a social institution supported by—and celebrated by—societies committed to the project of enlightenment. Yet it is not self-justifying. Insofar as its projects risk running afoul of notions of human integrity and dignity that are socially important, even if not universally held, responsibility requires that scientists defer to society's judgments, and not the reverse. Therefore, although the 14-day rule is informal and voluntarily self-imposed by researchers in most of the US, asking these questions as though they are purely matters of internal scientific and ethical judgment—between a researcher and his ESCRO (Embryonic Stem Cell Research Oversight) committee—may allow certain experiments to be done and papers to be published, but it risks doing grave damage to the position of science in the project of democracy.

Aaron D. Levine: The 14-day rule represented a compromise between competing views more than an elegant and convincing philosophical argument. Any revision to the rule will likely share this characteristic. If the 14-day rule were extended, one approach would simply be to choose a later time point in development, such as 21 or 28 days. Another approach would be to set a limit based on some other characteristic of development, such as sentience. From an ethical perspective, drawing a line based on some measurable characteristic of the developing embryo would be preferable; however, a time point is much easier to implement and enforce, and, as a result, might be preferred on pragmatic grounds. Given the moral disagreements surrounding embryo research, moral concerns would arise at different points for different people.

Aaron D. Levine studies human embryo and reproductive policy issues. His research at Georgia Tech has focused on understanding how controversy and policy choices in ethically contentious areas of the life sciences shape the development of emerging biomedical technologies.

R.L.-B.: If a new limit were to be set, then one of ~28 days might make sense. This would allow the 'black box' period to be spanned. It is the stage when the first organs, such as the heart (a tube at this stage), form. The central nervous system (CNS) will have expanded as neuroepithelial cells, and the embryo will have some patterning (anterior–posterior, etc.), but little differentiation of cell types. There will not be any functional neuronal connections; the sensory systems will also be absent.

I think the criteria for permitting research should be exactly as they are currently (at least as set by the HFEA (Human Fertilisation and Embryology Act, in the UK)) for research on human embryos up to 14 days. The work has to be addressing an important question that can only be carried out with human embryos, and the latter have to be obtained with appropriately informed consent. I would expect it to be very difficult to obtain an HFEA license to work on embryos beyond 14 days, but if it can be justified, then I can't see why new criteria would be necessary.

The answer to the question 'At what stage of embryonic development do moral concerns arise?' may depend on the cultural circumstances. In Israel, human moral status does not begin to be assigned to the embryo until after 40 days. In China, it is after birth. In the UK, as in these other countries, the 14-day limit operates to make a clear regulatory boundary, but it was always an arbitrary one. It has served as an important limit permitting any research to be done at all—without it, the pressure to ban all research might have prevailed. Scientists like to know where the boundaries are, and in 1990 keeping embryos in culture to 14 days would have seemed impossible, and the limit reassured the public that scientist were being controlled. I expect that the ability to feel pain and to have awareness will be the absolute limit—but these don't occur until well after 40 days. As a comparison, we are allowed to do research (with a license) on animal embryos to two-thirds of the way through gestation. A limit of 28 days would be very safe. As mentioned above, it is possible to obtain aborted fetuses from 28 days and to conduct research on these (with ethics committee approval).

J.E.L.: The current limit of the appearance of the primitive streak (or 14 d.p.f.), as proposed by the Warnock Committee and widely agreed upon, refers to the "strictly utilitarian view... the ethics of experiments on embryos must be determined by the balance of benefit over harm, or pleasure over pain"[1]. In my opinion, in the case of early embryos, experiencing 'pain' is merely a placeholder with symbolical meaning—looking far ahead into long-term development. The primitive streak is no more and no less than the precondition for future sentience, consciousness, and the experience of pleasure and pain. Only by 19 weeks post conception is it assumed that the fetal brain has matured sufficiently for the perception of pain.

The historical utilitarian criterion of balance of pleasure over pain was never meant to be applied to preconditions for nervous system development in early embryos, and I would argue for its abolishment in this context.

Given the importance of the development of the (central) nervous system for the future individual, I would suggest basing thresholds

on the concrete stage of development of this organ. The heart is another crucial organ and, moreover, one beset with many moral and cultural values. Therefore, I would propose considering the functional interaction of these organs, namely ongoing nervous system development in combination with a beating heart as a threshold of—moral—significance in embryo research. That might result in a threshold at 22 d.p.f.

A.M.: Although I am not, at present, convinced that the 14-day rule should be changed, I do accept that at some point the clinical indications for scientific questions to be answered may become imperative.

The Warnock solution to 'When does life begin?' was a consensus decision that led to the unscientific but legally precise definition of an embryo: the act of mixing an egg with sperm. The 14-day rule never intended to be a moral line; it was a compromise, a pragmatic decision based loosely on knowledge of embryo development in 1990. These time-related actions indicate the limits of regulation under the UK's HFEA.

With the knowledge and skills that have been acquired since 1990, we now need a better definition of the upper limit of regulation. A time limit is problematic because defining it on the basis of expected morphological changes (e.g., the appearance of a neural plate) is no longer tenable. Although derived from an embryo, an ESC (embryonic stem cell) line is not considered to be an embryo and may be cultured for many years. But if organized neural structures were derived from human ESCs, would they then become an embryo?

Clinically, implantation and placentation can occur up to about 12 weeks without the presence of a fetus. So would replication of such an event *in vitro* prompt moral concern? Perhaps, but maybe a consensus based on development potential could be found. UK legislation prohibits the replacement in the uterus of an embryo created under a Research License. Thus, an embryo following extended cultured would not have the potential to become a baby.

Peter Mills: It is important to recognize that the limit cannot be set just by knowing what happens at different stages of embryological development. Different developmental markers will have different significance and value for different people. Although it might be possible to describe the biological processes with growing confidence, it is not possible to determine scientifically whether culturing embryos to such and such a stage is right or wrong. This is a normative question. The production of normative conclusions requires debate, a debate that must be open to the broadest range of considerations. It is through open debate that we both produce moral knowledge and constitute the moral community.

Peter Mills is assistant director at the Nuffield Council on Bioethics. He previously held posts at the Human Fertilisation and Embryology Authority (HFEA) and the UK Department of Health. He recently coordinated the Nuffield Council's report *Human Embryo Culture*[7], which aims to clarify the considerations that would need to be addressed in any future debate about extending the 14-day limit.

M.F.P.: It is important to recognize that the 14-day rule was developed as a practical expedient to provide the public with the reassurance required to enable *in vitro* fertilization research to move forward. The rule was never intended as a bright-line criterion from either a scientific or an ethical standpoint. Any change to the 14-day limit will need to not only assess what medical benefits could be gained by extending the limit to a particular time point, but also ensure that the same outcome could not be achieved through other experimental means. If the limit were to be changed, it seems reasonable to replace a time limit with a mechanism that enables ethics committees and scientific review bodies to assess proposals individually on their merits and ethical level of risk. Here, the definition of the embryo is most important. If we define a mammalian embryo as an entity capable of continuous and integrated development towards live birth, then experimentally produced constructs that aim to duplicate only a particular stage of development or a particular anatomical structure would likely be excluded from such a definition. Much informative work would fall into this category.

M.Z.-G.: We can learn a huge amount about early development by culturing embryos up to day 14, as it's been only two years since scientists became able to develop human embryos *in vitro* until day 14, double the period previously possible. Extending the current 14-day limit by a further 7 days would take us to 21 days, which is far earlier than the nervous system becomes functional. I believe a time limit of day 21 should be under continual assessment not only by scientists but also by everybody concerned, meaning the general public.

Q.Z.: Defining a bright line for when human embryo culture should be limited involves not only the scientific issues but also many social, religious and ethical issues. We need to ask scientists, ethicists and policymakers to work together to discuss and define the onset of moral status in human embryos. The development of the nervous system should be an important consideration.

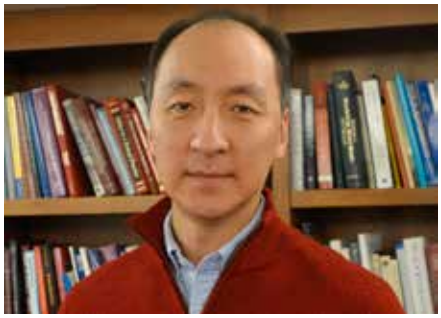
L.Z.: The establishment of the 14-day rule was the result of a careful, thoughtful and respectful conversation that took account of many competing moral and religious claims, and was worked out over a several-year period in the bioethics, theological and scientific communities. The question of when life begins and the moral status of the embryo is not new. Religious traditions have considered the question of pregnancy and its interruption for centuries—including the question of the moral status of a human embryo, the time at which it becomes a member of the community, and the duties we owe to the embryo and the woman who carries it at various stages of development. In the traditions of classic Jewish and Islamic thought, for example, the moral status of the embryo is developmentally acquired, and relative, of course, to the woman who is pregnant. In both of these traditions, the embryo before it is 40 days old has very limited or null moral or legal status. However, in Catholic moral theory, the embryo achieves moral status as a full human being at the moment of conception, which makes experimentation on the embryo impermissible. Additionally, many secular philosophers regard the embryo as due respect but not rights or protection. Finally, a compromise was reached with some Catholic theologians and nearly everyone else that would allow research for nontrivial purposes on embryos before 14 days for the following five reasons: first, at that point, the embryo can still split into twins or triplets, so in that sense, it is not really one human, but an unstable entity and able to have more than one 'self' and be more than one individual; second, the neural streak, which will become the spinal cord, central nervous system and brain, has not yet appeared and thus

the embryo cannot have a consciousness or experience pain; third, 'conception' could be interpreted as occurring at several points in molecular and embryonic development and is not a bright line or a specific moment, and thus neither the Aristotelian term 'when the blood thickens' nor the term 'when the egg and sperm meet' are actual scientific categories; fourth, all religious boundaries ('pray at dawn', '40 days' fasting', 'moment of conception') that define and limit natural categories justify the drawing of moral lines across very subtle, but largely imperfect biological processes. And fifth, the 14-day rule emerged because it was a defensible boundary with the widest possible support among bioethicists from different traditions.

However, none of the above reasons make any sense after the 14-day limit. Every other stopping point becomes quite arbitrary, linked to no justifying tradition or narrative and inherently unstable, because scientists will be curious about more and more stages of development, and may well learn how to support increasingly longer gestational periods. Since this research destroys the embryo by design, and since the embryo begins to look more and more human, its destruction becomes increasingly troubling.

Would the decision about the appropriate time frame for culturing human embryos be different in the case of synthetic embryo-like entities?

I.H.: What actually matters for the 14-day limit is not the 14 consecutive days themselves but rather the developmental stage that the 14th day after fertilization typically represents. Thus, if a synthetic embryo-like entity were to be made in a lab in fewer than 14 days but was as biologically complete as a natural human embryo at that same stage, then there would be a real question as to whether the creation of such an embryo-like entity actually violated the spirit of the 14-day limit, especially if the synthetic entity were biologically capable of producing a pregnancy. I think, however, that this concerning scenario could and should be avoided altogether because there is no real scientific necessity to create a singularly complete embryo-like entity to study early human developmental events. A recent paper in *Nature Communications*[6] nicely illustrates this point, as researchers were able to model early amniotic sac formation without modeling the complete human embryo at that stage. If prudent engineering choices are made early in the design phase of one's synthetic embryo research, one can avoid creating morally ambiguous embryo-like entities that have all the features of 'real' embryos.



Insoo Hyun has an interest in the ethics of human embryo research and currently serves on the ISSCR's Ethics Committee. He is the former chair of the Subcommittee on Human Biological Materials Procurement and served as co-chairperson of the ISSCR Task Force on International Guidelines for the Clinical Translation of Stem Cells.

J.B.H.: Yes, for several reasons. There is the question of just how human embryo-like such an entity would need to be to make it an object of ethical concern—and how and by whom that judgment would be made. From a governance perspective, the question of 'who decides' is fundamental. Its stakes go beyond the question of the 'moral status' of a specific laboratory construct, for instance to the question of whether it is appropriate and legitimate for a university ethics committee that meets behind closed doors to be the sole authority making judgments about 'how human is too human' given that the ramifications of the committee's judgment and of the research that it permits (or prohibits) are likely to extend well beyond a single lab or university. Such experiments will likely set consequential precedents or open new zones of ambiguity that are socially divisive or have the potential to undermine existing norms. Yet perhaps the most significant difference between synthetic and natural embryo research is that the former cannot easily be governed by applying simple limits. Whereas normal human embryos all have essentially the same morphological features and follow the same developmental trajectory, neither need be the case with synthetic entities. A synthetic entity could be constructed to have deficiencies or differences that distinguish it from a normal embryo in morally significant ways. Or it could be directly constructed to be morphologically similar to a later- (post-gastrulation-) stage embryo, in effect skipping earlier development. Thus, governance of this sort of research cannot rely on simple limits, but must describe zones of moral concern with sufficient detail that researchers can recognize them and steer clear of them. This in turn requires serious, sustained and inclusive deliberation about what ideas of human rights, integrity and dignity can guide research such that it is undertaken in light of, rather than in spite of, ethical uncertainty.

A.D.L.: Yes. In most cases, synthetic embryo-like entities would not have the same moral status as human embryos, and fewer ethical concerns would be raised if they were allowed to 'develop' past 14 days than if human embryos were allowed to proceed down this path.

R.L.-B.: We will not know how well these synthetic-embryo-like entities mimic real human embryo if we can't study the latter. However, if they do turn out to be a valid model, then they should reduce the need to use human embryos. But it is difficult to specify time limits because the rate of development of the entities may differ from that of real embryos. Processes could be speeded up or slowed down. Other criteria would have to be imposed if there were to be any limit—but I can't think what these should be. It is extremely unlikely that such entities could develop in culture to a stage where concerns about pain and awareness would become an issue.

J.E.L.: I regard the case of synthetic embryo-like entities as different from that of gamete-derived embryos. Synthetic embryo-like entities do not necessarily follow the canonical ('natural') developmental pathway. Stages of organ development can be (engineered to be) different from non-synthetic embryos, and the same applies to the functional interaction of organs and tissues in engineered systems.

Thus, certain biological benchmarks—that we may have agreed upon as morally significant in non-synthetic embryos—may not present in a similar way or even at all in synthetic embryo-like entities. For example, the primitive streak is currently a benchmark for moral considerability in non-synthetic embryos, but as this developmental stage may be absent in engineered synthetic embryo-like entities, its utility as a moral threshold may be lacking.

A.M.: The important distinction is between the embryo to be placed in the uterus for clinical treatment and that to be used for research.

P.M.: Synthetic embryo-like entities are a new phenomenon that does not fit

comfortably within our existing normative categories. Again, debate will be necessary to locate them ontologically and establish their moral significance. A key question is whether they constitute 'human embryos' for the purposes of regulation. In the UK, we have confronted this question with cloned embryos and again with what became known as 'human admixed embryos' (cytoplasmic hybrids, true hybrids, transgenic embryos and chimeric embryos). In both cases, these entities were brought within the scope of existing law. It seems unlikely that the definition of an embryo in UK legislation could be stretched to include synthetic embryo-like entities. They could, however, be brought within scope—and subject to the 14-day rule and the HFEA licensing regime—through regulations, if the UK Parliament wished to do so. This might come to be seen as the prudent approach, and one that is reassuring to the public, although it would place additional requirements on research. It does not, however, address the underlying question of the status and potential of embryo-like entities.

M.F.P.: No. In principle, if the embryo-like entities are considered equivalent to embryos, the same limits should apply. However, the key issue is how we define an embryo going forward. It is likely, for reasons I touched on above, that many synthetic embryo like entities will not be regarded as equivalent to human embryos, in which case a time limit is not relevant.

Martin F. Pera is a stem cell biologist with an interest in human development and the derivation of pluripotent cells from human embryos, who has long been involved in public discourse concerning the science and ethics surrounding this area of research.

M.Z.-G.: This is not a straightforward question, and I think the answer depends upon the nature of the synthetic embryo-like entity that has been created. If the structure only recapitulates part of embryo development, such as a specific organ, then it can have great value as a research tool while not being able to resemble a human embryo, and so this should not present an ethical problem. The problem will, however, arise if scientific skills were to develop to allow the development of a real synthetic human embryo, which is not what is currently possible. In this case, the research should be subject to the same rules as a natural embryo in culture.

Q.Z.: I think they should be the same, as the synthetic embryo-like entities also share the key features of natural embryos.

L.Z.: In some religious traditions, the synthetic nature of the embryo-like entities would be a factor. But if the entities are too different from natural human embryos, their scientific value will be diminished. If they are too close to natural human embryos, then many people would be disturbed no matter what the origin. This is because human DNA has become important as a marker of identity.

Assuming a change to the 14-day rule, what should be the process to change the policy while respecting the input of all concerned parties?

I.H.: If the 14-day rule were to be changed, extended or (as I favor) replaced with a principled case-by-case approach, the process for changing this rule should follow the appropriate steps specific to the type of rule this is in a particular locale. For instance, the 14-day rule is encoded into national law in 12 countries. In these cases, changes to the law must follow appropriate legislative procedures. In places where this limit is only a professional scientific guideline with no legal sanctions against those who cross it, then the process for changing the rule should follow appropriate channels for revising guidelines. In either case, however, all concerned parties should be allowed to voice their opinions.

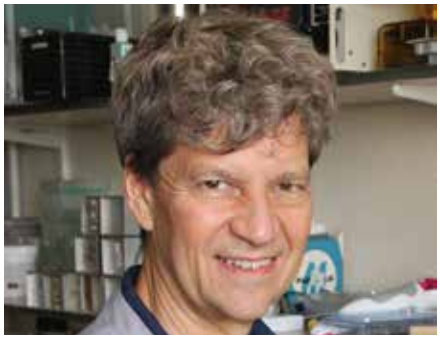
J.B.H.: Respecting the input of all concerned parties would mean *not* beginning by assuming a change to the rule. It is a remarkable—and problematic—assumption that the rule, codified as law in some jurisdictions, warrants changing simply because it is now possible to break it. Yet this is precisely what some prominent voices have suggested. Whatever one thinks of the 14-day rule, for decades it has been the most explicit and definitive limit to a controversial and ethically concerning area of scientific research. It was—and remains—a key pillar of the regulatory regime in the UK, a regime that many UK citizens cite as an example of particularly effective and trustworthy governance. Thus, what is at stake in the 14-day rule is not merely whether certain lines of research will be permitted, but also the prior commitments made by science to society to accept limits on research in deference to widely shared ethical concerns. In short, governance of scientific research more broadly is at stake.

When the Ethics Advisory Board of the US Department of Health Education and Welfare first proposed the 14-day rule in 1979, the committee treated it as an arbitrary limit and gave it little weight. Yet in the decades that followed, a host of public bioethics committees, professional societies and scientific experts have vigorously argued that the limit made ethical sense because it made scientific sense: they argued that the morphological changes that take place at approximately 14 days of development distinguish an entity of limited concern (what some prominent experts called the 'pre-embryo') from a human organism that, after this point in development, ought not be used instrumentally. If those arguments, which were reaffirmed innumerable times over the course of four decades, disappear as soon as adhering to them becomes scientifically inconvenient, then they appear in retrospect to be mere arguments of convenience.

Thus, a robust and inclusive process for evaluating the rule would continue to affirm the assumptions that have long underwritten it: that it was not contingent on the state of the science, but was grounded (at least in the UK) in public moral judgment—and in accounts of how democratic societies *ought* to go about making such judgments. Thus revision ought not be taken lightly. At stake is society's trust in scientists to abide by ethical limits and to treat public ethical concerns as serious and significant and not as a mere political problem.

A.D.L.: Changing the 14-day rule would be hard. It is enshrined in law in numerous countries and has been endorsed by numerous ethical commissions in other countries around the world. If the rule were to be changed, it seems like it would be best approached through a series of national and international deliberations on the ethics of the policy and exploring various alternatives. These deliberations could be designed to collect input from a wide variety of parties. Although international consensus would be ideal, changes would be more likely to come at the national or even subnational levels, at least initially.

R.L.-B.: The process should be the same as occurred for the changes to the [UK] Human Fertilisation and Embryology Act in 2008 and 2015. This involved extensive public engagement and political debate.



Robin Lovell-Badge is an embryologist whose first independent lab was in the UK Medical Research Council's Mammalian Development Unit directed by Anne McLaren (see **Box 1**). He also established a facility for human embryos and pluripotent stem cells at the MRC National Institute for Medical Research (now the Francis Crick Institute). As a co-opted member of the Scientific and Clinical Advances Advisory Committee of the Human Fertilisation and Embryology Authority (HFEA), he provided input that led to changes to the Human Fertilisation and Embryology Act in 2000/2001 and 2008, and most recently to regulations that permit mitochondrial donation.

J.E.L.: As the rapid technological advancements and the windows they open into the study of early human development are the key drivers for reconsidering the 14-day rule, the initial burden of proof for a needed change rests with the scientists and their international professional organizations.

Openness on the part of the profession about ongoing research and foreseeable new directions is the necessary—though not sufficient—basis for ethical, legal and social analysis and broad discussion.

A.M.: In the UK, the process would be via primary legislation through Parliament. But I question the definition of 'concerned parties' as applied in the current discussions. The most important stakeholders and concerned parties should be the potential patients, the embryo donors, their healthcare providers and those undertaking research on their problems. All others have a 'third-party' interest. In many cases, their views are predetermined, for example, by doctrine, academic pursuit or media interest. Notwithstanding respect for their opinion, historically they have largely drowned out the voices of the main stakeholders. Greater positive effort should be made to listen to the patients and take account of their needs.

In the UK, debate about mitochondrial replacement, the voice of the patient was deliberately dominant, and I believe this was the main reason that the procedures were supported. Although the voices of subfertile couples were secondary in the debates that led to the Human Fertilisation and Embryology Act of 1990, IVF was permitted in the UK because the needs of the patients justified the creation of human embryos and embryo research.

P.M.: The scientific case needs to be made that there is valuable and achievable knowledge to be gained by extended embryo culture. Previous debates over the case for permitting somatic-cell nuclear replacement and 'human admixed' embryo research will no doubt be recalled. Once the scientific case has been clarified, there would need to be wide-ranging debate. Independent bodies like the Nuffield Council on Bioethics could help to inform such a debate through initiatives such as the one that led to the report *Human Embryo Culture*[7]. Changing the limit is not simply a political question, but it is not a question that can be answered without a political process. There needs to be time for diverse voices to be heard, and it is likely that religious and faith groups will have important views both for and against any change. In the UK, the limit is within the gift of Parliament, but Parliament has a lot on its plate and will be nervous both of public opinion and of those who might wish to seize an opportunity to make this limit and other provisions more stringent.

Juliet Tizzard: In the UK, the 14-day rule is enshrined in law, so any change would need the support of the majority of members of Parliament and of the House of Lords.

M.Z.-G.: I think that this requires the activity of a working party with representation from all walks of life as well as all the concerned parties. The report of such a working party could form the basis of future legislation.

Q.Z.: We definitely need a widespread consultation with professionals, including scientists, doctors, ethicists, legal experts and government policymakers, to reach a consensus. Before making any reform, the general public should also be consulted, to make sure that, if not everyone, at least most will agree with the reform.

L.Z.: This is a moral and ethical question, rather than a scientific question, and it matters a great deal to many Catholic and Protestant theologians and believers, and societies need to understand and respect these differences. The 14-day rule allowed many Christians to support, for example, stem cell research or research on advanced reproductive technologies like IVF, which does use and destroy embryos. Thus, it was a fair social compact about a very difficult conflict because researchers need to understand that for many, embryo destruction is simply murder, and that that number could grow to include many more should the 14-day compromise end. Furthermore, if such a careful compromise is changed, and changed because scientists want it to and not because of change in the moral argumentation, questions will arise as to whether researchers can keep their promises to society. And of course we do want to have broad public support for research. Do we want to conduct research that a significant proportion of our fellow citizens believe is murder?

How should the public be engaged in any change to the 14-day rule?

I.H.: Although I do support public engagement on this issue, the specific form of engagement should depend on the proper channels for either legal change or guidelines revision, as I noted above. In either case, the public should engage in debate first by being properly informed about the scientific rationale for any proposed change.

J.B.H.: Yes, the public should be engaged—and in the various jurisdictions where the 14-day rule is law, the public *must* be engaged because the rule was originally the product of democratic rulemaking. Yet even where it is only a voluntarily adopted guideline, as at many American universities, it is important that the 14-day rule be approached as a question that requires public deliberation. There is a growing sense in the scientific community that 'public engagement' is important for governing ethically difficult scientific research in a robust and democratically accountable way. Yet it would be a mistake to think of public engagement as something that can be choreographed according to a singular, universal recipe. Scientifically advanced democracies have developed a diversity of mechanisms and practices for contending with ethically complex problems in the biosciences. They have likewise developed different cultures of deliberation that give more or less deference to particular forms of expertise and authority, and frame questions about the same scientific projects in different ways. One important first step in achieving robust public engagement would be for different nations to learn

from each other with an eye to exposing the blindnesses and deficiencies of their own systems of governance and experimenting with new outreach approaches. Revision of the 14-day rule is a high-stakes proposition, not least because it comes at a moment when there is increasing interest in human embryo research in the scientific community and when advances in genetic engineering and synthetic biology are opening the way to a wide range of extraordinary, but ethically concerning, science. Efforts at public engagement should therefore be explicitly approached as experimental attempts to expand and deepen opportunities for democratic deliberation to calibrate emerging science to public ethical sensibilities. As such, these efforts must make space for dissent, solicit critique and invite difficult deliberation.

A.D.L.: Public perspectives should certainly be included in discussions about the 14-day rule and whether it should be changed. A variety of approaches could be used to achieve this. An easy step would be to invite public comment at as many of the national and international ethical deliberations on the topic as possible. This would permit public input, but it may present a skewed view, as only the most motivated members of the public are likely to attend. Public comment at ethics meetings could be complemented by other approaches designed to garner a wider set of views, including web and social media based approaches. Another possibility would be citizen deliberation panels, which have the potential to incorporate views from a broader range of people, including those without pre-existing positions on the topic of debate.

R.L.-B.: There are now reasonably good (although still improving) ways to conduct public engagement on issues like this. The program of public engagement conducted by the HFEA with respect to mitochondrial donation (replacement) has been broadly accepted as having been an excellent way to gather both quantitative and qualitative views.

J.E.L.: Although input from scientists is necessary, any change in norms of ethical acceptability and in actual limits to research will depend on public decisions. However, there are many 'publics'. The current 14-day rule meets with widespread agreement, yet it has no universal binding force or acceptance. This will be the case with any new proposed threshold and, moreover, with the acceptability of human embryo research at all. Although very broad, potentially global, public engagement is nowadays feasible, this does not mean that all publics can indeed participate in decision making, as this depends on national structures of government.

Aram Boghosian

Jeantine E. Lunshof is a philosopher and ethicist, working in a synthetic biology lab. She is interested in the moral status of the human embryo and the conditions for and limits of embryo research; her current interest is more specifically in questions that arise in the context of research into synthetic embryo-like entities.

A.M.: UK legislative changes require well-established public engagement procedures. For example, there were numerous well-attended debates during public engagement events related to human ESCs and mitochondrial replacement. The overwhelming interest indicated that the public are far more supportive of the developments in reproductive technologies than is apparent from the louder voices of the minority 'third-party' interest groups.

P.M.: It would be hard to justify a change in the human embryo culture limit without allowing adequate opportunity for public debate; without such debate, the consequences for public confidence in science would be damaging. Researchers must leave their laboratories to explain to the public the benefits (or costs) of extending the limit, but they must do so with patience and humility, as advocates, not as judges. The important thing is engagement, which involves listening as well as speaking; but it first requires establishing a common language. Engaging the public must have the object of developing understanding within the public sphere and finding where the public interest lies. It cannot be achieved by a single exercise (say, a media campaign, survey, public consultation or citizens' jury), although all of these contribute to bringing the issue to salience.

J.T.: You can't make public policy like this without public involvement. It's crucial.

Q.Z.: I think the public should be engaged at later stages. After the professionals finish a proposal for the change, they can let the public know the proposal and the advantages of the change, and then the public or their representatives can vote for the proposed change.

L.Z.: The public needs both information and the ability to engage with scientists. Scientists need to thoughtfully engage in the debate about human embryo research in a serious manner, with leaders of communities that range from religious to those who are concerned on moral (and not religious) grounds about the power of scientists. Tragically, and historically, scientific communities have not always been the best arbiters of their own limits, and the nature, goal and meaning of any scientific practice needs public discussion.

The 14-day rule, it is important to remember, was established when scientists doing stem cell research made the argument that the need to do it was fundamental and imperative, and that it would surely lead to the saving of many more lives. The public very much supported this research, as they did IVF research, and justified this support in the face of embryo research because they believed that scientists deeply needed to experiment in this way.

What can the international community learn from the experience in UK with establishing rules for research on human embryos?

I.H.: What the UK experience seems to show is that the UK public is generally supportive of new embryo research and other embryo activities (such as assisted reproduction or mitochondrial replacement trials) if they believe that proposed changes or policies could lead to advances that would help people in need. In the case of IVF in the late 1970s, for example, the majority of the public accepted this radical new technology as soon as they saw that infertile couples could be helped through this advance. I think the same could hold true for new techniques in embryo research. If people can be helped through new rules, then the public may tend to be more supportive.

J.B.H.: The UK's regulatory regime for human embryo research has been widely lauded. It is worth remembering, however, that it took nearly a decade of debate from the formation of the Warnock Committee to the passage of the Human Fertilization and Embryology Act. One of the celebrated achievements of the Act is that the regulatory

system it put in place reflects a kind of social consensus that important questions are being adequately addressed and research is proceeding responsibly. But that consensus was hard won and reflects a certain trust in the elite figures who stewarded debate towards consensus. It is worth remembering, then, that UK parliamentary affirmation of the 14-day rule, and of the distinction between the 'pre-embryo' and the embryo that it was grounded in, was a turning point in this process. Behind trust in the regulatory regime is a sense that its architects, and their judgments about what distinctions—scientific and moral—should decide the day, were trustworthy. Such trust is hard won and easily lost.

A.M.: The moral debate will never go away and is of interest for all stakeholders. Moral concerns are addressed alongside the clinical and scientific justifications before legislative decisions are made. To quote Warnock, "...that moral conclusions cannot be separated from moral feelings does not entail that there is no such thing as moral reasoning"[1]. Such reasoning resulted in legislation that provides for permissive but restricted and regulated research. The resulting structure provides the reassurance both for researchers and for patients and volunteers under which successful research can be achieved.

P.M.: The international community has tended to follow the UK, both historically and orientationally, except in relation to the creation of embryos for research purposes. The Warnock Report, and the tradition that it established of informed debate and careful regulation around assisted conception and human embryo research, has worked to maintain confidence and facilitate research. These are useful precepts. The UK conditions are not typical, however: UK public opinion has broadly conformed to a normal, rather than a polarized, distribution—the middle ground has proved reasonably progressive so long as there is confidence in effective regulation. The UK's approach cannot necessarily be transplanted into other jurisdictions with the expectation of similar results, particularly in the absence of the kind of regulation that the UK enjoys via the HFEA.

M.F.P.: I regard the UK experience in establishing rules for embryo research as the best existing model for such discussions. Some key features of the UK approach were the critical preamble of an extensive analysis by an authoritative, balanced and interdisciplinary group of highly regarded experts (the Warnock Committee), widespread public engagement in discussions, and a trial period of conduct of research with responsible scientific and ethical oversight, all before the enactment of legislation.

Juliet Tizzard is policy director for the HFEA and has worked in this policy area for many years.

J.T.: The most important lesson from the UK experience of establishing policy for human embryo research is that it takes time and proper public debate. When the Warnock Report was published back in 1984 and recommended new legislation to permit embryo research, parliamentary opinion was not particularly supportive. Six years later, after extensive public and political discussion, the bill passed with a large majority in both houses of the UK Parliament. Public debate—with all voices heard—was crucial. Researchers, patients, funders, religious leaders, philosophers and the public at large all had an important part to play.

But public support for human embryo research doesn't come merely by playing the long game. Although the British public is generally supportive of research using human embryos, their support is not unconditional. There has to be a need to change the rules; a benefit that will flow; a medical treatment that might arrive as a result. Without an identifiable benefit of extending the time that human embryos can be kept in the research lab, any argument to change the 14-day rule risks falling on deaf ears.

M.Z.-G.: It would seem reasonable that a common international framework should be devised for human embryo work. In embryo research, there is a history of the UK taking a lead with such discussions, but parallel debate is likely to, and should, arise in other countries in order that an internationally agreed consensus can be achieved.

L.Z.: The UK has established a careful, consensus-driven and well-informed public discourse about this research and has the discourse within a healthcare system in which all have a stake. The leaders of the discourse are philosophers who are respected and honored, and many people have access to participation in the debates. However, the complexities of faith, the market, and political will make the American discussion quite different.

To what extent should the political climate in a country influence the timing of when the research community reassesses the 14-day rule?

I.H.: Although I believe that the political climate in a country ought not to influence the timing of reassessment, unfortunately the reality is that it actually could. Thus, if science policymakers in the US believe that raising the issue of the 14-day rule would mobilize political backlash against embryo research, then the prudent course of action would be to wait until that risk is reduced under a different administration.

J.B.H.: The scientific advances that have led to calls for reassessing the 14-day rule are coming so quickly that delaying discussions until a politically opportune moment would be irresponsible. Yet that is not the only reason to bring such questions out into the open irrespective of who is in political power. At its best, science, like democracy, is committed to transparency, deliberation and openness to critique. The practices that make scientific knowledge robust apply equally to evaluation of its ethical dimensions. The 14-day rule touches upon fundamental commitments to respect for human life. Treating such a fundamental issue as a matter of political strategy or timing denigrates both the significance of the ethical questions and the commitment of the scientific community to asking them in a responsible and democratically accountable way.

A.D.L.: Enacting policy change is difficult, and those who believe that extending the 14-day role would be a wise policy choice should certainly consider the full range of factors—including the political climate—that would affect the research policy debate. Raising the question of human embryo research policy in the US, for example, when key members of the current administration are on record strongly opposing human embryo research, certainly risks opening the door to a policy change that leads to a more restrictive, rather than more permissive, research policy.

R.L.-B.: This is a critical question. If the timing is wrong then it could indeed have negative consequences not just for research, but for the clinical practice of IVF and related methods, which always depends on research to allow the safest and best methods to be used, and for women's health. It is not just a problem for the US; for example, it would be unwise to push for a change in the UK at present with a government so preoccupied with Brexit.

J.E.L.: Such influence is real, and it underscores the point mentioned above, that decision making ultimately will take place in the context of the nation-state and conditions may vastly differ. The 'timing', therefore, should be part of the considerations of a national research community; outcomes will depend on their prudence. Outcomes in a given country, however, should not necessarily affect researchers in other countries. This underscores the importance of shared responsibility and guidance by the international professional organizations.

A.M.: The UK is fortunate that opinions about reproductive technologies cross party political lines. Thus, legislation is not dependent on which party is in power, and there is some stability. Revisiting legislation, though, is always a potential risk. I doubt that there are sufficient clinical or scientific needs to extend the 14-day rule to justify taking that risk at the present time.

P.M.: This is a question of strategy for advocates within particular jurisdictions. Regardless of the present climate, it is likely that raising the question of the 14-day rule will reinvigorate debates on other contested aspects of assisted conception and human embryo research. Depending on how they are linked (for example, in common legislation, as in the UK), the possibility exists both of a more stringent resolution and of collateral consequences.

M.F.P.: It is absolutely critical right now to assess how urgent the case for changing the 14-day rule actually is, in light of the political capital the scientific community will need to expend in the process of revising it. In the current climate, where science is facing a myriad of threats from a number of directions, changing the 14-day rule would not seem to me to be the issue of highest priority. There is much that can be done with pluripotent stem cell models *in vitro*, and much that can be learned from the embryology of the nonhuman primate, in the interim; if such approaches prove to have shortcomings, this would clearly strengthen the argument for the study of the post-implantation human embryo itself. And yes, there is unquestionably a significant risk that any attempt to 'liberalize' rules on embryo research will provoke a backlash of restrictive countermeasures.

M.Z.-G.: There is likely to be a bigger risk in not discussing the 14-day rule with a view to its re-evaluation. It is important to convince pro-life representatives of the value of this research that would be carried out on surplus embryos from IVF clinics. Such embryos are not created for the purpose of research, and they would otherwise be destroyed. The ultimate goal of this research is to save the lives of babies lost in early stages of pregnancy through better understanding how developmental defects and what the triggers are for natural abortion (miscarriage).

Magdalena Zernicka-Goetz has a 20-year track record in mouse embryo research. She has recently begun to apply her methods for culturing mouse embryos beyond the stage at which they implant into the uterus to the point of gastrulation to similar studies of human embryos. This has shown that human embryos can develop to this stage—at least a week longer than previously possible—which brings *in vitro* human embryo research right to the current limit of the 14-day rule[2]. She has also developed the first synthetic embryo-like structures using mouse stem cells[8].

L.Z.: Of course, there is always a risk that openly and transparently speaking about human embryo research will outrage people, and additionally ours is not a political climate in which scientific arguments have carried much weight. But if the scientific question is desperately vital, then the scientific community should not be intimidated. Furthermore, the arguments for 14 days are not arbitrary, they satisfy the greatest possible number of our fellow citizens and neighbors, they allow the public to trust scientists, and this is important in any political climate. This trust took a very long time to establish. If people worry that scientists can only keep a promise to stop when they can't go any further, then a fundamental problem emerges—where do you stop? Is any promise stable?

How important is it for there to be international consensus on the 14-day rule?

I.H.: A plurality of approaches to the 14-day rule would be welcome, in my view, because different societies and cultures have different belief traditions that could come to bear on the moral status of human embryos in a dish. However, I can appreciate that a more harmonized approach to embryo research internationally would be more favorable for collaboration and journal publishing standards for research conduct.

J.B.H.: There is value to the diversity of national perspectives and policies—on human embryo research and on many other issues. There is no particular imperative for international consensus, even if that means that some jurisdictions are more restrictive than others. It is also an unrealistic goal in light of existing differences in policy relating to human embryo research, for instance, in Germany where it is banned, in the UK where it is regulated, and in the US where the governance of publicly and privately funded research differs radically. More important than seeking consensus is an effort to invite public deliberation and exchange. For instance, in US ethical oversight, there tends to be remarkable ignorance of policies and practices in other countries, even at the highest levels. Crafting consensus depends on first developing mutual understanding.

A.D.L.: International consensus would be ideal but is quite unlikely. Indeed, policy heterogeneity has been a defining characteristic of the policy environment for both human embryonic stem cell research and assisted reproduction for decades; it would be naïve to think that this heterogeneity will disappear anytime soon. The 14-day rule is one of the few areas of embryo research policy where substantial international agreement has existed, and opening this rule up to debate will likely lead to more heterogeneity, rather than promoting consensus

R.L.-B.: I don't think international consensus is essential, and it may well be impossible to achieve. Currently, some countries don't allow any research on human embryos, even if IVF is practiced (for example, Germany). Others don't have any laws that restrict experiments to 14 days (for example, the US and China), but scientists there still stick to the limit.

J.E.L.: Rules and regulations will always differ. Outliers in either direction are an inevitable part of reality. Broad consensus may be desirable, and it would promote international collaborations as well as increase equal access to diagnostic and therapeutic procedures for citizens, but it

Box 1 Genesis of the Warnock Report

The 1982 Warnock Committee, chaired by Mary Warnock, a philosopher and member of the UK's House of Lords, was first group in the UK to consider the ethical, legal and social implications of the science of human fertilization and embryology. The 1984 *Report of the Committee of Inquiry into Human Fertilisation and Embryology*[1]—commonly called the Warnock Report—made recommendations that would eventually regulate emerging technologies, such as artificial insemination, in vitro fertilization (IVF) and embryo research. The report cites the social concern that followed the birth, in 1978, of the world's first 'test-tube baby' Louise Brown, as the signature event that prompted the committee's actions and recommendations.

Thirty years on, the report is remarkable for its breadth and normative staying power. The public deliberation and consultation process was explicitly pluralistic. Nearly 300 organizations and individuals working in reproductive sciences submitted evidence to the committee, and an additional 695 submissions came from the public[9]. The report, which ranges over 13 chapters, wrestles with diverse topics such as surrogacy and the moral permissibility of assisted reproductive technologies. It considers the problems of egg and embryo donation, sex selection, donor anonymity and informed consent. It ventures into the methodological minutiae of freezing and storage of eggs and sperm. It devotes a chapter to prophetic uses of the technology, presaging controversies about cloning, human–animal chimeras and trans-species fertilization[10]. Twenty years before human ESCs reignited the moral debate about when life begins, the Warnock Report deftly navigated the utilitarian merits of using embryos in scientific research[1].

In her work with the committee, Baroness Warnock understood that the beliefs of supporters and opponents of embryo research could never be fully reconciled. Recognizing this diversity of opinion, the committee concluded the following: first, that the embryo should be accorded some protection in law; second, that licenses to work with embryos would be required; third, that unauthorized use would be a criminal offense; and fourth, that embryos should not be kept alive beyond 14 days after fertilization. In particular, the 14-day limit was a compromise solution between conflicting moral views, designed to maintain public trust while allowing the research to go forward[6,11]. Today, the 14-day limit is used to guide research all over the world and has been legally adopted in over a dozen countries.

Christopher Thomas Scott is a bioethicist and science policy expert at Houston's Baylor College of Medicine, where he studies the ethical, legal, and social implications of emerging biotechnologies. He is an emeritus faculty at the Stanford University Center for Bioethics and was formerly director of the Stanford Program on Stem Cells in Society. He is an Editorial Advisor for Nature Biotechnology.

Mary Warnock is a philosopher and crossbench member and Life Peer of the UK's House of Lords. She has chaired several national UK committees, including the influential 1984 report dealing with the ethics of embryos and human fertilization entitled '*A Question of Life: The Warnock Report on Human Fertilisation and Embryology*'. She also discussed the ethics of human reproduction in her 2002 book '*Making Babies: Is There a Right to Have Children?*'

Ethics and policy experts Christopher Thomas Scott and Kirstin R.W. Matthews interviewed Warnock about the report's influential ideas and recommendations, and asked her what made the Warnock Committee so special.

What was the public and policymaking reaction to IVF technology and the committee before and after the Warnock report?

Mary Warnock: The birth of Louise Brown in 1978 was hailed as a wonderful event and a great breakthrough in the treatment of some fairly common forms of infertility. But there was quite soon a reaction against the techniques involved, both because embryos fertilized in the laboratory but not placed in the uterus were destroyed and because such 'spare' embryos could be frozen and later used for research. For instance, the *Daily Mail* called on readers to contribute money for a new building where [IVF pioneers Robert] Edwards and [Patrick] Steptoe were working, but when the foundations had been laid, they withdrew the money.

The evidence that the committee received showed that by the time the report was published, in 1984, public opinion was fairly evenly divided. There was no known policymaking opinion before we started; but judging from the papers that the civil servants prepared before our first meeting, there was a fairly strong feeling that it would be a pity to ban IVF altogether, after a British 'first'. [The] Committee had been set up specifically to advise Ministers with a view to legislation, so once the report was presented to Parliament, it would be for Parliament to decide.

Box 1 Genesis of the Warnock Report (continued)

The report has been hailed as an exemplar for how to engage the public in science policy. How was it organized? Which strategies worked? Which did not?

M.W.: I think that to engage the public as fully as possible, it is necessary to set up a Committee of Inquiry, composed partly of nonscientists and chaired by a nonscientist. [In the UK], the general public is suspicious both of scientists and of politicians, though slightly less of scientists now than they were in the 1980s. We didn't really need to work to get a wide response to the issues we were considering; the press did it for us. It was a topic that caught the public imagination, and not only that of couples who were trying and failing to conceive a child. Scientists on the whole want to be left in peace to get on with their research and leave policymaking to others. A live embryo in the laboratory was a completely new object which had never existed before, and its moral status had to be discussed and clarified. Was it to be treated as a collection of cells or as a baby? It was some time after the first meeting of our committee that this emerged as the central question and a crucially moral question.

I think philosophers are professionally and by training accustomed to getting to the essence of a problem and expressing it intelligibly. But I don't think that I succeeded altogether in getting members of the committee, let alone members of Parliament, to grasp that this was not a question of fact ('When does life begin?', as they persisted in asking) but a question that had to be decided. How ought we to regard this new entity, the live human embryo outside the uterus? The difficulty we had in communicating with the public, insofar as it existed, was nothing to do with means of communication, but all to do with getting people to think along the lines of the committee and not stick to their prejudices.

Why was the 14th day of embryogenesis chosen? Were alternative time points of human development considered?

M.W.: Most fortunately, we had as a member of our committee the then head of the Mammalian Development division of the UK's Medical Research Council, Dame Anne McLaren, who was not only a specialist in embryogenesis but an absolutely brilliant teacher. I asked her whether she would treat the second meeting as a seminar, so that we could make an informed decision as to when the barrier should be erected to block what I knew would be seen as a slippery slope: the worry that embryos would be kept alive outside the uterus until they were 9 months old, and that scientists, having observed them in such an experiment, would possibly kill a fully formed baby.

This Anne agreed to do; and our second meeting was one of the most marvelous days of my life, so ignorant had I been (along with most of my colleagues) and how amazingly enlightening was it. We picked on 14 days because we learned that at about that time the cells in the loose cluster that then existed began to differentiate into different types of cells and tissues, and that after this, the progress grew much faster, there could be no further division into twin embryos, and the primitive streak would appear, the first sign of what would be the spinal cord. I chose 14, rather than 13 or 15, simply because everyone can count up to 14; a fortnight is a good, memorable number, and records can be kept week by week. We were criticized because it 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; and Anne was very happy with this. 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.

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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.

Is public engagement improving or more challenging today than in the 1980s?

M.W.: I am sincerely thankful that our committee was not engaging with the public in the days of Twitter and e-mails. I think it would have been even more abusive than it was in the days of snail mail. Otherwise, I believe we are living in a period of marginally greater trust by the public in scientists and doctors that may partly have come about because of a generation of good popular writers and broadcasters on scientific matters. I believe that a wider section of the press should engage with ethical issues such as mitochondrial transfer, which, after all, potentially interests all women. In the US, especially it would be helpful if ethical issues could cease to be the preserve (as they are sometimes seen to be) of fanatics, such as the anti-abortion lobby.

is not a necessity for the advancement of science. It may be good to recognize differences in the acceptance of technologies that touch upon deep moral values for many people.

A.M.: Irrespective of its desirability, the likelihood of an enforceable international consensus on a moral issue is slim. Scientists already move between countries to undertake embryo research within the 14-day rule. Patients who have the financial means make a mockery of prohibitive legislation, and reproductive tourism is well established. Clinical procedures that have been researched and developed in one country then become established in others that do not permit such research. Accepting that international consensus may be unlikely, the wider consequences of restrictive legislation must be taken into account.

P.M.: If any jurisdiction elects to move the time limit on embryo culture, there will inevitably be a period of international incompatibility, which will have consequences for research and for researchers. History may judge first movers to have been pioneers or pariahs, particularly if the benefits of research are delayed or fail to materialize. It is unlikely, however, that all countries will follow suit if the limit is changed in some, although this is less important than ensuring that all research, under whatever regime it is carried out, is carried out responsibly. The international scientific community has a major part to play in defining and upholding responsible research practices.

M.F.P.: In this field, science policy does not recognize borders. Events in the US, Europe, or elsewhere impact on the field internationally. To the extent that it is possible, we should aim for international consensus.

J.T.: International consensus in human embryo research is always desirable and rarely achievable! Harmonization of rules helps cross-border collaboration and gives clarity to researchers and funders alike, but scientists are used to dealing with different regulatory environments in different countries.

M.Z.-G.: Science is an international endeavor that aims to achieve common goals for humankind. We should all respect the same rules, as they are devised for the benefit of all.

Q.Z.: International consensus is very important, as 'science has no borders'.

L.Z.: I believe that there needs to be an international consensus on research of this type. Human embryo research needs to be done for public good and not for personal or private gain; guidelines need to be internationally established as they are for many other research projects.

1. Warnock, M. *et al. Report of the Committee of Inquiry into Human Fertilisation and Embryology* (Her Majesty's Stationery Office, London, UK, 1984).
2. Shahbazi, M.N. Self-organization of the human embryo in the absence of maternal tissues. *Nat. Cell. Biol.* **18**, 700–708 (2016).
3. Deglincerti, A. *et al.* Self-organization of the *in vitro* attached human embryo. *Nature* **533**, 251–254 (2016).
4. Bedzhov, I. & Zernicka-Goetz, M. Self-organizing properties of mouse pluripotent cells initiate morphogenesis upon implantation. *Cell* **156**, 1032–1044 (2014).
5. Bedzhov, I., Leung, C.Y., Bialecka, M. & Zernicka-Goetz, M. *In vitro* culture of mouse blastocysts beyond the implantation stages. *Nat. Protoc.* **9**, 2732–2739 (2014).
6. Partridge, E. *et al.* An extra-uterine system to physiologically support the extreme premature lamb. *Nat. Commun.* **8**, 15112 (2017).
7. Nuffield Council on Bioethics. *Human Embryo Culture* http://nuffieldbioethics.org/wp-content/uploads/Human-Embryo-Culture-web-FINAL.pdf (Nuffield Council on Bioethics, 2017).
8. Harrison, S.E., Sozen, B., Christodoulou, N., Kyprianou, C. & Zernicka-Goetz, M. Assembly of embryonic and extraembryonic stem cells to mimic embryogenesis in vitro. *Science* **356**, https://dx.doi.org/10.1126/science.aal1810 (2017).
9. Hammond-Browning, N. Ethics, embryos, and evidence: a look back at Warnock. *Med. Law Rev.* **23**, 588–619 (2015).
10. Cavaliere, G. A 14-limit for bioethics: the debate over human embryo research. *BMC Med. Eth.* https://dx.doi.org/10.1186/s12910-017-0198-5 (2017).
11. Warnock, M. Moral thinking and government policy: the Warnock Committee on Human Embryology. *Milbank Mem. Fund Q. Health Soc.* **63**, 504–522 (1985).

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Erratum: Revisiting the Warnock rule

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In the version of this article initially published, J.E. Lunshof's affiliation was given as "Center for Bioethics, Harvard Medical School, Boston, Massachusetts, USA"; the affiliation should have included her main affiliation at the University of Groningen and read, "Department of Genetics, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands, and Department of Genetics, Church laboratory, Harvard Medical School, Boston, Massachusetts, USA." In addition, "Divinity School, University of Chicago," should be "University of Chicago Divinity School." The errors have been corrected in the HTML and PDF versions of the article.