HUMAN EMBRYO CULTURE

Discussions concerning the statutory time limit for maintaining human embryos in culture in the light of some recent scientific developments

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NUFFIELD COUNCIL ON BIOETHICS

This document collects together a number of reflections on the statutory time limit for maintaining human embryos in culture. This issue was raised for consideration at the Nuffield Council's annual 'forward look' meeting in February 2016. It was given an additional impetus the following month by the publication of research that suggested, for the first time, the possibility that embryos could be cultured for longer than 14 days (the current statutory limit in the UK). This led the Council to hold a workshop with the range of experts to discuss whether, after 25 years, there may be persuasive reasons to review this legal limit or whether the reasons for its introduction remain sound.

The workshop was held in December 2016. The present document contains a background paper that was commissioned to inform the workshop, together with a report of discussions at the workshop itself. This is supplemented by a series of individual contributions from those who were invited to participate, in which they have been encouraged to elaborate their personal views on significant aspects of the debate. The document begins with an introduction from the Council's former Chair, Professor Jonathan Montgomery, who led the workshop.

All views expressed in this document are those of the authors and not those of the Nuffield Council on Bioethics. While the Council has no plans for further work in this area at present, it is hoped that this document will provide an informative resource for anyone who, in the future, may wish to consider the case for reviewing the limits placed on human embryo research.

Links to websites that appear in the document were verified on 20 July 2017.

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Introduction

Jonathan Montgomery[*]

Through the Human Fertilisation and Embryology Act 1990, lawful human embryo research was restricted to specific conditions in the UK. Prior to the enactment of the legislation, there was no legal prohibition on such research, and the only regulation was voluntary. In 1990, local research ethics committees were not yet universally established; they were not formally mandated by NHS administrative norms, let alone a legal requirement.[1] The context in which the statutory limit on embryo research was debated was thus not one in which no research was happening, but one in which there was no legally binding regulation.[2]

When the legislation came before them, parliamentarians were offered a choice between prohibiting all embryo research and permitting it in defined circumstances and for a limited range of prescribed purposes. They chose the latter course and legislated that embryos could not be kept or used 'after the appearance of the primitive streak'. This is a potentially ambiguous biological term, but it has been given more precise legal definition by the gloss that 'the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with the day on which the process of creating the embryo began, not counting any time during which the embryo is stored'.[3] Strictly, therefore, the rule should be described as the 'primitive streak rule' not the '14-day rule'. This possible significance of this distinction between biological and chronological divisions is discussed below.

Although initially controversial, this statutory limit has been maintained for over 25 years.[4] During this time, there was no scientific prospect of sustaining embryos *in vitro* beyond the permitted period. That changed in 2016 with the publication of two papers in *Nature* and *Nature Cell Biology*.[5] Some have asked whether this meant that the question of the limitations on embryo research should be revisited. The Nuffield Council on Bioethics decided to convene a workshop with group of experts from a range of fields and disciplines to explore whether there was a case for a more detailed piece of work on the issue.

This report contains the background paper that was commissioned to provide a context for the discussion along with a note of the discussions from the day. The discussions were held under the Chatham House Rule so that themes and issues are recorded but not attributed to individuals in order to facilitate the most candid exchange of views possible. Participants, including those who were invited but were unable to attend the meeting, were given the opportunity to provide short comments in order to ensure that a broad range of perspectives was adequately represented. These observations are also set out later this this document. We hope that these materials

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* Professor Montgomery is Professor of Health Care Law, University College London and was Chair of the Nuffield Council on Bioethics (2012-17).

will provide a resource for those, who are considering whether there is a case for revisiting the limits on embryo research. For the present, the Council does not aim to reach any conclusion on the merits of the issue, which would require much more detailed work, but to draw out the questions that would need to be addressed by those who advocate a review.

Jurisdictional functions of the rule

It is perhaps helpful to remind ourselves of the jurisdictional functions of the 14-day rule. These serve to explain those roles that are played by a rule of this sort, which are independent of the point at which the rule is fixed. It is likely that any proposal to revisit the rule will need to take these functions into account.

First, the rule limits the jurisdiction of the licensing authority to authorise research involving human embryos. This is a regulatory tool, and is not necessarily a mechanism for directly translating a moral judgment on the status of the embryo. Fourteen days is not the point at which special respect is conferred by the law. That is accorded to all human embryos, which are protected by the prohibition of unlicensed storage and use.[6] Behind this prohibition lie the creation of a dedicated ethics committee and the specification of limitations on the purposes for which research may be permitted. However, the structure of the regulatory system is essentially similar to that for the use of non-embryonic human tissue, and so is not necessarily connected with personhood issues and the particular status issues around the human embryo. It is also similar to the regulatory structure for oversight of animal research. Each of those creates a prohibition of activities, with powers in a licensing authority to permit them within certain limits and subject to oversight. The 14-day rule sits within a regulatory framework that accords some respect to all human embryos at whatever stage of development. The specific questions raised by the rule are, therefore, not concerned with whether respect should be accorded to the human embryo but with what respect requires when it comes to be balanced against other competing, publicly valued, interests.

The relationship between this aspect of the rule and the moral status of the embryo is therefore indirect. It plays a function *within* a wider regulatory system and it is necessary to consider that system as a whole in order to assess whether due regard has been paid to the moral significance of the embryo. The 14-day rule serves to distinguish those cases where the law has determined that the moral value of the embryo will *always* preclude the pursuit of knowledge through research from those in which a 'balancing exercise' needs to be separately undertaken into each research proposal.[7] Under the current framework, human embryo research cannot be lawful in pursuit of the recognised objectives after 14 days, no matter how important the results might be. However, in the period before this, the Human Fertilisation and Embryology Authority (HFEA) is empowered to license projects provided that the statutory purposes that Parliament laid down are being pursued. In effect, it distinguishes ethical

questions that are to be regarded as closed from those which are to be treated as open to further reflection.

The second of the jurisdictional functions that is served by the 14-day rule is to reserve the decision to amend (or not) the rule to Parliament. In most areas of reproductive ethics, the HFEA was given supervisory stewardship responsibility.[8] However, its opportunities to determine the ethics of embryo research have been severely curtailed by the Act. This applies to the grounds on which such research can be justified[9] as well the time- or development-based limit.[10] Parliament has reserved its sovereignty over these aspects of embryo research and any change would need to be justified in terms that would persuade it to legislate differently. The next section considers some implications of this for the structure of an argument for reform.

There is also little or no scope for the courts to have a say in the point of embryo development at which the line between 'acceptable' and 'unacceptable' research is drawn. In principle, the need to classify new entities, such as the recently generated 'synthetic human entities with embryo-like features' (SHEEFs), might be seen as an opportunity for judges to drive policy.[11] However, litigation over how cloning should classified suggests a recognition that the intention of Parliament to create a comprehensive regulatory framework will lead to judges construing new techniques in a way that incorporates them into the special regulatory framework rather than developing a judicially defined legal status.[12] Provision is already made for Parliament to make regulations to bring within the definition of embryo entities that contain human DNA but would not otherwise be included.[13] Arguments based on current definitions, common law and human rights law, are therefore not material to the question with which we are concerned here.

The 14-day rule played a third jurisdictional function during the Parliamentary debates on embryo research in 1990. This was to maintain a focus on the question that the Government wanted to be considered, that is, research on very early embryonic development. Without such a limit, the debate could properly have encompassed a range of developmental stages from a small number of undifferentiated embryonic cells to a fully formed fetus with a reasonable chance surviving outside the womb.

The recommendations in the 'Warnock Report' of 1984, which foreshadowed the 1990 legislation, were concerned with 'the very earliest stages of human embryonic development' and were crafted in order to limit permissible research to this period.[14] The Report was fully aware of the possibility of scientific development and the demand that might lead some to seek research at a later stage. It identified a number of potential future developments, including use of human embryos to test drugs and ectogenesis ('creating a child entirely *in vitro*').[15] The former becomes a particular issue of interest with the advent of SHEEFs.[16] It noted that some argued that the latter 'would make it possible to study in detail normal and abnormal human development at the embryonic and foetal stages'.[17] The Report addresses this issue by saying the following:

> "We appreciate why the possibility of such a technique arouses so much anxiety. There are however two points to make about this. First, such developments are well into the future, certainly beyond the time horizon within which this Inquiry feels it can predict. Secondly, our recommendation is that the growing of a human embryo *in vitro* beyond fourteen days should be a criminal offence."[18]

Thus, the 14-day rule served the jurisdictional purpose of limiting the discussion of human embryo research in a way that ensured that some concerns, such as those about sentient beings becoming non-consensual research subjects, could be excluded from the scope of debate. This did not stop them being raised by some parliamentarians in debate, but it enabled Ministers to respond reasonably by saying the strict limits provided reassurance that such developments were not under consideration in the vote before them. It is probable that any re-opening of the 14-day rule would need to find an equivalent jurisdictional device to delineate the debate.

This continuing need for a clearly defined line is independent of the question of how a proposed limit might be justified. As the discussion of the origins of the current rule set out in this report show, there may be a variety of justifications offered for a limit and, if the decision is for Parliament, it is not necessary for there to be agreement on these justifications. Lawmakers may have independent, and even incompatible, reasons for supporting a particular limit provided that a consensus is reached on the desirability of the outcome. However, it is unlikely that a different line would be acceptable to legislators if it were considered 'arbitrary' in the sense of being random and without any reasoned basis.[19]

The justification of a jurisdictional division to play the equivalent function of the 14-day rule need not necessarily be found in biological development, although much of the discussion explores such possibilities. The legislation explicitly links this time limit with the emergence of the primitive streak but there has never been a consensus on why this is morally significant. The Warnock Committee explained it in terms of the beginning of individuation.[20] In Parliamentary debates, this was elaborated as indicating the final point at which twinning might occur.[21] The Warnock Committee considered a range of other points at which a line might be drawn. It noted that for utilitarians, there might be significance in the beginnings of a central nervous system (at around 22–23 days) or functional activity that would show that pain could be felt (not known in 1984), with the precautionary assumption that the legal limit should be fixed a few days earlier in order that there would be no possibility of pain.[22] Some have taken this as a supplementary justification for the 14-day rule. This is not explicit in the original Warnock Report, although there is a reference to the view of the Royal College of Obstetricians and Gynaecologists that a 17-day limit might be appropriate, corresponding to the point at which early neural development begins.[23] These are developmental markers. However, there was also some discussion of the relevance of implantation, which will never be an actual stage for an embryo *in vitro*.[24]

Discussions at the Council's workshop also hinted at a different type of argument, based on the availability of other sources of information. This approach would suggest a limit that was fixed to ensure that embryos were not used in research when the relevant data could be gathered in other ways. As explained later in this Report, knowledge of early human development is based on the Carnegie Collection of human embryos.[25] Where this is incomplete, early human development is a 'black box' into which we cannot see.[26] This knowledge base can be supplemented and refined in a number of different ways. The current legal framework enables research up to the end of day 14. From around 28 days, scientists can glean information from examining embryos that have been lost in miscarried pregnancies. We might see this an 'obscured window' into human embryo development. A veil of ignorance lies over the period between 15 and 28 days.[27] The time limit on embryo research thus might be fixed not by reference to a developmental stage but by the availability of other sources of information.

The structure of the case for embryo research

Building on these reflections on the origins and functions of the 14-day rule, it is possible to draw out from the debates over human embryo research in the period that led up to the Human Fertilisation and Embryology Act 1990 the structure of any future case for revisiting it. The parliamentary decision constituted a collective conclusion that the prospects for public benefit from embryo research could sometimes outweigh the restraining presumption against it. If legislators were persuaded that this might sometimes be the case, then decisions on individual research projects could properly be delegated to the HFEA. Parliament has already revisited this question in relation to the component of the law relating to embryo research that concerns the permitted purposes, and been persuaded that the prospect of useful scientific knowledge is sufficiently important to justify extending the permitted purposes.[28]

The first limb of any case for changing the 14-day rule would therefore need to be a compelling case that significant scientific gains can reasonably be expected from an extension of the period in which research was permitted. Without such a case, there is no reason to reopen the rule. This case could be based on arguments that we have good reason to think that an extension in the time permitted for research would bring knowledge within our grasp that would enable us to address issues of public importance. It would also be appropriate to show that only extended embryo research can be expected to deliver those benefits.

Those who are concerned about the possibility that the 14-day question should be revisited point to a number of weaknesses in the scientific case. The benefits of extending research further have not been clearly articulated. Critics of existing embryo research raise concerns that it has not delivered the benefits that it promised and counsel about being taken in by hype. They also point out that, until very recently, researchers have only been able to sustain embryos *in vitro* for about seven days. It

may be premature to be thinking about extending the rule until we know more about the period between days seven and 14. The interest in doing so now looks to many critics like a classic example of a 'slippery slope', where regulatory measures that were claimed to curtail a scientific free-for-all are removed as soon as they begin to operate in that fashion.[29] But it is not necessary to be a critic of embryo research to conclude that public confidence in its governance depends on the 14-day rule operating as a real constraint and, if there is to be change, then the scientific case will need to be compelling.[30]

The second limb of such a case would be the identification of a new regulatory constraint that could play the jurisdictional roles identified in the previous section. That is: it needs to be clear enough to provide a workable definition of the powers of the HFEA for the purpose of legal accountability; it needs to be narrow enough to ensure that Parliament retains oversight; finally, it needs to be robust enough to give Parliamentarians confidence that they are not committing themselves to a broader acceptance of research than they are being invited to consider.

Untimely arguments

The explanation of the role of the 14-day rule that was outlined above suggests that some of the arguments about human embryo research that could be made should be disregarded for the purposes of a narrow reconsideration of the rule. These can crudely be summarised as those that argue for two positions that would make the rule superfluous. For those who believe that no research involving human embryos is ever permissible and also to those who believe that no special respect is owed to such embryos, the 14-day rule is merely a tactical device that secured a truce in a deeper clash of values. Our workshop did not seek to engage with that wider debate, although it is noted by a number contributors.[31] It is, of course, difficult to exclude the fundamental question of the status of the human embryo from discussion but our brief was to concentrate on the ways in which it becomes intertwined with arguments addressed more specifically to the 14-day rule itself and any possible replacement. This report is intended to make a contribution to understanding the role and rationale of the rule. If it were decided to revisit the regulation of embryo research, these two positions would need to be given full consideration. It is not necessarily the case that the 14-day rule, or an alternative playing a similar set of jurisdictional roles, would ultimately be considered appropriate if the issue of embryo research were revisited.

A second set of arguments that were outside the scope of this piece of work but that would be relevant to a full reconsideration concern the relationship of the 14-day question to other social currents. We have already noted concerns about 'slippery slope' arguments that are held in some quarters. It is likely that any discussion of the embryo research rules would be affected by public confidence in the integrity of scientists. The experience of recent Parliamentary interventions, such as the developments in the regulation of mitochondrial replacement therapies, would also be

relevant. It is likely, also, that connections would be made between the embryo research debate and discussions about the law on abortion.

For these reasons, and no doubt for others besides, this brief review of the issues is much more narrowly focused than would be required if we were hoping to reach a conclusion on whether it was appropriate to extend the circumstances in which embryo research could be licensed. Nor has our discussion aimed to move towards any recommendation about the form any replacement for the 14-day rule might take. Rather, we have aimed to scope the issues that would need to be examined so that an informed view can be taken on whether this is the correct time to consider a change in the law.

Reflections

In the light of these considerations, the contributions here recognise the scientific value of the recent advances in sustaining embryos (not just human embryos) *in vitro* for longer periods of time. This offers exciting prospects for learning more about embryo development. Our current knowledge of embryo development is much less secure than many might imagine. In general terms, there is reason to think that understanding early embryo development better is likely to shed light on the causes of miscarriage. This is a major cause of distress and unhappiness. However, the workshop did not identify particular reasons for thinking that rapid progress could be made with research into embryos for extended periods. It seems unlikely that Parliament would entertain a change in the law without having a much more clearly articulated scientific case to consider.

The workshop did not set out to establish whether there was a preferred candidate for a new limit for research that could satisfactorily replace the existing one. However, we anticipated that some plausible options would emerge in the discussion. A number of biological markers were identified and there was also some discussion of incremental progression based on time alone. Some possible adaptations to the way in which the rule functioned were raised. It might, for example, be possible to consider extending permissible embryo culture for some or all of the period between 15 and 28 days but only in order to permit observational studies, with interventional research being proscribed during this period. It might be possible to restrict the range of legitimate purposes for any extended period more narrowly than those that currently apply up to the end of day 14. It might also be possible to improve the regulation of embryo research by introducing a principle of economy, equivalent to the ‘refine, reduce and replace’ (3Rs) objective in relation to animal research.[32] These are all valuable observations. There was no consensus as to which approach would be most ethically satisfactory, nor which would be most likely to secure the public acceptance that is widely thought to be the key to the durability of the current 14-day rule.

Insofar as there are conclusions to be drawn from this workshop, it would seem that

there is not at this stage a clear case for change of the sort that would persuade legislators of the need for action, either in relation to the prospect of scientific benefit or in relation to the availability of a satisfactory alternative regulatory tool. The regulation of human embryo research remains an important and interesting bioethical question but it is not clear why the question of the 14-day rule should be regarded as a priority for those charged with developing public policy in the area at present.

Notes

1 Circular HSG(91)5 required the creation of committees by February 1992 in accordance with the guidance in Department of Health (1990) *Local research ethics committees* (London: Department of Health).

2 Warnock M (2004) *Nature and mortality: recollections of a philosopher in public life* (London: Continuum), at page 123; Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), ('Warnock Report'), at paragraphs 11.16-7. (The Committee was chaired by the English philosopher Dame Mary (now Baroness) Warnock.)

3 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents (as amended by the Human Fertilisation and Embryology Act 2008), section 3(4). The original (1991) text was phrased slightly differently: "beginning with the day when the gametes are mixed…" See also: section 4A(3).

4 Session Two of the Workshop considered why this might have been so and how it should be interpreted.

5 Deglincerti A, Croft GF, Pietila LN *et al.* (2016) Self-organization of the *in vitro* attached human embryo *Nature* **533(7602)**: 251-5; and Shahbazi MN, Jedrusik A, Vuoristo S *et al.* (2016) Self-organization of the human embryo in the absence of maternal tissues *Nature Cell Biology* **18(6)**: 700-8.

6 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, at section 3.

7 A further jurisdictional distinction between research and reproductive uses of embryos is discussed in the background paper, see especially paragraph 43ff.

8 On this point more generally, see my early discussion of the regulatory structure created by the Act in Montgomery J (1991) Rights, Restraints and Pragmatism, 54 *Modern Law Review* 524-34.

9 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, at schedule 2 paragraph 3A.

10 ibid, at section 3(4).

11 Synthetic human entities with embryo-like features have been produced in the laboratory using stem cells from somatic tissues; see: Aach J, Lunshof J, Iyer E and Church GM (2017) Addressing the ethical issues raised by synthetic human entities with embryo-like features *eLife* **6**: e20674.

12 *R. v. Secretary of State for Health ex p. Quintavalle (on behalf of Pro-Life Alliance)* [2003] UKHL 13.

13 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, at section 1(6).

14 *Department of Health & Social Security (1984) Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384) (London: HMSO)*, at paragraph 11.1.

15 ibid, at chapter 12.

16 See n.13 (above).

17 Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human*

Fertilisation and Embryology (Cmnd.9384) (London: HMSO), at paragraph 12.7.

[18] ibid, at paragraph 12.8.

[19] The issue of 'arbitrariness' is explored further in the background paper, esp. paras 37, 47-8, in Session One of the workshop report and in the contribution from Dave Archard.

[20] Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at paragraph 11.22.

[21] Kenneth Clarke MP, *Hansard HC deb.,* 23 April 1990 (col.31).

[22] Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at paragraph 11.20.

[23] ibid, at paragraph 11.21.

[24] ibid, at paragraph 11.21.

[25] See especially the background paper paragraphs 7-8, and Julian Hitchcock's contribution.

[26] The Guardian (5 June 2016) *Inside the 'black box' of human development*, available at: https://www.theguardian.com/science/2016/jun/05/human-development-ivf-embryos-14-day-legal-limit-extend-inside-black-box.

[27] See Sheny Chen and Andrew Chisholm's contribution for discussion of what is thought to occur in this period.

[28] Legislation.gov.uk (2017) *The Human Fertilisation and Embryology (Research Purposes) Regulations 2001*, available at: http://www.legislation.gov.uk/uksi/2001/188/contents/made.

[29] See the contribution from David Jones, although he does not use the language and examines the corrosion of public reason and weakening of regulation as different elements of the problem.

[30] See the contributions from Katrien Devolder and Dave Archard.

[31] See especially those from David Jones and Shaun Pattinson.

[32] See the contribution from David Jones for this point.

The statutory time limit for maintaining human embryos in culture

Background paper

Charlotte Elves and Sheelagh McGuinness[*]

Summary

1 Somewhere between person and property, the embryo occupies a liminal space in UK law and challenges foundational legal categorisations of human/ non-human; person/ non-person. The Human Fertilisation and Embryology Act 1990 was enacted to set limits for what it is acceptable to do with and to embryos while at the same time facilitating potentially beneficial embryo research. However, technology in this area develops quickly. This has given rise to various legal challenges as precise statutory definitions were thrown into legal uncertainty by novel techniques which present new ways to create embryos and gametes. Where in the past 'law [might have] turned to medical science to attempt to find that missing certainty'[1] it now seeks to respond to scientific advances which serve to question the certainty of existing legal categorisations. Accordingly, when the 1990 Act was revised and amended in 2008, the regulations needed to not just place limits on what it was acceptable to do with embryos but also needed to pay considerable attention to the thorny question of what embryos are. Lawmakers faced the challenge of drafting legislation which could cope with the fact that '[s]cientifically, 'embryo' is a basket category'[2]. As a consequence, in their review leading to the 2008 Act, the House of Commons Science and Technology Committee[3] proposed a strict definition of an embryo that could be used for reproduction and a more open-ended definition for an embryo used in research.

2 Notwithstanding the broadening of the statutory definition of 'embryo' so that the 2008 amendments facilitate what Hennette-Vauchez describes as a 'conceptual severance'[4] of the activities of reproduction and research, there has been no reconsideration of the statutory time limit for maintaining human embryos in culture currently set at 14 days.

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[*] Dr McGuinness is a Senior Lecturer at the University of Bristol Law School; Charlotte Elves is a DPhil Candidate in the Faculty of Law at the University of Oxford. The authors were commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the authors' own and not those of the Nuffield Council on Bioethics. The authors would like to thank John Coggon, Katrien Devolder, Peter Mills and Jonathan Pugh for thoughtful comments and discussion of an earlier draft of this paper.

3 Following the publication of two articles in *Nature* in 2016, fresh consideration of the '14-day rule' laid out in section 3(3)(a) of the Human Fertilisation and Embryology Act 1990 has been stirred.[5] Researchers at the University of Cambridge and Rockefeller University have sustained human embryos *in vitro* before destroying them in accordance with international guidelines and UK law. While previously the 14-day rule did not stifle research due to the inability to sustain embryos *in vitro* beyond 7–9 days, this is no longer the case. Deglincerti and Shahbazi's findings now provide a viable protocol for the culturing of embryos up to and beyond 14 days, where previously there was none. The significance of such an advance is hard to overstate, but so too is the significance of the limitations the 14-day rule poses to future advances. Although we can only speculate on its potential impacts, the new system for the *in vitro* culture of human embryos allows a previously unattainable understanding of human development post-implantation and human embryogenesis. These recent developments, along with gene-editing techniques such as CRISPR-Cas9, offer real promise in providing insight into early human development capable of aiding research into disorders that result in early pregnancy losses and congenital defects, as well as clinical applications of stem cell research. However, due to the current regulatory framework these research goals are hindered by the prohibitions imposed by section 3(3)(a). Given the current and likely future state of scientific knowledge, and the associated media and public interest, the time is now ripe to revisit the moral and legal status of the primitive streak and the 14-day rule.[6]

Introduction

4 Until recently the '14-day rule' has posed few barriers to research given our inability to maintain embryos in culture beyond 7–9 days.[7] However, this changed when two separate research teams at the University of Cambridge and Rockefeller University developed a protocol for the culturing of embryos *in vitro* up until the 14-day mark.[8] Both labs were able to maintain at least one embryo in culture for 14 days at which point the embryos were destroyed by the team at Cambridge in accordance with section 3(3)(a) of the Human Fertilisation and Embryology Act 1990[9] and, in the case of the Rockefeller lab, in accordance with national guidelines.[10] This technological advancement now raises questions about the continuing utility and justification of the 14-day rule. Before these questions can be answered, or indeed correctly put, it is instructive to understand how the 14-day rule came to be enshrined in law. Once the background and origins of the 14-day rule have been outlined, this paper sets out briefly some of the other questions that are important to a consideration of reopening the debate around the 14-day rule.

The origins of the 14-day rule

5 The14-day rule was first suggested in a report of the Committee of Inquiry into Human Fertilisation and Embryology, 'the Warnock Report'.[11] This Committee of Inquiry was established in 1982 to examine technologies of assisted reproduction and human embryo research. The import of the14-day rule has come to be framed in two quite different ways; the first as a pragmatic compromise between two reasonably contested positions and the second as a rule safeguarding a moral value. The compromise-interpretation will be sketched here, whilst the moral value-interpretation will be sketched below as part of a wider exploration of moral values and the 14-day rule. Post the Warnock Report and prior to the Human Fertilisation and Embryology Act 1990 Margaret Brazier argued:

> "Before endorsing any 14-day limit Parliament should ensure that the consequent violation of what may be a human being is justified by the ensuing advantages to humanity as a whole. The selection of 14 days has to be recognised as a compromise. It would be unfortunate if it proved to be a compromise with which nobody was comfortable."[12]

6 Brazier points to the important role of 14 days; it was a compromise. Compromise in general is an acknowledgement of disagreement rather than agreement and the Oxford English Dictionary defines compromise 'as an intermediate state between conflicting opinions, reached by mutual concession'.[13] Brazier describes how the 14-day rule was a compromise based on *promise* and *proof*. Research until 14 days would be permitted because of the promise of therapies which might result from the research. The unsettled moral status of the embryo meant that there was a burden on the proponents of research to make the case for why research, which necessitated embryo destruction, should be permitted. Brazier points to another important point about this compromise. The point of compromise is to bring sides together and once a compromise no longer achieves this aim, it is redundant.[14] Thus we must ask whether recent scientific breakthroughs destabilise the compromise to the extent that "the ensuing advantages to humanity as a whole" that might now be derived from embryo research beyond 14 days, override previous concerns. Equally, we should ask whether the compromise brokered by the Warnock Committee was only ever acceptable because the rule it stipulated could not be breached. At the time it was introduced it was not possible to keep embryos in culture up until 14 days so the limit did not in reality circumscribe any activities. Further, if we accept the compromise-interpretation of the 14-day rule, and find that its first iteration has indeed been destabilised by recent breakthroughs, we must ask whether there exist new moral considerations that might move to justify the continuance of a compromise position, but for different reasons.

The scientific advances

7 The present state of scientific understanding with regard to early human development is surprisingly limited, referred to by some as the "black box of human development".[15] Current approaches rely on extrapolation from research on the embryonic period for other species and the use of the twenty-three 'Carnegie stages'.[16] The Carnegie stages were developed by studying a collection of human embryos, gathered from the 1880s onwards, and whilst this method has regularly updated its classifications since then, it is still only able to highlight observable morphological changes.[17] Further, research shows that understanding human embryogenesis by extrapolating from the embryonic period of other species may be insufficient, given evidence highlighting significant differences between the species studied and early human embryonic development.[18] For these reasons early human development, particularly around the developmental stage giving rise to the primitive streak and gastrulation, have remained little understood.

8 Culturing embryos up to and beyond the 14-day limit would provide insights into the molecular mechanisms, gene and protein expression that drive the observable morphological changes provided by the Carnegie stages. Such progress represents a significant advance in basic research and brings with it potential therapeutic applications. Studying embryos in culture beyond 14 days would aid research into the causes of infertility and recurrent miscarriage. Given that a key driver for a facilitative approach to embryo research has been the improvement of our understanding of reproduction and improved reproductive outcomes, this line of research is perhaps of particular significance in the context of the 14-day rule.

9 Any potential reconsideration of the 14-day rule must be sensitive to the wider state of scientific understanding and progress. The ability to maintain embryos in culture beyond 14 days could potentially lead to the development of new *in vitro* techniques for assisted reproduction and further understanding of the effects of toxic compounds in embryos.[19] Further, members of the scientific community have questioned whether advances in stem cell research might now lead to definitional difficulties in terms of understanding what constitutes an embryo for the purposes of the 14-day rule.[20] Although the advances achieved at Cambridge and the Rockefeller lab do not impact upon stem cell research directly, it might be anticipated that re-visiting the 14-day rule in the context of embryo research may well have policy implications for stem cell research too. A theme of this paper is a consideration of the wider social and scientific context of debates over embryo destruction and manipulation, and the debates over assisted reproduction.

Moral status and embryos

10 In this section we provide a brief sketch of arguments regarding the moral status of the embryo, paying specific attention to those who argue that moral significance can be attributed to the emergence of the primitive streak. Brazier concisely summarises that '[t]he trouble with the embryo is that… we cannot resolve [its] disputed nature'.[21] The contested status of the embryo is further complicated by the fact that often accounts of what is permissible to do to embryos depend on how the embryo is 'constructed'.[22] As Devolder and Harris explain:

> "Many people may have some respect and care for some kind of protection of the embryo, but these feelings can change and often depend on people's intentions, in particular on whether the embryo is included in a parental project."[23]

11 The moral and legal status of the embryo is something about which agreement is lacking. In relation to the 14-day rule, further difficulties arise, given that we are assessing the moral and legal status at a specific stage of development rather than the entity itself.

12 If something has moral status, then it demands our respect and consideration. Moral status means that something is a member of our moral community.[24] A general definition of what moral status means is suggested by Warren:

> "To have moral status is to be morally considerable, or to have moral standing. It is to be an entity toward which moral agents have, or can have, moral obligations. If an entity has moral status, then we may not treat it in just any way we please; we are morally obliged to give weight in our deliberations to its needs, interests, or well-being. Furthermore, we are morally obliged to do this not merely because protecting it may benefit ourselves or other persons, but because its needs have moral importance in their own right."[25]

13 The principles that should underlie moral status is a vexed question. There is much disagreement about what features give rise to moral status. Even within those groupings that hold with a particular account of moral status, for example personhood, we see much disagreement about the details.[26] In considering moral status we usually start with 'paradigm cases' – those which we are sure have moral status – and extrapolate from these cases to more 'marginal cases'. We may be less clear about those marginal cases where the status of the entity is unclear. It is here, Warren explains, that disagreement can occur:

> "There is, then, substantial consensus about the moral status of those entities which appear to occupy the extreme ends of the spectrum. At one extreme, stones and other inanimate objects are usually presumed to have no moral

> status at all, even though they may legitimately be valued and protected for other reasons. At the opposite extreme, human beings are usually held to have moral status which is at least as strong as that enjoyed by any other entity – or at least any that is part of the natural world."[27]

14 Further, consensus about the nature of moral status does not guarantee agreement over what indeed has this status.[28] It is usually accepted that moral status should depend on intrinsic properties; something has moral status by virtue of its own inherent characteristics. Moral status gives something importance in its own right. The views of others may provide further reasons in our consideration of how to act towards the entity but they do not affect whether it has moral status.[29] When we act towards those things with moral status, then, it is the effects on them that is our concern, not the effects that our actions may have on third parties. For example, our treatment of a seven-year-old child should not be driven purely by the views of that child's parents; it should rather be guided by the fact that the child in and of herself has moral status. The child is the type of thing that demands our consideration. The views of the child's parents may grant us additional reasons to act or avoid acting in certain ways, but only insofar as they are consistent with treating the child as a being with moral status.

15 A distinction has been made between moral status and moral value. Moral value is a weaker concept than moral status. That which has moral value need not have moral status. A thing's having moral value may give us reasons for acting in certain ways but it does not move us in the same way that moral status does. For instance, the child's view of her pet tortoise may give that tortoise added moral value but it will not give it moral status. When we consider the principles that underpin moral status this distinction becomes clearer. Some features may be sufficient for moral value without giving rise to an account of moral status. Moral value is subjective and need not be based on the intrinsic properties of an entity. In the tortoise example we see how the child's affection for the tortoise may give that tortoise a value it would otherwise not have. When we consider moral value it will not act as a trump card in terms of how we act towards an entity; it may simply give us pause. Legally it seems that some acceptance of 'value' has been transposed into the legal concept of 'respect', however what this means in practice is vexed.[30] This is summarised by Jackson in the following statement:

> "There is some debate over whether it makes sense to talk about treating embryos that are to be used in research, and will subsequently be destroyed, 'with respect'. Mary Warnock herself has said that she now regrets using the word 'respect', because 'you cannot respectfully pour something down the sink', and that it would be more accurate to refer to the 'non-frivolity' of legitimate embryo research (in Hansard, 2002: col. 1327)."[31]

16 It could be argued that embryos have an important moral value as a scarce resource which can be used for good ends.[32] Arguments against waste and for respecting those ends may give us good reason to act towards the embryo in certain ways. It could be argued then that the value of an embryo is 'realised' in its use for experimentation. If this is the case it may impact on perceptions of the permissibility of an extension to the 14-day rule, if this gives rise to possibilities in the future that fewer embryos will need to be destroyed in the course of research.[33]

17 While it is true that it is difficult to explicate what the notion of respect might mean this is not reason for rejecting it as a useful concept. It could simply be that embryo destruction is a wrong but one that might be outweighed by other considerations.[34] This would mean that all instances of embryo destruction or manipulation need to be justified. Such a position seems to fit with the current approach to regulation in this area. Adopting this approach to the regulation of embryo research provides the basis upon which diverging views can be accommodated and consensus maximised. Aiming to achieve absolute consensus on an area such as embryo research is futile; instead as Warnock noted we must: "necessarily be[en] mindful of the truth that matters of ultimate value are not susceptible of proof".[35]

Moral significance of the 14-day rule

18 A number of scholars have written on the moral significance of the primitive streak in embryo research, but it is perhaps Persson who offers the most thorough account.[36] Persson argues that the formation of the primitive streak constitutes the first developmental stage at which the embryo can develop into a more complex organism which can plausibly be nothing other than a human being. This is not true of the embryonic structures existing before the formation of the primitive streak. Until the blastocyst forms at day four-to-five post-conception, the existing cell mass consists of an organism that goes on to form separate entities in the form of the fetus, the placenta, and the amniotic sac. As Persson frames it, the post-primitive streak embryo possesses a *bearer-preserving potentiality*, which the embryo prior to the development of the primitive streak lacks.[37] In elucidating this concept, Persson explains that many potentialities are obviously bearer-preserving, much like the potentiality of a small child to grow to be over six feet tall as an adult, because as Persson explains, it is the individual that once was a child that is now above six feet.[38] As such, it can be argued that the appearance of the primitive streak demonstrates the first point in embryonic development at which it could be said that a potential human being exists.

19 Even if it can be said that the 14-day rule coincides, deliberately or otherwise, with the stage at which some argue a potential human exists, designations of moral status or weaker ascriptions of moral value need not automatically follow from such a conclusion. For some, that the post-primitive streak embryo can be said to belong to the class of 'human being' will be enough to imbue it with moral status

sufficient to designate its destruction absolutely morally impermissible.[39] For others however,[40] the mere fact that an entity belongs to the class of human being is insufficient to confer moral status. Rather, as Persson argues:

> "[T]he special intrinsic value of human beings resides in the fact that most of them are *persons*, that is, beings with advanced mental powers, such as self-consciousness and rationality, rather than in their species membership."[41]

20 As such, the post-primitive streak embryo, as an entity lacking all of the above capabilities, is considered by many to be without moral status, but rather the subject of a weaker ascription of moral value. On this assessment, whilst owing to the embryo's moral value there may be a presumption that destruction is morally impermissible, other values may mean that destruction is permissible in certain circumstances. For example, the benefits that embryo research might provide could be one such justification.

21 However, it is important to note that the 14-day rule does not protect the embryo from destruction but rather ensures destruction at a certain point in time.

Clash of meta-ethical approaches: consequentialism vs dignitarianism

22 A nation's flag may be considered to be of sufficient symbolic importance that destroying it in certain ways is a criminal offence. This does not mean that the law is there to protect the flag *qua* flag (as an object with a specific function) but rather the reason for protecting the flag is that it has symbolic value.[42] The flag's symbolic value exists in its representation of the values, beliefs, culture etc. of a group, community, or nation. Destroying, damaging or altering the flag does not necessarily change the form, nature or characteristics of future flags. Nor is it obvious that destroying, damaging or altering the flag will change social attitudes towards, or perceptions of flags *per se.* When the flag is damaged what we worry about is something more abstract, such as the denigration of cultural identity, social cohesiveness or the values and beliefs that the flag represents. With regard to embryos, the research that might proceed should the 14-day rule be extended may well have the ability to alter, damage or lead to the destruction of embryos grown in the lab, but also has the potential to alter the germ line of future embryos, intentionally or otherwise.

23 Here we want to consider the way in which accounts of 'moral value' may guide our assessment of the (im)permissibility of different scientific activities. We draw on the Nuffield Council on Bioethics' account of 'transformative potential' to situate the impacts of scientific advances not just within the technological realm but also to highlight the scope for broader potential societal transformation. The Council defines 'transformative potential' as:

> "The capacity that some emerging biotechnologies may have to transform or displace existing social relations, practices and modes of production, or create new capabilities and opportunities that did not previously exist, or may not even have been imagined. These outcomes might be entirely unexpected or unsought."[43]

24 Whilst there is a high degree of uncertainty in this context with regard to the transformative potential of research performed on post-primitive streak embryos, it seems that other branches of embryo research and biotechnology more generally might offer some relevant lessons. We highlight the possible future use of CRIPSR-Cas9 gene editing techniques in human embryos beyond 14 days should the 14-day rule be extended.

25 In 2016 the Human Fertilisation and Embryology Authority (HFEA) granted a research group at the Crick Institute a licence to use CRISPR-Cas9 genome editing in human embryos in order to further understand early human development, pregnancy failures and birth defects.[44] In recent years CRISPR has replaced previous gene editing techniques with a more precise, easier to use and cheaper alternative. Applications of CRISPR have led to many new discoveries, just one example being the development of CRISPR-Cas9 gene drives. In relation to mosquito-borne disease, CRISPR-Cas9 gene drives are in theory capable of superseding not just previous gene drive techniques but also other forms of vector control, e.g. pesticides.[45] This is just one example of new technology creating new opportunities not contemplated at the point of its initial development.

26 The use of cheap, simple and precise gene editing technologies such as CRISPR-Cas9 only increases this possibility. Such technologies may affect societal norms surrounding early human development and scientific intervention. The symbolic value assessment is relevant, but there are deeper issues. It is perhaps possible to be completely accepting of the destruction of a 25-day old embryo (for example) but still object to the extension of the 14-day rule, on the basis that we cannot possibly understand the consequences of research in this area – i.e. at the moment we need to be as concerned with what we do not know, as what we do know.

27 Inherent to the ethical underpinnings of regulation of embryology has been an attempt to balance these potential benefits of research against a level of respect for embryos. As such it could be argued that an ethical distinction exists between the possibility of culturing embryos past the appearance of the primitive streak in order to better understand early human development on the one hand, and the genetic manipulation of post-primitive streak embryos in order to develop therapeutics on the other. It is the distinction between research aims and therapeutic aims that brings the clash of meta-ethical approaches into sharp relief.

Consequentialist approaches may find the pursuit of therapeutics morally preferable to basic research. On a utilitarian calculation we might find that the use of gene editing to erase the autosomal dominant mutation that causes Huntington's chorea provides a far greater net benefit than an improved academic understanding of embryo development. Conversely, a dignitarian approach might find no violation of human dignity to have been committed by the destruction of a post-primitive streak embryo studied to gain a greater insight into early embryogenesis but sees a gross violation of dignity in respects of the genetic manipulation of the same embryo.[46]

28 When we consider issues of legal and moral status, we must be aware that much of what we are considering occupies a grey area in evaluative terms.[47] Devolder and Harris have argued that the embryo is an essentially ambiguous entity and that this means that there is little utility in ascribing moral value to embryos at a policy level:

> "We, humankind, must accept that human embryos are deeply ambiguous and problematic entities of a kind whose lives or ''dignity'' simply cannot be protected in ways consistent with other values that we hold."[48]

29 Here Devolder and Harris signal towards a consideration of more general factors that might contribute to assessments of the moral value of the post-primitive streak embryo.[49] The first is social attitudes and public perception of the moral permissibility of research on, and the destruction of, embryos. Whilst public views (or indeed the views of different 'publics') might present conclusions that diverge from the philosophical positions posited above, we must still ask whether they offer a genuine moral intuition. Further, we might ask whether public consensus, irrespective of the conclusions it provides, holds a relevant moral value in this context. If it were to be the case that the majority public opinion believed moral status to be instantiated at the appearance of the primitive streak, further questions might be raised about the moral value of that majority opinion in and of itself, in the vein of discussions centring on public reason and democracy.

From ethics to law and policy

30 In this final section of the paper we wish to highlight the pragmatic way in which the law has evolved in the area of embryology. Specifically, we draw from some of the literature on 'public ethics' to consider the nature of the deliberative approach that has been adopted in the regulation of assisted reproduction and embryology in the UK.[50] Public ethics, according to Jonathan Montgomery, "aspires more to acceptability than to philosophical neatness. … [M]embers of committees can adopt conclusions for a variety of reasons, which may be mutually inconsistent, provided they give a basis from which policy can be developed."[51] It

could be argued that a pragmatic approach or 'muddling through' is a hallmark of British policy making in the area of biotechnology.[52] Therefore, any reconsideration of the 14-day rule must be assessed in accordance with the aims it was originally sought to achieve.

31 Sarah Franklin notes the position that the UK finds itself in with regard to regulation of biotechnologies:

> "Britain has in many respects been at both the center and the forefront of the controversies surrounding a cluster of new technologies associated with reproductive biomedicine, not only because so many "firsts" were born in Britain but also because it has played a more substantial role than any other country in the creation of rigorous legislation and policy strictly limiting technological manipulation of human fertilisation and embryology."[53]

32 In comparison to other countries, the UK adopts a permissive approach to the regulation of assisted reproduction and embryo research. Current regulations are not underpinned by any particular moral principle although several are important. Legislation attempts to encapsulate a compromise that 'respects' the embryo while at the same time facilitating scientific advances; this is especially true in respect of the 14-day rule.[54] As noted above, 'respect' for the human embryo has, since the Warnock Report, been considered a central aspect of the regulations although there are no explicit guidelines as to what 'respect' may mean.

33 The lack of a unitary moral underpinning of the regulation of embryology and assisted reproduction has led many to criticise existing regulations. However, criticisms notwithstanding, the current framework is widely acknowledged as successfully navigating a tricky path between facilitation of research and acknowledging the deeply held concerns that many people hold regarding embryo destruction.[55] Many of the 'morally arbitrary' cut-off points that exist in the law relating to the prenatal human are ethically defensible as an aspect of regulation of a morally controversial area. If we really wish for regulation that is underpinned by a singular ethical position or principle then we would have to change the process of policy making and certainly this would constitute a significant shift in the approach adopted in the UK to date. As the Warnock Report stated:

> "Although questions of when life or personhood begin appear to be questions of fact susceptible to straightforward answers, we hold that the answers to such questions are in fact complex amalgams of factual and moral judgements. Instead of trying to answer these questions directly we have therefore gone straight to the question of how it is right to treat the human embryo."[56]

34 In the context of regulating embryo research, it should be noted that a major feature of the HFEA's activity includes public consultation on how regulation

should evolve.[57] There are many issues beyond morality at play in the debate over how we should regulate embryology. A glance through the ethical literature shows that there are many and varied positions on the legitimacy of embryology and assisted reproduction. The literature contains arguments which extend far beyond questions about the moral status of the embryo. This has led Ronald Green to describe the embryo as an 'epiphenomenon'.[58] The moral status of the embryo is genuinely disputed and there is room for reasonable disagreement between the varying accounts. But even if there were a 'winning account' of the moral status of the embryo, we still would not have a single guiding principle for how we should regulate the area. There would be many more questions to answer. John Harris was one of many critics of the approach taken by the Warnock Committee, believing that the committee 'fudged' its answering of the difficult ethical questions about the moral status of the embryo.[59] However, a 'fudge' may not be as problematic ethically as it first appears, as we will now explain.

Gradualism and arbitrary cut-off points

35 Once we move away from arguments which suggest that moral status is an absolute concept at either end of the developmental spectrum, a logical alternative approach is to suggest that moral status develops gradually.[60] Gradualism is a useful approach to take to moral status in a policy sense as it can accommodate compromises. It allows for the value of the embryo to balance against the prospects of new therapies and the interests of those in need of these therapies. The following quotation highlights that this is the approach adopted by the Warnock Committee:

> "The majority of the Committee was not moved by the argument that these cells could, if certain conditions were satisfied, become human beings. They did not rely, that is to say, as the minority did, on "potentiality", but on the consideration of what the embryo was at a particular time, its actual mode of existence immediately after fertilisation."[61]

36 Gradualism refers to a theory of moral status which states that the moral value of embryos increases with their biological development.

37 Arbitrary lines can helpfully delineate levels of protection along the spectrum of development from conception to birth. The Irish Council for Bioethics explains the logic of the relationship between these arbitrary lines and gradualism:

> "[M]any people holding a gradualist view of moral status think that there are indeed criteria that allow additional moral status to be assigned at specific times during the course of embryonic development, even though the exact points at which this occurs will necessarily be, to a certain degree, arbitrary. Plato discussed this view in his presentation of "the fallacy of the beard". One might

> argue that there is no sharp distinction between a clean shaven man and a man with a full beard because at every point in between the two there is the tiniest increment of length of hair. In Plato's view, this argument is weak and there is a discernible difference between the two states of clean shaven and bearded. Plato, therefore, suggests that we should be able to make reasonable judgements to delimit stages or phases within continuous processes." [62]

38 This quotation shows how apparently arbitrary lines may be justified in the regulation of embryology, assisted reproduction, and abortion.

39 Gradualism allows that the value of the embryo be weighed against other considerations. As mentioned at the start of this paper, Brazier suggests two standards by which the permissibility of embryo research can be considered: (i) is there a realistic promise of therapies / scientific breakthrough in this area?; and (ii) is it a cut-off point with which most are happy? The first of these standards is facilitated by a gradualist approach to the value of the embryo. This standard allows for the value of the embryo to be considered but weighed against the interests of those who might benefit from therapies derived from stem cells. It can do this without needing to default to the view that the embryo has no moral value. This allows for compromise to be reached between divergent positions. It facilitates the aim of respecting the human embryo in accordance with its moral value. Again this was an approach was endorsed by The Irish Council for Bioethics:

> "[T]he moral status of the embryo can be discussed as an absolute, *i.e.* an "on/off" situation, or it can be seen in gradual terms. In the latter case, the moral value of the embryo is not necessarily equivalent to possessing full moral status and may be balanced against other values. Similarly, when it comes to determining those elements of our humanity that we value, there will, undoubtedly, be some that we consider absolutely inviolable and others which are seen to be valuable, yet can at times be balanced against other interests. … On consideration of the various arguments relating to the moral status of the embryo, the Council adopts a gradualist position, granting significant moral value rather than full moral status to human embryos. The moral value they are seen to possess is based on recognition of their potential to develop into persons, as well as the value they derive from representing human life in its earliest stages."[63]

40 The Warnock Committee provided the following justifications for the necessity of cut-off points in the law on embryology and assisted reproduction:

> "While, as we have seen, the timing of the different stages of development is critical, once the process has begun, there is no particular part of the developmental process that is more important than another; all are part of a

> continuous process… thus biologically there is no single identifiable stage in the development of the embryo beyond which the *in vitro* embryo should not be kept alive. However we agreed that this was an area in which some precise decision must be taken, in order to allay public anxiety."[64]

41 When considering 'morally arbitrary' cut-off points in the law we see that the importance of these cut-off points is immense and most of them can be justified in a morally sound way (although the points themselves are apparently morally arbitrary).[65] A dominant theme to emerge from regulation of embryo research since Warnock has been the desire of legislators 'that regulation of assisted conception techniques and the use of *in vitro* embryos be acceptable to the general public'.[66] When we consider 'arbitrary' cut off points in law we must examine them against the background within which they came into existence; specifically the role they play in producing legitimacy or delivering public acceptability. Warnock summarises this approach as follows:

> "An absolutely central consideration in the work of [the] committee… was the difference between what one might personally think was sensible, or even morally right, and *what was most likely to be acceptable as a matter of public policy*… Time and again we found ourselves distinguishing not between what would be right or wrong, but between what would be acceptable or unacceptable."[67]

42 In assessing the utility of the 14-day rule, then, it is important to consider the role that it plays in public acceptance of embryo research and assisted reproduction. Here we are not seeking to guess at the attitudes of the public; that would require careful empirical work. Rather our focus is on some of the conceptual work the 14-day rule performs in delineating the boundaries between regulating reproduction and research.

Reproduction v. research

43 Embryos exist in a liminal position between reproduction and research.[68] One important function of the 14-day rule is the extent to which it is has provided a marker that delineates these activities. Brazier observed a key driver for the regulation of embryo research was facilitative and an attempt to ensure that such research would be seen as legitimate:

> "Unregulated embryo research was simply not an option, paradoxically because Warnock and ultimately the majority of Parliament favoured permitting such research. Regulation was the price for ensuring the 'legitimacy' of such research. Thus to ensure those opposed to embryo research could not undermine that 'legitimacy', any procedure which involved creating an embryo must fall within the jurisdiction of the 'legitimating' authority."[69]

44 The 14-day rule becomes important in this context as it becomes symbolic in the attribution of a particular legal categorisation.[70] Regulatory responses, of which the 14-day rule is one, attempt to shore up important legal categories. Current legislation incorporates a functionalist account of the embryo: that is, the legal protections afforded to the embryo are dependent on our intentions towards it.[71] 'Reproductive' function serves to protect principles which underpin how we treat the broader category of 'the unborn' in law and attendant legal principles such as 'sanctity of life'. 'Research' function facilitates treatment of the embryo as more akin to 'property' but also wider aims of law in this area to be permissive towards and facilitate biotechnological research and advances.

45 There are also important pragmatic reasons for maintaining a distinction between reproductive ethics and experimental ethics and this can be seen to provide a sound justification for the 14-day rule. Opponents of embryo research often perpetuate groundless scare stories about 'half human half animal' monsters or Frankenstein monsters.[72] There is strong rhetorical force in being able to point to the 14-day rule as a cut-off point that draws boundaries between research and reproduction.[73]

46 As a compromise position that has come to be relied on by both researchers and policy makers it seems that the rule will endure until a convincing case is made for changing it. This is a position endorsed by many groups.[74] Consider the following statements relating to using Human Admixed Embryos [HAE] in research.[75] The first comes from a briefing document prepared in 2008 by the Academy of Medical Sciences, the Medical Research Council, the Royal Society, and Wellcome to inform MPs about the importance of research involving HAE. The second comes from the government response to points raised about HAE in a report from the House of Commons Science and Technology Committee:

> "Including all four types of HAE in the legislation ensures that there are robust safeguards to regulate research. [HAE] production and use for research is only permissible under licence from the HFEA and subject to strict safeguards that prohibit development beyond 14 days and implantation into an animal or woman.[76]
>
> "However, we agree with the Committee that there would need to be strong legal safeguards on such research, in particular that they could not be implanted in a woman and that they must be destroyed within 14 days."[77]

47 These statements evidence the way in which the permissive underpinning of the current regulation of scientific experimentation on embryos is facilitated by the 14-day rule rather than hindered by it. The 14-day rule should be (and is) treated as a 'living' aspect of regulation in this area. It exists at present as a compromise

position whose legitimacy was earlier distilled from Brazier's quote. It is a compromise that is constantly under review and if a convincing case were put forward for why it should be extended or reduced then this is something that Parliament can consider.[78] Those who criticise the arbitrariness of the 14-day rule miss the point: the apparent arbitrariness in this instance is not problematic. It is a line in the sand that represents compromise and can be changed by primary legislation when necessary. This compromise position is in line with the acceptance by many in the scientific community that embryo research is a morally thorny area and is worth pursuing provided that the possible benefits of research outweigh the negatives associated with embryo destruction. Warnock stated that:

> "We recommended, for reasons set out in the report, a limit of fourteen days. The point was not however the exact number of days chosen, but the absolute necessity for there being a limit set on the use of embryos, in terms of a number of days from fertilisation. In this way the law would be clear. If the limitation on research were set in terms of stage of development or the capacity of the embryo to feel pain, then these limits might be subject to dispute. If the limit is in terms of days, on the other hand, this is a simple matter of counting, and there can be no dispute. This was the reasoning of the Committee."[79]

48 So arbitrariness was considered acceptable as long as both sides of the compromise sat in equilibrium. The question is whether the compromise is now destabilised.

49 An important point to consider here is how the law has evolved in regard to how embryos are defined and whether the 14-day rule is still necessary to quell fears about 'Frankenstein' science.[80] The 1990 Act contained the following definition: '[a]n embryo means a live human embryo where fertilisation is complete'.[81] Problems emerged as technological advances, such as cell nuclear replacement, gave rise to new ways of creating embryos. The HFEA's remit was subject to judicial challenge[82] as questions were raised about whether these entities were in fact embryos and whether they were 'human'.[83] Consequently, it was decided that amendment to the 1990 Act would offer an open-ended definition better equipped to accommodate scientific advances in embryology to 'future-proof' the Authority's remit against litigation.[84] In the lead-up to the 2008 amendments the House of Commons Science and Technology Committee[85] proposed a strict definition of the type of embryo that could legally be implanted into a woman (a "permitted embryo") and an alternative open-ended definition of what constituted an embryo in the research context ("unpermitted"). Thus the 2008 Act enshrines a distinction between permitted and non-permitted embryos.[86] Hennette-Vauchez has described this as a 'conceptual severance' between the activities of reproduction and research.[87] Given this conceptual severance, it could be argued that the importance of the 14-day rule is now diminished.

Future discussions of the 14-day rule

50 The Warnock Report describes the formation of the primitive streak as "heaping-up of cells at one end of the embryonic disc on the fourteenth or fifteenth day after fertilization".[88] The report notes that the appearance of the primitive streak designates the last point at which twinning might occur, and, furthermore, demonstrates the first of several identifiable features developing on the embryonic disc, in rapid succession after the 14-day mark.[89]

51 The primitive streak develops on the blastula, the oval shaped embryonic disc, no longer than fifteen days after fertilisation. Cell migration along the primitive streak causes gastrulation to occur, with the embryo taking the form of a three-layered oval disc. These three germ cell layers are the endoderm, the mesoderm and the ectoderm. The endoderm contributes to the gastrointestinal and respiratory tract, the mesoderm forms connective tissues and muscle tissue and the ectoderm forms the nervous system and the epithelial layer of skin covering the embryo. In the seven days that follow the appearance of the primitive streak, a number of changes take place. At day 18 to 19 the neural plate develops from the ectoderm, folding to form the neural grove, before fusing and forming the neural tube – widely understood to be the origin of the central nervous system, from which the brain and spinal cord develop. At around the 19-day mark, the first signs of haematopoiesis occur, haematopoiesis being the formation of blood cellular components. All current understanding of embryonic development noted here, has been established through the study of the Carnegie collection and extrapolation from research on non-human organisms. Recent research also suggests that along with the origins of central nervous system development, the embryo's first 'heartbeat' may occur in the days following the formation of the primitive streak. The presence of a heartbeat formed one point of consideration for the Human Embryo Research Panel in the United States when they made the recommendation for the 14-day limit in embryo research, adopting reasoning similar to that in the Warnock Report. The Panel noted that the presence of a heartbeat was one of a number of factors that form the physical basis for future sentience.[90] Unlike the report of the Human Embryo Research Panel, the Warnock Report made no mention of any purported moral significance of embryonic heartbeats. A paper published in *eLife* in October 2016 found that whilst most previous research places the presence of the first heartbeat at 22 days post-fertilisation, evidence now exists to suggest that the heartbeat may occur as early as 16 days post-fertilisation.[91] Thus, whilst the presence of a heartbeat may have few consequences for determinations of moral status, policy makers may need to be aware of attendant social attitudes in this regard, when considering the extension of the 14-day rule.

52 Any amendment of the 14-day rule would require an amendment to an Act of Parliament. The 2008 amendments do not allow for the possibility of changing this

cut-off point through regulation. Advances in the science of embryology have an impact on the regulation of abortion and it is likely that debating the extension of the 14-day rule will reignite the abortion debate once again.[92] The Warnock Report provided an opportunity to capitalise on the unease which many felt towards embryo research in order to garner more support for the anti-abortion cause. The apparent connection between approaches to abortion and embryology has been explored by Sheldon.[93] Sheldon argues that the mistake made by people who view abortion and embryology as ethically 'essentially' the same is that they are asking the wrong questions in each case.[94] This conflation of the two questions is, Sheldon highlights, driven by a view that two biologically identical entities should be treated the same regardless of 'geography'; i.e. regardless of whether the embryo is located in a woman's body or outside of it. Thus, in debating the extension of the 14-day rule at the policy level, players must be aware of the attendant implications for the politics of the abortion debate. This is not to say that the existence of such implications should stifle or restrict discussion of the 14-day rule, but rather that policy makers should be attentive to the ramifications of change in this arena for other areas of law and public policy.

53 Lindemann Nelson suggests that the Warnock Committee "took its task to be one of description and interpretation, to identify, rather than to constitute, social sentiment – or social sentiment as it would be if properly informed – insofar as that was possible."[95] Such an approach, he argues, may give less morally pure answers and allow moral positions to be compromised for the sake of consensus, but in doing so it aims to balance the interests of competing parties. This highlights an important fact about groupings such as the Warnock Committee: ethics is but an aspect of policy-making. When there is uncertainty over moral questions then a compromise must be found. Any reopening of the debate around the 14-day rule will need to balance a range of competing interests. Here we have sought to sketch out some of the contours of such a policy discussion.

Notes

1 Brazier M (2012) Can English law accommodate moral controversy in medicine? The case of abortion, in *Bioethics, Medicine and the Criminal Law Volume 1. The Criminal Law and Bioethical Conflict: Walking the Tightrope*, Alghrani A, Bennett R, and Ost S (Editors) (Cambridge: Cambridge University Press), at page 198.

2 Franklin S (2010) Response to Marie Fox and Therese Murphy *Social & Legal Studies* **19(4)**: 505.

3 House of Commons Science and Technology Committee (2005) *House of Commons Science and Technology Committee: Human Reproductive Technologies and the Law - Fifth Report of Session 2004–05*, available at: https://publications.parliament.uk/pa/cm200405/cmselect/cmsctech/7/702.htm, ibid

4 Hennette-Vauchez S (2009) Words count: how interest in stem cells has made the embryo available - a look at the French law of bioethics *Medical Law Review* **17(1)**: 52-75.

5 Deglincerti A, Croft GF, Pietila LN *et al.* (2016) Self-organization of the in vitro attached human embryo *Nature* **533(7602)**: 251-4; and Shahbazi MN, Jedrusik A, Vuoristo S *et al.* (2016) Self-

organization of the human embryo in the absence of maternal tissues *Nature Cell Biology* **18(6)**: 700-8.

6 The Guardian *It's time to extend the 14-day limit for embryo research*, available at: https://www.theguardian.com/commentisfree/2016/may/06/extend-14-day-limit-embryo-research; and Hyun I, Wilkerson A and Johnston J (2016) Embryology policy: Revisit the 14-day rule *Nature* **533**: 169-71.

7 Hyun I, Wilkerson A and Johnston J (2016) Embryology policy: Revisit the 14-day rule *Nature* **533**: 169-71

8 Deglincerti A, Croft GF, Pietila LN *et al.* (2016) Self-organization of the in vitro attached human embryo *Nature* **533(7602)**: 251-4; and Shahbazi MN, Jedrusik A, Vuoristo S *et al.* (2016) Self-organization of the human embryo in the absence of maternal tissues *Nature Cell Biology* **18(6)**: 700-8.

9 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, at section 3(3)(a).

10 National Institutes for Health (1994) *Report of the Human Embryo Research Panel* (Bethesda, Maryland: National Institutes for Health).

11 Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO).

12 Brazier M (1988) Embryos' rights: abortion and research, in *Medicine ethics and law: current legal problems*, Freeman M (Editor) (London: Stevens), at page 16.

13 See: http://www.askoxford.com/concise_oed/compromise?view=uk

14 See also Montgomery J (1991) Rights, restraints and pragmatism: the Human Fertilisation and Embryology Act 1990 *The Modern Law Review* **54(4)**: 524-34.

15 The Guardian (5 June 2016) *Inside the 'black box' of human development*, available at: https://www.theguardian.com/science/2016/jun/05/human-development-ivf-embryos-14-day-legal-limit-extend-inside-black-box.

16 Hill MA (2007) Early human development *Clinical Obstetrics and Gynecology* **50(1)**: 2-9.

17 embryology.med.unsw.edu.au (2017) *Carnegie Collection*, available at: https://embryology.med.unsw.edu.au/embryology/index.php/Carnegie_Collection.

18 Enders AC, Schlafke S and Hendrickx AG (1986) Differentiation of the embryonic disc, amnion, and yolk sac in the rhesus monkey *American Journal of Anatomy* **177**: 161-85; and Luckett WP (1978) Origin and differentiation of the yolk sac and extraembryonic mesoderm in presomite human and rhesus monkey embryos *American Journal of Anatomy* **152(1)**: 59-97.

19 Reardon S (2016) Human embryos grown in lab for longer than ever before *Nature* **533(7601)**

20 Pera MF, de Wert G, Dondorp W *et al.* (2015) What if stem cells turn into embryos in a dish? *Nature Methods* **12(10)**: 917-9.

21 Brazier M (1988) Embryos' rights: abortion and research, in *Medicine ethics and law: current legal problems*, Freeman M (Editor) (London: Stevens); at page 15.

22 See further Fox M (2000) Pre-persons, commodities or cyborgs: the legal construction and representation of the embryo *Health Care Analysis* **8(2)**: 171-88; and McGuinness S (2012) The construction of the embryo and implications for law, in *Stem cells: new frontiers in science & ethics*, Quigley M, Chan S, and Harris J (Editors) (Singapore: World Scientific).

23 Devolder K and Harris J (2007) The ambiguity of the embryo: ethical inconsistency in the human embryonic stem cell debate *Metaphilosophy* **38(2-3)**: 153-69.

24 Bortolotti L (2007) Disputes over moral status: philosophy and science in the future of bioethics *Health Care Analysis* **15(2)**: 153-8.

25 Warren MA (1997) *Moral status: obligations to persons and other living things* (Oxford: Clarendon Press).

26 Consider the different accounts developed by Harris J (1985) *The value of life: an introduction to medical ethics* (New York: Routledge); Tooley M (1983) *Abortion and infanticide* (Oxford: Oxford University Press); and Singer P (1993) *Practical ethics* (Cambridge: Cambridge University Press).

[27] Warren MA (1997) *Moral status: obligations to persons and other living things* (Oxford: Clarendon Press), at page 5.

[28] See the commentary by Williams M (2004) An ethics ensemble: abortion, Thomson, Finnis and the case of the violin-player *Ratio Juris* **17(3)**: 381-97 on Thomson JJ (1971) A defense of abortion *Philosophy & Public Affairs* **1(1)**: 47-66; and Finnis J (1973) The rights and wrongs of abortion: a reply to Judith Thomson *Philosophy & Public Affairs* **2(2)**: 117-45.

[29] Harman E (2007) Sacred mountains and beloved fetuses: can loving or worshipping something give it moral status? *Philosophical Studies* **133(1)**: 55-81.

[30] See also recent Human Tissue Authority Guidance which in a similar vein requires that fetuses be disposed of respectfully: Human Tissue Authority (2015) *Guidance on the disposal of pregnancy remains following pregnancy loss or termination*, available at: https://www.hta.gov.uk/sites/default/files/Guidance_on_the_disposal_of_pregnancy_remains.pdf

[31] Jackson E (2006) Fraudulent stem cell research and respect for the embryo *BioSocieties* **1(3)**: 349-56.

[32] Devolder K (2005) Creating and sacrificing embryos for stem cells *Journal of Medical Ethics* **31(6)**: 366-70.

[33] Savulescu J, Pugh J, Douglas T and Gyngell C (2015) The moral imperative to continue gene editing research on human embryos *Protein & Cell* **6(7)**: 476-9.

[34] Hare RM (1988) When does potentiality count? A comment on Lockwood *Bioethics* **2(3)**: 214-26.

[35] Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at page 2.

[36] Persson I (2003) Two claims about potential human beings *Bioethics* **17(5-6)**: 503-17.

[37] ibid, at pp509-13.

[38] ibid, at page 510

[39] For a detailed consideration of this point see Human Fertilisation and Embryology Authority (2006) *"And if the body were not the soul...": the status of embryos created artificially from human and non-human components* available at: http://webarchive.nationalarchives.gov.uk/20130402210658/http://www.hfea.gov.uk/2124.html

[40] See also Singer P (1993) *Practical ethics* (Cambridge: Cambridge University Press).

[41] Persson I (2003) Two claims about potential human beings *Bioethics* **17(5-6)**: 503-17, at page 509.

[42] Steinbock B (1992) *Life before birth: the moral and legal status of embryos and fetuses* (Oxford: Oxford University Press), at page 166.

[43] Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: Technology, Choice and the Public Good*, available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/Emerging_biotechnologies_full_report_web_0.pdf, at page 40.

[44] The Francis Crick Institute (2016) *Use of CRISPR-Cas9 genome editing technique in human embryos*, available at: https://www.crick.ac.uk/research/a-z-researchers/researchers-k-o/kathy-niakan/hfea-licence/.

[45] Hammond A, Galizi R, Kyrou K *et al.* (2016) A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae Nature Biotechnology* **34(1)**: 78-83.

[46] For detailed discussion of dignity based arguments see Brownsword R and Beyleveld D (2001) *Human dignity in bioethics and biolaw* (Oxford: Oxford University Press); Brownsword R (2003) Bioethics today, bioethics tomorrow: stem cell research and the dignitarian alliance *Notre Dame Journal of Law, Ethics and Public Policy* **17(1)**: 15; Deryck Beyleveld D and Pattinson SD (2004) Globalisation and human dignity: some effects and implications for the creation and use of embryos, in *Global governance and the quest for justice - Volume 4*, Brownsword R (Editor) (Oxford and Portland, Oregon: Hart Publishing), at pages185-202.

[47] This paper was a response to Harris J (1983) *In vitro* fertilization: the ethical issues (I) *The Philosophical Quarterly (1950-)* **33(132)**: 217-37. For Harris's reply to the reply see Harris J (1985) Full humans and empty morality *The Philosophical Quarterly (1950-)* **35(138)**: 70-3.

[48] Devolder K and Harris J (2007) The ambiguity of the embryo: ethical inconsistency in the human embryonic stem cell debate *Metaphilosophy* **38(2-3)**: 153-69, at page 163.

[49] See further Devolder K (2015) *The ethics of embryonic stem cell research* (Oxford: Oxford University Press), at Chapter 5.

[50] Montgomery J (2013) Reflections on the nature of public ethics *Cambridge Quarterly of Healthcare Ethics* **22(1)**: 9-21.

[51] ibid, at page12

[52] See further Jasanoff S (2007) *Designs on nature: science and democracy in Europe and the United States* (Princeton, New Jersey: Princeton University Press); and Wilson D (2014) *The making of British bioethics* (Manchester: Manchester University Press), particularly at Chapter 4. The idea of 'muddling through' in regulation of embryos is considered fully in Fox M and McGuinness S (2015) The science of muddling through: categorising embryos, in *Pioneering healthcare law: essays in honour of Margaret Brazier*, Stanton C, Devaney S, Farrell A-M, and Mullock A (Editors) (London and New York: Routledge), at pp199-210.

[53] Franklin S and Roberts C (2006) *Born and made: an ethnography of preimplantation genetic diagnosis* (Princeton, New Jersey: Princeton University Press), at page 2.

[54] See House of Commons Science and Technology Committee (2005) *Inquiry into Human Reproductive Technologies and the Law - Eighth Special Report of Session 2004–05*, available at: https://publications.parliament.uk/pa/cm200405/cmselect/cmsctech/491/491.pdf. In this report an amendment is made to the House of Commons Science and Technology Committee (2005) *House of Commons Science and Technology Committee: Human Reproductive Technologies and the Law - Fifth Report of Session 2004–05*, available at: https://publications.parliament.uk/pa/cm200405/cmselect/cmsctech/7/702.htm. This amended text leaves out reference to the principled underpinning to law in this area.

[55] Scott R (2007) *Choosing between possible lives: law and ethics of prenatal and preimplantation genetic diagnosis* (Portland, Oregon: Hart Publishing), at page 256.

[56] Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at Chapter 11.

[57] Montgomery J (1991) Rights, restraints and pragmatism: the Human Fertilisation and Embryology Act 1990 *The Modern Law Review* **54(4)**: 524-34.

[58] Green RM (2008) Embryo as epiphenomenon: some cultural, social and economic forces driving the stem cell debate *Journal of Medical Ethics* **34(12)**: 840-4.

[59] Harris J (1983) *In vitro* fertilization: the ethical issues (I) *The Philosophical Quarterly (1950-)* **33(132)**: 217-37. Mary Warnock replied with Warnock M (1983) *In vitro* fertilization: the ethical issues (II) *The Philosophical Quarterly (1950-)* **33(132)**: 238-49. For Harris's reply to the reply see Harris J (1985) Full humans and empty morality *The Philosophical Quarterly (1950-)* **35(138)**: 70-3.

[60] Lockwood M (1988) Warnock versus Powell (and Harradine): when does potentiality count?* *Bioethics* **2(3)**: 187-213, at page 189.

[61] Warnock M (Editor) (1985) *Question of life: the Warnock report on human fertilisation and embryology* (Oxford: Wiley-Blackwell), at page xv.

[62] See page 35, The Irish Council for Bioethics, (2008) *Ethical, scientific and legal issues concerning stem cell research - Opinion*, available at: http://health.gov.ie/wp-content/uploads/2014/07/Ethical_Scientific_Legal_Issues1.pdf'

[63] ibid, at page 41.

[64] Warnock M (Editor) (1985) *Question of life: the Warnock report on human fertilisation and embryology* (Oxford: Wiley-Blackwell), at page 65.

[65] Holm S (1996) The moral status of the pre-personal human being, in *Conceiving the embryo: ethics, law, and practice in human embryology*, Evans D, and Pickering N (Editors) (The Hague, London, Boston: Martinus Nijhoff Publishers), at pp198-99.

[66] Callus T (2007) Patient perception of the Human Fertilisation and Embryology Authority *Medical Law Review* **15(1)**: 62-85, at page 62.

[67] Mary Warnock as quoted in Franklin S and Roberts C (2006) *Born and made: an ethnography of preimplantation genetic diagnosis* (Princeton, New Jersey: Princeton University Press), at page 5.

[68] See further Fox M and McGuinness S (2015) The science of muddling through: categorising embryos, in *Pioneering healthcare law: essays in honour of Margaret Brazier*, Stanton C, Devaney S, Farrell A-M, and Mullock A (Editors) (London and New York: Routledge), at pp199-210

[69] Brazier M (1999) Regulating the reproduction business? *Medical Law Review* **7(2)**: 166-93, at page 188.

[70] See further Marie Fox M and McGuinness S (2015) The science of muddling through: categorising embryos, in *Pioneering healthcare law: essays in honour of Margaret Brazier*, Stanton C, Devaney S, Farrell A-M, and Mullock A (Editors) (London and New York: Routledge), at pp199-210.

[71] Mulkay M (1994) The triumph of the pre-embryo: interpretations of the human embryo in parliamentary debate over embryo research *Social Studies of Science* **24(4)**: 611-39, at page 634.

[72] The Times (24 March 2008) *Embryology Bill: Bishop's 'Frankenstein' attack smacks of ignorance, say scientists*, available at: https://www.thetimes.co.uk/article/embryology-bill-bishops-frankenstein-attack-smacks-of-ignorance-say-scientists-grtpqsr5ddx.

[73] Agar N (2007) Embryonic potential and stem cells *Bioethics* **21(4)**: 198-207.

[74] Wellcome Trust, (2005) *Response to Department of Health: Review of the Human Fertilisation and Embryology Act: a public consultation* available at: http://webarchive.nationalarchives.gov.uk/20100407210813/http://www.dh.gov.uk/en/Consultations/Responsestoconsultations/DH_4132358

[75] See further on this point Fox M (2000) Pre-persons, commodities or cyborgs: the legal construction and representation of the embryo *Health Care Analysis* **8(2)**: 171-88; Marie Fox M (2009) Legislating Interspecies Embryos, in *The legal, medical and cultural regulation of the body: transformation and transgression*, Smith SW, and Deazley R (Editors) (Farnham: Ashgate).

[76] Brief on the Human Fertilisation and Embryology Bill Amendments relating to Clause 4 'Human Admixed Embryos' Prepared by the Academy of Medical Sciences, the Medical Research Council, the Royal Society and the Wellcome Trust, available at: https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2008/7938.pdf

[77] HM Government (2005) *Government response to the report from the House of Commons Science and Technology Committee: Human Reproductive Technologies and the Law* available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/272164/6641.pdf.

[78] ibid.

[79] Warnock M (Editor) (1985) *Question of life: the Warnock report on human fertilisation and embryology* (Oxford: Wiley-Blackwell), at page xvi.

[80] Clare Williams C, Kitzinger J and Henderson L (2003) Envisaging the embryo in stem cell research: rhetorical strategies and media reporting of the ethical debates *Sociology of Health & Illness* **25(7)**: 793-814, at pp797-798.

[81] Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, at section 1.

[82] For an overview of the litigation see Johnson MH (2006) Escaping the tyranny of the embryo? A new approach to ART regulation based on UK and Australian experiences *Human Reproduction* **21(11)**: 2756-65.

[83] See further Human Fertilisation and Embryology Authority (2006) *"And if the body were not the soul...": the status of embryos created artificially from human and non-human components* available at: http://webarchive.nationalarchives.gov.uk/20130402210658/http://www.hfea.gov.uk/2124.html

[84] See paragraph 53, HM Government (2007) *Government response to the report from the Joint*

Committee on the Human Tissue and Embryos (Draft) Bill, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/243182/7209.pdf.

85 House of Commons Science and Technology Committee (2005) *House of Commons Science and Technology Committee: Human Reproductive Technologies and the Law - Fifth Report of Session 2004–05*, available at: https://publications.parliament.uk/pa/cm200405/cmselect/cmsctech/7/702.htmo.

86 Schedule 3ZA in Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents

87 Hennette-Vauchez S (2009) Words count: how interest in stem cells has made the embryo available - a look at the French law of bioethics *Medical Law Review* **17(1)**: 52-75, at page 54.

88 Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at paragraph 11.5.

89 ibid.

90 National Institutes for Health (1994) *Report of the Human Embryo Research Panel* (Bethesda, Maryland: National Institutes for Health), at page 39.

91 Tyser RCV, Miranda AMA, Chen C-m *et al.* (2016) Calcium handling precedes cardiac differentiation to initiate the first heartbeat *eLife* **5**: e17113.

92 Mulkay M (1997) *The embryo research debate: science and the politics of reproduction* (Cambridge: Cambridge University Press), at page 18.

93 Sheldon S (1997) *Beyond control: medical power, women and abortion law* (London: Pluto Press), at Chapter 6.

94 Harman E (2007) How is the ethics of stem cell research different from the ethics of abortion? *Metaphilosophy* **38(2-3)**: 207-25.

95 Nelson JL (2005) The Baroness's Committee and the President's Council: ambition and alienation in public bioethics *Kennedy Institute of Ethics Journal* **15(3)**: 251-67, at page 258.

Statutory time limit for maintaining human embryos in culture

Report of the workshop

Introduction

1 In December 2016 , the Nuffield Council on Bioethics hosted a workshop of invited guests to explore the ethical considerations involved in altering or maintaining the current statutory time limit for maintaining live human embryos in culture (the '14-day rule').

2 The meeting, chaired by Professor Jonathan Montgomery, was held in accordance with the Chatham House rule, under which what was said may be freely reported but not ascribed to named individuals, and this summary takes the same approach. Each session was introduced by one or more participants, followed by open discussion; key points are summarised below under the session headings, organised by theme rather than the order in which they were made. It should not be assumed that all those present agreed with all the points made.

Session one: Setting the scene – challenges and opportunities

This session began with a presentation delivered by one of the participants. This presentation pulled out and developed the key themes of the background paper. Following the presentation, responses were invited.

3 There are three contexts that must be taken account of when considering the future of the 14-day rule: the social context; the political context and the scientific context. This approach echoes the approach taken by other academics in their discussion of the original debates around the time of the 1984 Report of the Committee of Inquiry into Human Fertilisation and Embryology (the 'Warnock Report'). When considering the social context around the time of the Warnock Report a relatively sanguine public attitude towards embryo research and assisted reproduction becomes apparent. For instance, with regard to IVF therapies the birth of the first 'test tube' baby, Louise Brown, in 1978 was a positive media story. In the 1980s, there was a noticeable change in the broader political atmosphere. Following the election of Margaret Thatcher and the Conservative government there was a rise in rhetoric surrounding the ideals of family life and a 'return to Victorian values'. It is within this social and political context that the Warnock Report must be situated. In responding to the social and political context of the time, the Committee chaired by (then) Dame Mary Warnock and comprising trusted experts and the great and the good was formed. The pervasive rhetoric in the current political climate rejects experts and the notion of expertise and that is

just one starting point for considering the current political and social context of this debate.

4 In the current political context, it should be asked whether there is the political appetite for looking at specific questions – such as the status of the 14-day rule or whether at present a wholesale review of the legislation in this area would be more favourable in the eyes of politicians and policy makers. If the latter is the case, it must be considered whether such an approach is appropriate and what opportunity costs such a review might entail. It has to be recognised that such a review might not necessarily lead to more liberalised reform.

5 In terms of the scientific context, the background paper notes the potential influence that CRISPR technologies might have on this debate. Another relevant consideration here is the impact of mitochondrial donation policy. The decision by the Human Fertilisation and Embryology Authority (HFEA) to permit mitochondrial donation is either scientific progress or a slippery slope, depending on one's values and beliefs. These events can be seen either as instances of scientific progress or signs that the regulation can be shifted as necessary. The mitochondrial donation case is an important example of this because, in the original framework, the prohibition on germ line intervention was seen as an important 'red line' that has now been shifted.

6 One might question why a limit is needed. Many agree that the 14-day rule is arbitrary but necessary: it is a rhetorical device that allows us to point to something concrete where otherwise it might not be possible to do so. However, if this concrete point is shifted or moved or altered in any way, one might have to wonder whether it will hold the same force in future.

7 There are three possible ways to think about the time limit provided for by the 14-day rule.

- The first is to think that there is some sort of moral value attached to embryos and that the 14-day rule is a reflection of that moral value. However, the function of the time limit is to mandate the destruction of the embryo, so it is hard to say that it reflects a particularly strong estimation of intrinsic moral value. One might say that, because one of the promises of this area is better understanding of early pregnancy loss and that fits well within the original aims of the legislation, an extension of the 14-day rule might lead to less embryo wastage in future. In that way, it might be said that the rule does reflect some sort of moral value.

- The second is to suggest that the 14-day rule should be thought about from the standpoint of public acceptability. In the absence of a time limit, research would not be acceptable. Whether that is the case is a straightforward empirical claim that could be tested. What is, perhaps, more difficult to ascertain (but arguably

more interesting) is what impact any change to the 14-day rule might have on public perceptions of science.

- The third way to think about the 14-day rule is from the legal perspective. For lawyers the 14-day rule is interesting because it enables them to contain an entity that has a somewhat liminal status. At a recent conference organised by the Progress Educational Trust a participant asked: "If I can make embryos with my own skin cells, are they my property or are they embryos?" This question highlights the difficulty the embryo presents to the foundational legal categories of property and person. Research is traditionally perceived to concern itself more with property, whilst reproduction sits within the personhood-based frameworks. If we think about the legal provisions laid down in relation to 'permitted embryos' since 2008, we might conclude that they indicate a conceptual severance of some sort that makes the 14-day rule less important than it was previously.

8 Finally, the issue of uncertainty, and how it might be addressed should be considered. One option to consider is whether it would be possible to have a 'twin track' approach to regulation: the 14-day rule could be retained for interventional activities, but you remove the time limit, or have an extended time limit for observational research activities.

Responses

9 One participant suggested that the difference between arguments for clarity and arguments about arbitrariness should be flushed out because any discussion of the 14-day rule risks conflating the two. For instance, Baroness Warnock (as she now is) has argued that there is value in setting a limit that is easy to measure, but discussing the value associated with a measurable limit is quite different from discussing whether that limit is sensible. In response, another participant argued that Warnock would object to any suggestion that the 14-day rule was arbitrary – the limit was chosen for specific reasons. These reasons ranged from considerations of moral theory to issues of policy and pragmatism. This argument led some to suggest that time must be spent disentangling different aspects of the historical context of the 14-day rule. It was suggested that these strands encompass the scientific knowledge and political realities of the time, as well as the dominant philosophical and moral frameworks of the era.

10 Moving away from the discussions of arbitrariness, one participant suggested that there is a need to consider where research embryos come from. These embryos are generally not created for the purpose of research but rather are surplus IVF embryos that would otherwise be destroyed. However, the issue of fetal research is often not discussed. Fetuses used in research are gathered following termination of pregnancy and the participant suggested that one should ask why

the rules and regulations that were being discussed do not apply to fetal tissue – a tissue that is more developmentally advanced than embryonic tissue. It was submitted by that whilst this was an interesting point being flushed out elsewhere, it was not central to the theme of this workshop.

11 Challenging the historical view offered above, one participant suggested that it was not the case that IVF was a generally well-received technology. Further, with regard to issues surrounding the relevance of the source of embryos, it was suggested that this was not a concern for the HFEA in the early days – the concern was only that embryo research *per se* was acceptable.

12 In drawing the first session to close, participants reflected on what it means to think about the status of the specific embryo being used for research as opposed to the status of embryos more generally. It was suggested that when thinking about these issues, we should not lose sight of the fact that the way we treat embryos may be taken to reflect the nature of our respect for human life and the views that we project as a society.

Session two: What has the current limit achieved?

The purpose of this session was to discuss what having the limit has achieved in terms of providing a socially and scientifically acceptable arrangement (both having a limit and having the limit set at 14 days) and began with a detailed presentation on the technique for maintaining embryos in culture up to 14 days.[*]

13 One contributor highlighted the fact that the 14-day rule was first posited before the Warnock Report, by the National Institute for Health Advisory Board in the United States in 1979. This board originally considered three possible rules: no research, research until sentience and research until implantation (14 days). This contributor went on to assert that aside from the science the rule has enabled, the rule has been important for public policy, and further questioned whether the rule would continue to be as effective as a policy tool if it were changed.

14 In response, another participant asked whether the rule has been a success as a policy tool because it has functioned as a ‘ceasefire’ or because it succeeded in reconciling a multiplicity of values. Answering the question, one participant said they thought that whilst some groups accepted the rule with ‘quiet resignation’, for the majority it created a settlement that they could happily defer to. This narrative fiction was said to be the idea that before the 14-day mark what exists is not a human being, and so the period prior to 14 days is neutral territory. Further, if the debate were to be reopened, one would have to consider what the new narrative

[*] See individual contribution from Magdalena Zernicka-Goetz (below)

would be. Adding to that, another participant suggested that, in the Christian tradition, notions such as ‘quickening’ (where the fetal movement is felt by the mother) simulate the narrative fiction being discussed. One participant advised that despite various disagreements between scholars in the Islamic tradition with regard the status of the embryo, Islamic scholars are able to agree that the existence of the rule is positive in that it reassures and enables dialogue between groups. Another participant suggested that by virtue of its legislative status, the rule was designed to attract the views of ‘swing voters’ who would not otherwise support embryo research. The rule, it was suggested, like those governing controls, licensing and inspection in animal research, buys the confidence of people who are unaware of the precise details of laboratory research. Expanding on that view, someone else spoke about public opinion in the United Kingdom as both a condition and a consequence of the regulatory system here; progressive or deferential public opinion both makes a regulatory solution possible and is confirmed by effective regulatory experience. A contrast was drawn between the situation in the United States and the United Kingdom, and it was suggested that the higher level of public confidence here is attributable to the thorough regulatory process.

15 The consensus reflected the view that, although it is unclear whether the 14-day rule reconciled all the different values expressed, it was successful as a policy that enabled scientific progress whilst also ensuring public confidence in both research and the regulatory system.

Session three: How would a new limit affect scientific opportunities?

This session was designed to discuss what scientific opportunities might be available if the limit were to be extended (or lost if it were not).

16 Opening the discussion, one participant outlined a number of benefits of this research including advances in regenerative medicine and biology, better understanding of epigenetics, cell signalling and how to control the fate of cells. It was suggested that all these avenues of progress would ultimately contribute to the development of various clinical therapies. Other possible benefits include a better understanding of the causes and prevention of neural tube defects and the effects of teratogens. In response to the possible benefits being discussed one participant expressed concerns about whether these benefits were deliverable. This participant highlighted concerns about hype around research that, if undeliverable, could damage public confidence in the long term. Taking this into account, it was suggested that before extending the rule beyond 14 days, scientists should first deliver on the promises of research within the scope of the 14-day rule. Responding, a number of participants argued that the idea that science can somehow reach an upper limit of understanding [i.e. a complete

understanding of everything up to 14 days] was incompatible with the scientific method. It was further suggested that an increase of knowledge *per se*, which would surely follow from research beyond 14 days, should be considered a benefit in and of itself.

17 One participant asked whether the benefits that re-drawing the limit might entail could in future be used to justify research on living fetuses. A number of participants responded that such research is very far from being a reality and likely to be unnecessary given that research can be performed on fetuses donated following terminations of pregnancy.

18 It was queried whether attempts to tackle all of the previously mentioned research goals might result in science spreading itself too thinly and ultimately achieving very little. It was suggested that such an effect might result from a lack of scientific capacity, a lack of resources and / or a lack of expertise. With regard to a possible lack of resources and capacity another participant pointed out that new findings often attract new funding opportunities.

19 One participant questioned the merits of taking the benefits of research into account when making policy decisions. It was argued that, at the time of the Warnock Report, the Committee did not attempt to quantify the good that might flow from embryo research. This may have been because if one allows ideas relating to benefits to factor into the decision making process, one is confronted with an incommensurability problem: no common scale is available against which the benefits of such research as well as the perceived risks might be measured, so that weighing such factors against each other in order to reach a conclusion is impossible.

Session four: The moral and policy significance of developmental thresholds

This session was designed to discuss the significance of developmental thresholds.

20 One participant highlighted that there are a variety of positions one might adopt with regard to the moral status of the embryo, full moral status or mere 'vicarious' value being just two of those positions. It was said that the most common view, and the one that is projected in both the Warnock Report and in the current regulatory framework, is that the embryo has proportionate value, which grows as the embryo develops. Further, the current law that developed from the Human Fertilisation and Embryology Act 1990, which modified the Abortion Act 1967, delineates four thresholds: conception, implantation, 24 weeks gestation and birth. However, the law does not elucidate the rationale for treating the embryo and developing fetus differently in each of the three periods (conception to implantation, implantation to 24 weeks and 24 week to birth) between these

thresholds or why increasing protection is bestowed upon the growing embryo. In this area, moral theory does not map onto political theory or policy. In raising this, it was also recalled that the Warnock Report reflects an amalgam of arguments in support of the 14-day rule and it is important to ask, in each case, whether these arguments still hold. In response, one participant argued that it was unhelpful to talk about the moral status of 'the embryo' as if it were a single homogenous thing – people assign moral status differently depending, for example, on whether they consider it as the product of fertilisation, or as a potential human being. Further, some queried what effect the divergence between *in vitro* and *in vivo* development might have on any attempt to elaborate a thorough account of moral status. It was also suggested that in trying to divine useful thresholds, one might also look to changes in the imputed embryo's interests as important markers. A discussion about our ability to tie moral evaluations to developmental markers ensued, with a number of participants arguing that attributions of moral value should be far more epistemologically complex than mere developmental or biological markers. In this vein, notions of extrinsic value, value derived from various environmental or contextual factors and symbolic value were mooted. One participant noted that Islamic scholarship draws a distinction between 'life' and 'personhood': whilst life begins at conception, the acquisition of personhood happens later (although there is much debate regarding the exact point at which personhood begins).

21 A second participant spoke to the difficulties of a proportionate or gradualist account of moral status of the embryo referring to the sorites paradox (a philosophical paradox of vagueness), as well as problems of incommensurability of different considerations. This participant argued that the Warnock Report expressly avoided any attempt to weight the different values at stake. Further, there was some discussion of the position in Warnock as a compromise. It was suggested that unlike most compromises observed in economics and the behavioural sciences, the Warnock Report offered a 'moral compromise'. By their very nature, it was argued that moral compromises are more complex than non-moral compromises and the picture was further complicated by arguments about whether moral discourse should be a 'sovereign' discourse.

22 One contributor recalled the analogy to the symbolic value of flags, discussed in the background paper. It was suggested that the point raised by the flag analogy was that making permanent alterations to embryos (as might be a possibility should the 14-day rule be extended) might lead to changes in the perception of ourselves and our humanity. As such, this risk calls for pause and caution in handling these issues. In response, it was suggested that whilst notions of symbolic or expressive value are very important, they are, nonetheless, socially constructed. That being the case, although there may be real risks involved with changing a thing irreversibly, we should be careful not to reify or reinforce views that should not be reified or reinforced.

23 With regard to arguments about ensoulment (the process by which, in some faith traditions, the soul is thought to enter the developing fetus), one participant questioned whether ensoulment was a useful category for reconciling the exogenous features that give an embryo moral value and the intrinsic features that might enable us to say something more categorical about the moral status of the embryo.

Session five: International context and implications

The purpose of this session was to discuss the significance of international consensus or consistency of principles.

24 One participant, drawing on the example of mitochondrial donation in Mexico, raised the risk of indirect knock-on effects. They argued that we should not consider the United Kingdom to be an automatic baseline for what a good regulatory system looks like – there are different sets of cultural norms and risk profiles across different countries and we have to be aware and sensitive to that. Taking all of those things into account, the participant suggested that we must be careful not to try to shape public opinion to give licence to science but rather we should have science reflect public opinion and social consensus. In response, another participant suggested that, whilst we should not think about the United Kingdom as a baseline, realistically we might have to think about it as a frontrunner and, in turn, we must think about how our regulation might affect other countries that have adopted the 14-day rule. It was further suggested that when thinking about credibility within the wider community, rigorous processes and regulation can be a very effective means of gaining credibility. A good example of rigorous processes granting credibility were said to be the stringent animal research regulations.

25 A second participant raised the issue of arguments that favour doing research here, on the basis that the research will be performed elsewhere but potentially under laxer regulation. The participant noted that, whilst this was often an extremely attractive form of reasoning, it is potentially very disingenuous. In certain contexts, it may well be more virtuous to avoid performing certain sorts of research altogether. Picking up on that theme another participant questioned whether a backlash against regulation in another country might influence our course of action. Other participants noted the risk of a ‘race to the bottom’ and knock-on consequences such as a ‘brain drain’. However, countering this it was said that well-regulated research environments often attract rather than repel highly skilled researchers and that there are good historical examples of scientists calling for more regulation rather than less.

26 In concluding the session, it was agreed that the following points were in need of further consideration: Where does the UK want to be placed? Where do we wish to place ourselves in terms of our bioethics credibility? How do we negotiate the risk of brain drain?

Session six: Reviews of interests engaged

The purpose of this session was to identify the key interests at stake in this discussion and how they might find expression or be engaged in any continuing or further initiative.

27 Opening the discussion, one participant suggested that patients and family members who might be aided by research beyond 14 days should be considered the main interested parties. However, it was countered that, unlike in the case of mitochondrial donation, there are no easily identifiable groups of individuals likely to benefit. Further, it was questioned what significance should be attached to the interests of UNESCO or the signatories of the Oviedo Convention. In response, a number of participants suggested that public opinion in the United Kingdom was a more crucial concern than the views of international organisations. Responding to this claim, one participant asked whether the discussion was beginning to concern itself with populism i.e. ascertaining and building on majority public opinion, rather than the range of views that might actually be available. It was reiterated that it is the Nuffield Council's job to listen to and address the views of all interested parties.

Session seven: Conclusions and representations

28 In conclusion, it was said that, in terms of the possible scientific benefits that might be achieved should the 14-day rule be re-visited, a case pointing to specific advances (such as those promised by mitochondrial donation) could not yet be made. Some participants suggested that while the scientific case had not been made out effectively in the present meeting it could still, potentially, be made by others in other contexts. There had been a good amount of lively discussion surrounding the ways different biological or developmental thresholds might be connected to regulatory or moral norms. It was felt that nothing novel had been drawn out of these discussions, as compared to the discussions that might have been had following the publication of the Warnock Report. Further, it was agreed that this workshop had highlighted that the international context was perhaps both more important and more complicated than it had been in the 1980s at the time the Warnock Committee was convened.

Individual contributions

When they were invited to attend the workshop, prospective participants were asked to submit a short written contribution (of approximately two pages) to inform discussion and for publication along with the record of the meeting. The brief was to raise, from their personal perspective, what they regarded as the most significant points to consider in discussing the 14-day rule. All submissions received in time were collated and circulated to all participants prior to the workshop, and some participants were invited to expand on their submissions at particular points during the proceedings.

After the workshop, contributors were invited to revise their submissions for inclusion in the present publication if they wished to do so. A number of other people who declined our invitation to attend the meeting or who had to withdraw at short notice made valuable and informative submissions via correspondence, both before and after the workshop. Some of these are also included below.

Academic and professional affiliations are as stated at the time of submission.

Human development between 14 and 28 days

Chiann-Mun (Sheny) Chen and Andrew Chisholm[*]

> *"It is not birth, marriage or death, but gastrulation, which is truly the most important time of your life".* Lewis Wolpert 1986.
>
> *"To those familiar with the mouse gastrula, the human embryo at this stage may seem like an alien landscape".* Eakin and Behringer in *Gastrulation*, 2004, (ed. Claudio Stern).

Proposals to extend the current 14-day statutory limit on human embryo culture have suggested revised limits of 21 or 28 days, with the rationale that a better understanding of weeks three and four of development would be of high biomedical significance. Weeks three and four are well established as the onset of critical susceptibility periods to teratogens and other environmental stresses. Here we summarise events of the third and fourth weeks of human development and outline the potential relevance of research on this period for human health.

The third week of development is dominated by gastrulation, the cell movements by which the three germ layers of the embryo are formed. The formation of the primitive streak marks the beginning of gastrulation. The primitive streak is the term used in vertebrate development for the region of cell thickening resulting from migration and proliferation of epiblast cells. The first signs of the primitive streak appear at about 15 days, hence the 14-day limit is also known as the primitive streak rule. Over the course of the third and fourth weeks, cells that have migrated through the primitive streak establish the inner germ layers of mesoderm and endoderm.

By 19 days, the neural plate, the first structure of the future central nervous system to develop, is visible. The major morphogenetic event of the fourth week is neurulation: the formation of the neural folds and their closure and fusion, thereby shaping the neural plate into the neural tube. Neural tube closure occurs over the fourth week and is not complete until day 30. Other major cell movements in the fourth week are the migration of neural crest cells and the segmentation of the mesoderm into somites.

The heart is the first major organ to become functional in the embryo. The primitive heart tube forms by the middle of the third week and is thought to pump blood by day 24-25. A recent study of mouse heart development implies that coordinated contractions ('the first heartbeat') may be slightly earlier than previously thought.[1]

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[*] Dr Chen is Senior Portfolio Developer at Wellcome; Professor Chisholm is Head of Cellular and Developmental Sciences at Wellcome.

Neurulation is the process by which neural progenitors are positioned in the developing embryo, prior to neuronal differentiation and circuit formation. At 28 days, the developing spinal cord is devoid of synaptic connections. The first differentiated neurons with synaptic connections are not seen until late in the fifth week (34-36 days). The first reflex arcs are not believed to function until the seventh week. Thus, nervous system function and any potential sensory capacity are unlikely to exist until the seventh or eighth week.

The above summary is based on historic collections of embryos from procedures such as ectopic pregnancies or hysterectomies. More recent collections such as the Human Developmental Biology Resource contain embryos from 26 days onwards.[2] A general picture of the events of the third and fourth weeks can be inferred from other mammals, although it is increasingly recognised that early development of different mammalian groups (in particular rodents) can be highly divergent. At present it is unclear to what extent other mammalian models (rabbit, pig and nonhuman primates) are accurate models for the events of weeks three to four in the human embryo.

A key rationale for studies of weeks three and four is that the developmental events in these stages are entirely distinct from the processes of blastula formation and implantation in weeks one and two, and therefore are of unique interest for understanding the genetic and environmental basis of birth defects. The study of birth defects (teratology) established the concept of critical stages of susceptibility to teratogens or environmental influences. The period of three to eight weeks covers the stage of maximum sensitivity to teratogens; critical periods for the nervous system and heart begin in week three. Neural tube defects result from failure in closure of the neural folds during weeks three to four and represent one of the most common types of congenital abnormality. The third and fourth weeks are especially vulnerable to maternal alcohol or other drug use, as the mother may not be aware of the pregnancy until after four weeks. Besides these common birth defects, the early embryonic environment is also increasingly recognised as influencing many aspects of subsequent post-natal health. The ability to study embryos during weeks three and four would illuminate mechanisms of known genetic or environmental teratogens, allow tests of additional teratogens, and catalyse the development of potential therapies.

Notes

1 Tyser RCV, Miranda AMA, Chen C-m *et al.* (2016) Calcium handling precedes cardiac differentiation to initiate the first heartbeat *eLife* **5**: e17113

2 hdbr.org (2017) *The MRC-Wellcome Trust Human Developmental Biology Resource (HDBR)*, available at: http://www.hdbr.org/

A need to expand our knowledge of early development

Magdalena Zernicka-Goetz[*]

We know a great deal about the development of mammalian embryos prior to their implantation into the womb because they can be easily maintained in culture. To study such early development, we use the mouse as an experimental model because mouse embryos are relatively easy to maintain, we possess genetics tools to study them and therefore transgenic animals can be readily made. Before the embryo implants into the womb it has to develop three tissue types: the pluripotent epiblast that will make all tissues of the foetus as well as two extra-embryonic tissues, the primitive endoderm and the trophectoderm that will make the yolk sac and the placenta, respectively, but also guide the development of the epiblast after implantation.

However, what happens upon implantation has been unknown because the embryo becomes hidden from view and inaccessible for experimentation. To overcome these hurdles, my laboratory has spent the past five years developing methods for culturing mouse embryos through the implantation stages.[1] These have revealed an amazing ability of the pluripotent lineage of cells, the epiblast, to self-organise into rosettes of cells in response to signals from the extra-embryonic tissues. We can now finally reveal the dynamic interactions between the three tissues that allow the embryo to establish the basic form of the embryo and where its major body axis (head and tail) will be (Fig. 1).

Encouraged by these successes, we wished to adapt this method to culture human embryos in a similar way until gastrulation. There was so much to learn; whereas mouse embryos had been difficult to study through these stages, the study of human embryos had been impossible. In fact, most of our knowledge came through extrapolation from findings with monkey embryos. Now, with the permission of patients from IVF clinics, we were in a position to take unwanted embryos, which otherwise would have been destroyed, and attempt their culture in a dish.

Why did we want to do this? In part because defects in implantation represent one of the major causes of pregnancy loss with IVF embryos, which fail to implant in 30-70 per cent of cases. Secondly, we wanted to learn about our own development. The basic body shape is determined soon after implantation and we wanted to follow the first transformation of the cells that will form the future organism. This is the most enigmatic and difficult stage of embryo development and we wanted to know whether, like mouse embryos, human embryos could self-organise and develop through the implantation stages in a dish in the absence of maternal tissues. Finally, these studies would also give invaluable insight into the biology of the different stem cell types in the

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embryo, giving us new capabilities of using such cells for therapy in regenerative medicine.

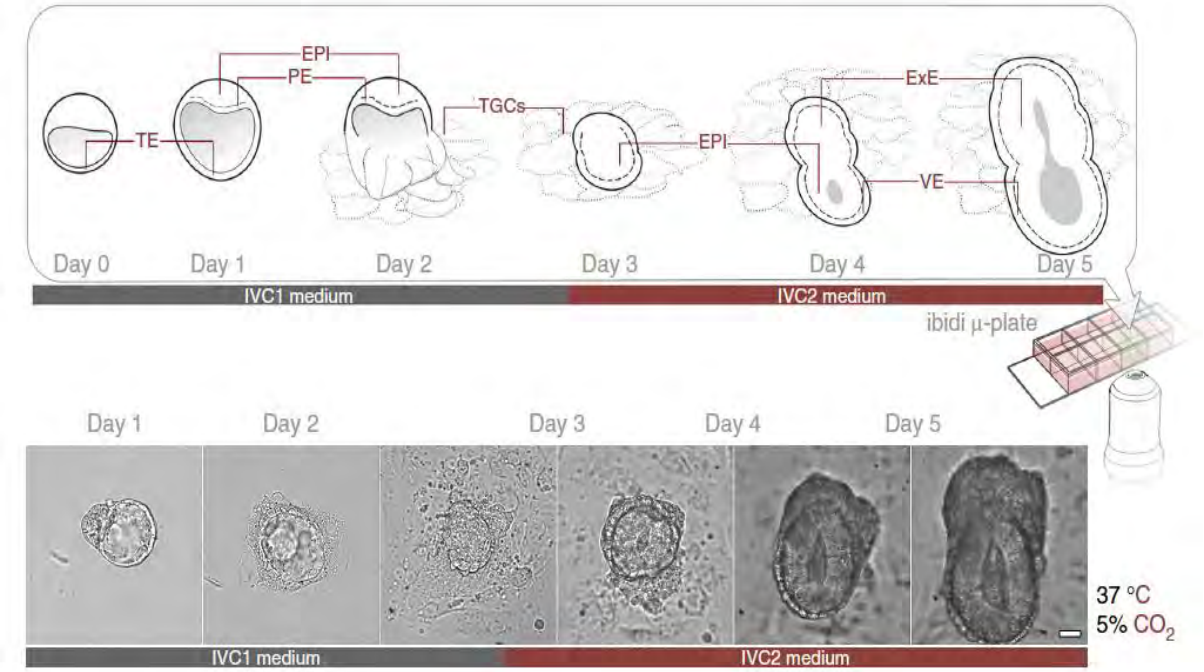

Figure 1. Culture of mouse embryos from the blastocyst to the egg cylinder stage
These procedures were first developed by Magdalena Zernicka-Goetz's team[2] using a hydrogel support for the blastocysts and medium supplemented with human umbilical cord serum. Subsequently we have developed a synthetic medium to allow development without the cord serum or the hydrogel support.[3]

We were uncertain what would happen, because although human and mouse embryos look very similar at the blastocyst stage, they go on to develop different morphologies – the mouse embryo develops into an elongated cup-shaped structure whereas the human embryo develops as a disc. We set ourselves a set of five specific criteria that we needed to achieve to demonstrate that development was following its normal course (Fig. 2). First, the segregation of the epiblast and primitive endoderm lineages from the inner cell mass of the blastocyst. Second, the formation of the pro-amniotic cavity within the pluripotent cells which, third, has the effect of separating the pluripotent cells into the epiblast disc and the amniotic epithelium. Fourth, we wanted to see the formation of the yolk sac within the hypoblast and, finally, we need to see the differentiation of the trophoblast to give way to its characteristic polyploid cell types. In fact, it appears that we might have been able to achieve all of these goals. We could get embryos to develop *in vitro* almost to the point of gastrulation (Fig. 2).[4] Dr Samantha Morris, who participated in the early days of establishing our *in vitro* system,[5] has recently reviewed our progress and the current state of what we have learnt.

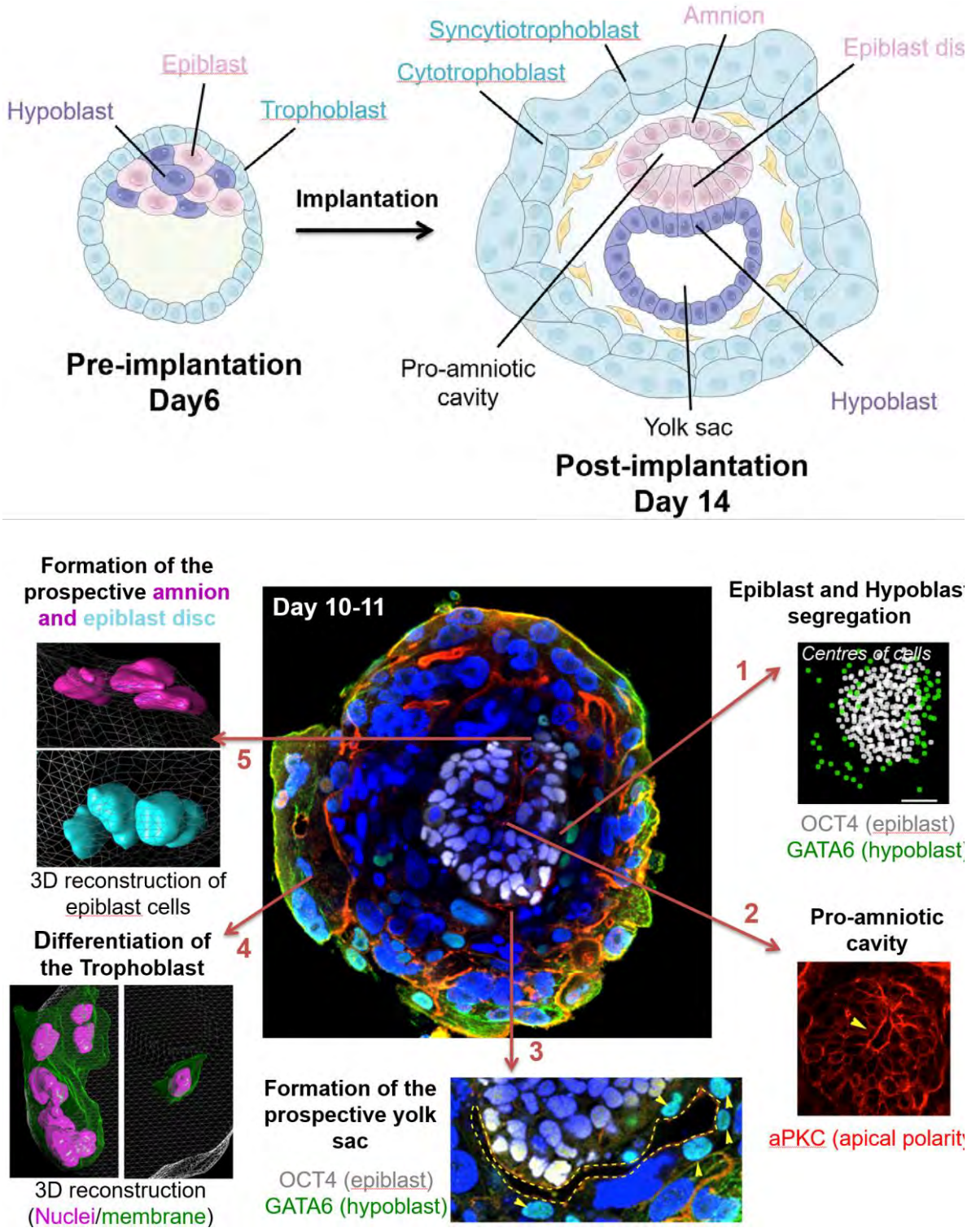

Figure 2. Development of the human blastocyst up to day 14 *in vitro* successfully meets five criteria

Upper panels: Development of the main tissues of the implantation-stage human embryo from the blastocyst. Lower panels: The five criteria that indicate successful development *in vitro.*[6]

The experimental system we have established is bringing new knowledge of how the different tissues develop through these stages. In particular, we can now learn how pluripotent cells transit through different states of pluripotency, which enables them to undergo morphological alterations that change the architecture of the embryo to allow the body plan to develop. We are learning how the different compartments of the embryo form, and how the compartments interact at their boundaries to undergo the correct sequence of developmental events. However, there is a growing feeling that the current restriction of 14 days for *in vitro* culture might be limiting, as many extraordinary developmental events take place during the following week and these will set up the architecture of all the major tissues.

Why might society want to follow these events? Largely because these are the developmental stages at which many defects in early human development occur. The failure to establish a pregnancy or its termination through natural miscarriage resulting in the spontaneous death and loss of a baby is a misery for many would-be mothers. It is believed that almost half of all fertilised eggs die spontaneously before a woman knows she is pregnant. Thereafter, it is believed that as many as 25 per cent of pregnancies fail within the first seven weeks (before a heartbeat can be detected). These huge numbers of spontaneous deaths are largely due to defects in development. Even when pregnancies develop to term, many new-borns die within weeks of birth every year due to congenital anomalies (mainly abnormalities in heart and neural tube development). These place great strain on families, the healthcare system and society. Understanding early post-implantation development will enable us to predict when developmental defects are likely to arise and, with time, to establish treatments. This will help to address the causes of spontaneous abortion; congenital defects in the heart and central nervous system; as well as childhood cancers of the germ line. But for this to happen, we would need to understand the development of the central nervous and cardiovascular systems and the germ line. These are all initiated following gastrulation (day 14) through development of the primitive streak and formation of distinct cell lineages and primordial germ cells.

To know how these events take place will be the first step in saving the many lives lost in failed pregnancies and early childhood. It would therefore be very beneficial to study embryo development beyond two weeks. What should be the limit? Should it be an additional week? Should it be extended to day 28 or to the time when the first neural markers appear? We need informed debate in order to address these questions. If we were to extend the current limit by one or two extra weeks, we would then have access to study all of the stages of human development, as beyond day 28 the scientific community has access to aborted foetal tissue (Fig. 3).

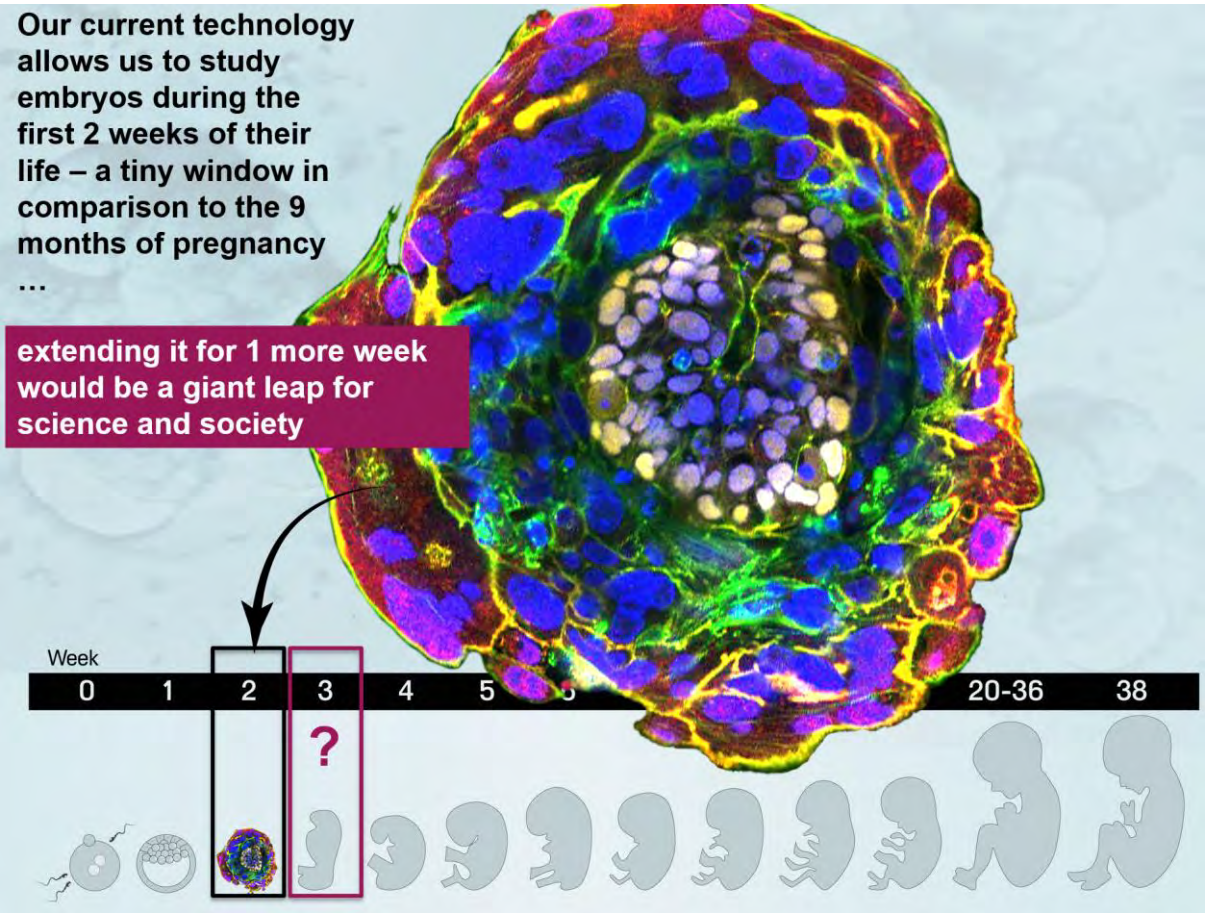

Figure 3. The 14-day limit – extending culture beyond this point will inform us of the next stage of human development that establishes the rudiments of the major organ systems
Extending the current limit for embryo culture has the potential to bring enormous insight into these critical stages and aid future medical advances in understanding loss of pregnancies and facilitating regenerative medicine using stem cell biology.

To summarise, our currently established technology now allows us to initiate studies on human embryos for the first two weeks of development, doubling the time human embryos can be cultured *in vitro*. Our work has reopened the debate about the limits for the study of embryos developing *in vitro*. Yet, what we have been able to achieve represents a tiny window in comparison to the nine months of pregnancy and extending it for one or two more weeks would be a little step forward but a giant leap for science and society in the longer term.

Acknowledgement: The work in our laboratory was supported by the Wellcome Trust.

Notes

1 Morris SA, Grewal S, Barrios F *et al.* (2012) Dynamics of anterior–posterior axis formation in the

developing mouse embryo *Nature Communications* **3**: 673; Bedzhov I and Zernicka-Goetz M (2014) Self-organizing properties of mouse pluripotent cells initiate morphogenesis upon implantation *Cell* **156**: 1032-44; Bedzhov I, Leung CY, Bialecka M and Zernicka-Goetz M (2014) In vitro culture of mouse blastocysts beyond the implantation stages *Nat Protocols* **9**: 2732-9.

[2] First described by Morris SA, Grewal S, Barrios F *et al.* (2012) Dynamics of anterior–posterior axis formation in the developing mouse embryo *Nature Communications* **3**: 673.

[3] Bedzhov I and Zernicka-Goetz M (2014) Self-organizing properties of mouse pluripotent cells initiate morphogenesis upon implantation *Cell* **156**: 1032-44.

[4] Shahbazi MN, Jedrusik A, Vuoristo S *et al.* (2016) Self-organization of the human embryo in the absence of maternal tissues *Nat Cell Biol* **18**: 700-8; Deglincerti A, Croft GF, Pietila LN *et al.* (2016) Self-organization of the in vitro attached human embryo *Nature* **533(7602)**: 251-4.

[5] Morris SA (2017) Human embryos cultured in vitro to 14 days *Open Biology* **7**.

[6] Shahbazi MN, Jedrusik A, Vuoristo S *et al.* (2016) Self-organization of the human embryo in the absence of maternal tissues *Nat Cell Biol* **18**: 700-8.

How might scientific opportunities change if the limit were redrawn?

Azim Surani [*]

Advances in very early human post-implantation development and cell fate decisions have relied on *in vitro* models created with human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC). These experimental models can simulate events associated with perigastrulation and gastrulation, and provide insights on mechanisms of early cell fate decisions. These studies have revealed critical differences between humans and mice; the latter is the most commonly used mammalian species for studies on early development. There are also differences in the regulation of the pluripotency network of stem cells, which is likely to affect mechanisms of cell fate decisions.

Mouse post-implantation embryos develop as egg cylinders, while human embryos (and possibly all non-rodent mammals) develop as flat bilaminar discs when gastrulation occurs. Some non-rodent mammals could be used as surrogates for early human development. Non-human primates are the obvious choice but the costs of research on them is considerable, and they are not readily accessible. In some instances, porcine embryos that can be retrieved from slaughterhouses could serve as surrogates; these embryos also develop as flat bilaminar discs and share similarities with early human development as they progress through gastrulation.

In contrast to the overall conservation of development of embryos with bilaminar discs, development of extraembryonic and placental tissues show greater diversity, perhaps because there were lesser evolutionary constraints on these tissues. Studies on human embryos in this instance are important for understanding, for example, some causes of infertility due to implantation failures, and for placental diseases such as pre-eclampsia.

To address questions relating to epiblast and fetal development, surrogate models are potentially useful as they can be easily manipulated, and allow the use of tools such as genome editing and imaging techniques amongst others. Nonetheless, there is a need to check if the predictions from surrogate models match with direct observations on early post-implantation human development.

There are particular areas of research that would benefit significantly if the limit to the 14-day rule were extended. Below I give two examples.

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[*] Professor Surani is Director of Germline and Epigenetics Research at The Gurdon Institute, University of Cambridge. Professor Surani was not able to attend the workshop on 16 December.

1. Specification of human primordial germ cells and development of the germ line

Primordial germ cells (PGCs), the precursors of sperm and eggs, are considered to be 'immortal' in the sense that a fertilised egg gives rise to a new organism, and theoretically at least, to endless new generations. Germ cells transmit genetic and epigenetic information to all subsequent generations, with long-term impacts on human health and disease. The most likely time of PGC specification in human embryos is around week 2.5 of gestation. The current '14-day rule' precludes investigations on their origin.

Recent studies on surrogate models provide insights on the likely mechanism of human PGC specification during week 2.5 of development, which show significant differences compared with mice. For later stages, authentic human PGCs can be isolated from aborted human fetuses from around week four and beyond to around week 15. To increase our understanding of the overall events of germ line development, it is possible to use bioinformatics analysis of *in vitro* derived PGCs from surrogate models, in conjunction with knowledge gained from characterisation of authentic PGCs from week four onwards. However, if the 14-day rule were modified for research on human embryos until around day 28, this would allow direct investigations on PGC specification until the time when material from aborted fetuses becomes available from around week four. An extension of the limit to 28 days would considerably improve opportunities to investigate the initiation of the unique germ line-specific epigenetic program, together with mechanisms affecting the transmission of genetic and epigenetic information to subsequent generations.

2. Mitochondrial biology

A number of human diseases are attributed to aberrant mitochondria, which requires better knowledge of basic mitochondrial biology. A phenomenon called the mitochondrial bottleneck occurs during early human embryonic development when the number of mitochondria in individual cells is reduced to a minimum. This is followed by 'purification' of mitochondria in early PGCs, when some mutation in mitochondrial DNA might be repaired, and/or aberrant mitochondria are eliminated from early PGCs. Mitochondria are transmitted through the female germ line only, and each precursor cell of human oocytes inherits a mixed population of normal and defective mitochondria, which is known as heteroplasmy. The number of mitochondria then increases significantly in mature oocytes. There are no detrimental consequences provided the number of normal mitochondria outnumbers defective ones.

There is a particular need to understand the mechanism regulating mitochondrial bottleneck and the subsequent 'purification' events. Being allowed to study human embryos for 28 days would help this research, which can be followed by research on PGCs from aborted fetuses from week four onwards.

Conclusion

An extension of research on human embryos to 28 days would increase research opportunities, covering the critical period of perigastrulation–gastrulation development, when key cell fate decisions occur. Later stages of development can be investigated by examining cells isolated from aborted fetuses from week four onwards.

The politics of an agreed limit

Sam Alvis[*]

The limit of fourteen days for research involving embryos is acknowledged across the world either in legislation or scientific guidelines. At least 12 countries legislate with another five to ten using scientific guidelines.

For example:

- Australia/New Zealand – legislation
- Africa - 14 days in legislation in South Africa
- China – scientific guidelines, same in Japan. Law in South Korea
- Brazil – permitted to use excess IVF embryos that have been frozen for at least three years
- North America – legislation in Canada, scientific guidelines in the USA.
- Europe – devolved EU authority: Iceland, Sweden, UK, Netherlands (very recently), Spain, Denmark and Slovenia all have individual laws. Equally, it is illegal in Germany, Austria, Ireland, Italy and Portugal. The EU will only fund research from Horizon 2020 in embryos up to seven days. This is a political compromise to meet expectations of different cultural norms.
- India – scientific guidelines

There will always be those seeking to exploit variance in regulatory frameworks. Assuming this, researchers need to be sure that there will be no knock-on effects on local systems. For example, the recent birth of a baby using mitochondrial replacement therapy in Mexico may have acted as an impetus for more restrictive IVF legislation, as lawmakers try to address other regulatory gaps. When is legislation is passed quickly to address gaps, and without a consultative process, it can lead to negative consequences.

It is important to ask the question whether, if embryo research limits are a public policy tool, there needs to be the political capacity and desire to make adjustments. We must also appreciate that cultural norms will make consensus positions, and engagement will look different across the world. Agreeing limits, or creating legislation where there is none, may be impossible. Different strategies and methodologies are needed to allow research in countries where embryo research is currently not allowed, and create longer limits in already permissive settings. In seeking to fit embryo research limits with cultural practice, what weight is then given to opposing voices in different settings?

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Where regulation doesn't exist, codes of practices and principles are all the more important. We must seek equivalence of principles but not harmonisation. We must also be mindful of individual nations' political and scientific capacity, and, therefore, their ability to implement new regulation.

Global communities are well placed to find agreement on codes of practice. For example, funders of research are looking to commit to universal principles for research on gene drives. These are necessarily high-level but can shape processes and actions. Principles might include committing to public engagement, considering societal and ethical issues, and developing frameworks for governance and accountability.

Public engagement on all of these issues is vital and must be undertaken significantly in advance of any changes to the regulation. We must understand the values and opinions of the public before seeking to discuss how embryo research fits with that context. The difficulty with issues such as this is to bring that engagement to scale, across whole countries and regions – not just in small focus groups.

To support public confidence, context-dependent but robust governance needs to be in place wherever research takes place. Cultural variance should not stop the UK advancing a pragmatic and rigorous research framework here, which might offer leadership to those elsewhere. When considering other countries' regulation we cannot use the UK as a baseline but we can demonstrate the processes that have led to success, for example in mitochondrial donation.

Islamic perspectives on the moral and policy significance of developmental threshold

Mehrunisha Suleman[*]

Embryonic stem cells, with their therapeutic potential for myriad acute and chronic conditions, have functioned as a catalyst within the Islamic scholarly sphere. This biomedical advancement is compelling religious experts into discussions about its prospective uses and moral challenges. The deliberations often consist of an evaluation of (i) the promise of emergent therapies as well as (ii) theological deliberations about the beginning of life, ensoulment and personhood. With regard to the first component, embryonic stem cell research finds wide theoretical justification amongst Islamic ethico-legal scholars, under the principle of public good (*maslaha*) or necessity (*dharurah*).[1] Such support, however, has recently been challenged as 'naive' by authors flagging current limitations in stem cell research.[2] This summary will, however, focus on the second component, or the moral assessment of the embryo through an appraisal of Islamic perspectives on human embryology and ethico-legal declarations on embryonic research.

Islamic perspectives on human embryology

Islamic perspectives on human embryology commonly rely on two approaches: medico-philosophical and religio-ethical.[3] The former has been developing since the medieval period, through the translation movement of Greek texts into Arabic.[4] The latter relies on Islam's normative texts, the Quran (word of God) and Sunnah (example of the Prophet Muhammad). These normative sources are interpreted by Islamic scholars through the process of *ijtihad* (independent scholarly reasoning) that collectively contribute to *fiqh* (Islamic jurisprudence). Unsurprisingly, within *fiqh*, the numerous schools of thought, although rooted in the same primary sources, may arrive at differing and often contradictory judgements.[5]

Islamic scholars rely on the references made to human embryology in the Quran,[6] and the Sunnah, as they respond to questions and challenges posed by stem cell research. Although they principally depend on these normative sources for articulating their ethico-legal declarations (*fatwahs*), Islamic scholars often consult and consider complementary biomedical understandings of human embryology.[7] Ghaly offers a summary of the key questions pertinent to the development of Islamic ethico-legal perspectives on maintaining and researching human embryos:

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> "When does an embryo become formed (*yatakhallaq*) or fashioned (*yataṣawwar*)? When does an embryo start moving (*yataḥarrak*) inside the uterus? When is a soul breathed into the unborn (*yunfakh fīh al-rūḥ*)? These questions all relate to the key question: When does an embryo acquire the status of a human being, that is to say, when does human life begin?"[8]

The Quran provides some description of human embryological development, however it does not distinctly indicate when ensoulment occurs or when life begins and/or whether these two points are synonymous. There are two Prophetic Traditions (*hadith*), namely the Ibn Masud[9] and Hudhayfa[10] *hadith* that are considered relevant by Islamic scholars for discussions on human embryology. Islamic scholars have, however, been unable to reach a consensus on the interpretation of these *hadith* in relation to the above questions. Some contemporary ethico-legal declarations on embryonic research are listed below.

Islamic ethico-legal declarations on human embryonic stem cell research

IOMS 1985

The Islamic Organisation for Medical Sciences (IOMS) convened a meeting of 80 Islamic scholars in 1985 to discuss Islamic perspectives on the question: "When does life begin?" A recent study of these proceedings[11] summarises that there was marked variation amongst Islamic scholars on the beginning of life. The main positions considered that (i) human life begins at conception; (ii) human life begins when the embryo settles in the wall of the uterus, and (iii) human life begins when the soul gets breathed into the embryo, which at the earliest occurs at 40 days, and the latest at 120 days. The latter was given most support and the final recommendation from IOMS states that: "life has three grades: it starts by conception, then gains dignity (*ihtiram*) by implantation, and finally acquires sanctity (*hurma*) just after breathing the soul."[12] The ethico-legal definitions of the terms *ihtiram* and *hurma*, as well as their implications, however, are debated.

Ghaly reports in a related study that: "On the basis of textual analysis, they (the IOMS symposium) concluded that ensoulment takes place after 40 or 120 days of pregnancy. If human life starts after either one of these two dates, what is the status of the unborn before that occurrence? In their response to this question, these jurists quoted extensively from Ibn al-Qayyim's discussions of embryology, especially his idea about the two types of movement made by the unborn inside the uterus: spontaneous movement before ensoulment, and conscious movement after ensoulment. Contemporary jurists make a similar distinction between two types of life: life in the absolute sense, which they sometimes call vegetative or cellular life, that can be observed before ensoulment; and human life, which starts only after ensoulment. This is also the position adopted in the final recommendations of the IOMS symposium."[13] Amongst Islamic scholars as well as Muslim biomedical

professionals and the general public, those who oppose embryo research adopt the first position and those who are in favour rely mainly on the third position. Guidelines that have been developed purporting Islamic ethico-legal support or approval for embryo research rely on this third position from the IOMS symposium.

Fiqh Council of North America, 2001

The Fiqh Council of North America, which consists of healthcare professionals, Muslim jurists and scientists, concluded that implanted embryos cannot be used for research, however, they supported the use of spare embryos from *in vitro* fertilisation for stem cell research.[14]

Shi'i perspective from Iran

With a centralised religious authority, Iran legislatively represents the national view of Shi'i scholars as well as the Grand Ayatollah, who occupies the highest religious authority. In 2002, Ayatollah Khamenei issued a *fatwah* declaring stem cell research as being consistent with Shi'i Islam and congratulated scientists working on this nascent field.[15] With such religious endorsement, embryonic stem cell research has burgeoned in Iran.

Plurality of views

Recent studies[16] of Islamic scholarly views from across the Muslim world indicate a variation in perspectives globally, and what appears to be an unsystematic and bewildering variation in views is an expression of the intrinsic ethico-legal plurality in Islam. Beyond the small range of unambiguous or prescribed duties found in the foundational texts of Islam, Islamic scholars are called upon to navigate the large spectrum of emerging concerns or to revisit previously encountered problems that require a fresh approach.

Moral and policy significance

Recent research demonstrating biomedical capability of maintaining embryos beyond the statutory 14 days will likely provoke new discussions amongst Islamic scholars on the implications of such advancement on existing views about Islamic perspectives on the moral status of the human embryo. For policy and the need to cultivate consensus, it will be critical for the UK ethico-legal landscape to remain sensitive to such discussions and developments as well as the plurality of Islamic perspectives. As indicated in the discussion above, it is likely that such discussions and debates will contribute to broader theological, philosophical and ethico-legal discussions around the moral and legal status of the embryo, as well as embryo storage and research.

Notes

1 Al-Aqeel AI (2009) Human cloning, stem cell research. An Islamic perspective *Saudi Med J* **30**: 1507-14; Sachedina A (2009) *Islamic biomedical ethics: Principles and application* (Oxford: Oxford University Press), pp101-124.

2 Ilkilic I and Ertin H (2010) Ethical aspects of human embryonic stem cell research in the islamic world: positions and reflections *Stem Cell Reviews and Reports* **6**: 151-61.

3 Ghaly M (2014) Human embryology in the islamic tradition *Islamic Law and Society* **21**: 157-208

4 Fakhry M (1991) *Ethical theories in Islam (Vol. 8)* (Leiden, The Netherlands: Brill).

5 Kyriakides-Yeldham A (2005) Islamic medical ethics and the straight path of God *Islam and Christian–Muslim Relations* **16**: 213-25.

6 The Holy Quran, Chapter 22 verse 5: "O People, if you should be in doubt about the Resurrection, then [consider that] indeed, We created you from dust, then from a sperm-drop, then from a clinging clot, and then from a lump of flesh, formed and unformed - that We may show you. And We settle in the wombs whom We will for a specified term, then We bring you out as a child, and then [We develop you] that you may reach your [time of] maturity. And among you is he who is taken in [early] death, and among you is he who is returned to the most decrepit [old] age so that he knows, after [once having] knowledge, nothing. And you see the earth barren, but when We send down upon it rain, it quivers and swells and grows [something] of every beautiful kind." Online: http://corpus.quran.com/translation.jsp?chapter=22&verse=5; The Holy Quran, Chapter 23 verses 12-14: "And certainly did We create man from an extract of clay. Then We placed him as a sperm-drop in a firm lodging. Then We made the sperm-drop into a clinging clot, and We made the clot into a lump [of flesh], and We made [from] the lump, bones, and We covered the bones with flesh; then We developed him into another creation. So blessed is Allah, the best of creators." Online: http://corpus.quran.com/translation.jsp?chapter=23&verse=14; The Holy Quran, Chapter 32 verses 7-9: "Who perfected everything which He created and began the creation of man from clay. Then He made his posterity out of the extract of a liquid disdained. Then He proportioned him and breathed into him from His [created] soul and made for you hearing and vision and hearts; little are you grateful." http://corpus.quran.com/translation.jsp?chapter=32&verse=9.

7 Bakar O (2004) Abortion: III. Religious traditions: D. Islamic perspectives, in *Encyclopedia of bioethics, Volume 1, 3rd edition*, Post SG (Editor) (New York: Macmillan Reference).

8 Ghaly M (2014) Human embryology in the islamic tradition *Islamic Law and Society* **21**: 157-208.

9 40 hadith of Nawawi – Hadith number 4: "On the authority of Abdullah ibn Masud, who said: The Messenger of Allah, and he is the truthful, the believed, narrated to us, "Verily the creation of each one of you is brought together in his mother's womb for forty days in the form of a nutfah (a drop), then he becomes an alaqah (clot of blood) for a like period, then a mudghah (morsel of flesh) for a like period, then there is sent to him the angel who blows his soul into him and who is commanded with four matters: to write down his rizq (sustenance), his life span, his actions, and whether he will be happy or unhappy (i.e., whether or not he will enter Paradise)…" Online: https://sunnah.com/nawawi40/4.

10 Sahih Muslim Book 46 Hadith 3: "Hudhaifa b. Usaid reported directly from Allah's Messenger that he said: When the drop of (semen) remains in the womb for forty or fifty (days) or forty nights, the angel comes and says: My Lord, will he be good or evil? And both these things would be written. Then the angel says: My Lord, would he be male or female? And both these things are written. And his deeds and actions, his death, his livelihood; these are also recorded. Then his document of destiny is rolled and there is no addition to nor subtraction from it." https://sunnah.com/muslim/46/3.

11 Ghaly M (2012) The beginning of human life: Islamic bioethical perspectives *Zygon*® **47**: 175-213

12 ibid, at page 208.

[13] Ghaly M (2014) Human embryology in the islamic tradition *Islamic Law and Society* **21**: 157-208, at page 202.

[14] Ilkilic I and Ertin H (2010) Ethical aspects of human embryonic stem cell research in the islamic world: positions and reflections *Stem Cell Reviews and Reports* **6**: 151-61.

[15] Frontline World (8 June 2009) *Iran: The stem cell fatwa*, available at: http://www.pbs.org/frontlineworld/rough/2009/06/iran_stem_cell.html; Saniei M (2010) Human embryonic stem cell research in Iran: the role of the Islamic context *Scripted* **7**: 324-34

[16] Fadel HE (2012) Developments in stem cell research and therapeutic cloning: Islamic ethical positions, a review *Bioethics* **26**: 128-35; Ilkilic I and Ertin H (2010) Ethical aspects of human embryonic stem cell research in the islamic world: positions and reflections *Stem Cell Reviews and Reports* **6**: 151-61; Eich T (2008) Decision-making processes among contemporary 'Ulama': Islamic embryology and the discussion of frozen embryos, in *Muslim medical ethics: from theory to practice*, Brockopp JE, and Eich T (Editors) (Columbia, South Carolina: University of South Carolina Press), at pp.61-77.

A response to the report of the workshop

David Katz[*]

The report of the workshop is a very valuable reflective document, and it is perhaps invidious to express any views that are not being subjected to the type of scrutiny and balanced evaluation by peers that has applied to others. In addition, I assume that others had to provide some personal background during the workshop: I would have had to declare a personal faith background in observant Judaism (but I am not a Rabbinic authority); a professional background in laboratory medicine (cell and molecular pathology); and a role in ethics review and education. I would also have to take into account past documents in this field, in one of which – the submission made by the then Head of the Court of the Chief Rabbi to the House of Lords Select Committee on use of embryonic stem cells – it was stated that, if a process or intervention is permissible in Jewish law (known as *halacha*), this does not mean that it is ethically appropriate to implement it.

Against this background, there are some points which I might have made at the workshop and which I would like to draw to your attention. Judaism places no particular value on the limit of 14 days. At the time that this was promulgated in 1984, the point was made that there is Talmudic mention of 40 days, possibly based on observation of fetal development at miscarriage. Also in Judaism, safeguarding the life of the mother during pregnancy is generally regarded as taking priority, which contrasts with some other faiths. These two views would seem to position Judaism as permissive for a longer time limit. Furthermore what is effectively a utilitarian approach – that embryo research has as its objective relief of suffering, morbidity and mortality – provides further justification, along the moral value lines suggested.

However, this does not imply that there would be Judaic blanket endorsement of any time period. Case-by-case scrutiny would be required, which in turn implies a regulatory system that is cognisant of risk, and is practical. It is important that these criteria seem to have been satisfied by adopting the 14-day rule, and the comments made about public acceptability are very pertinent. Given that, as the workshop report states, “scientific progress whilst also ensuring public confidence in both research and the regulatory system” seem to have been achieved, change is not indicated. This theme seems to have arisen in several contexts – for example, it is also mentioned in the section that discusses developmental thresholds, where the Jewish perspective is probably very much in line with the Islamic view in general terms, except that 40 days rather than conception would be the ‘life-determining’ time point. The ‘personhood-

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time point' in Judaism may be the gestational age of viability (which is itself the subject of a separate current debate).

Reference is made in several places to mitochondrial donation, correctly observing that approval of this procedure represents a significant shift into germ line intervention. The Jewish perspective on mitochondrial donation has been generally in line with the UK position: that it is permissible, provided that risk is taken into account. This risk assessment has to be both of mitochondrial disease itself, and of the donation process. Case-by-case permission and a regulated environment are considered important back-up conditions.

CRISPR (and other similar techniques) will raise many new and different problems, and I am aware that the Council is looking at this in other fora. This does resemble mitochondrial donation, but precision and accuracy as to how the latter is to be implemented is much less well-established. In addition, while the laboratory medicine physician would be very interested in studying an embryo with a known Tay-Sachs mutation, monitoring at what stage neural development is damaged, and then looking at another similar embryo which had undergone CRISPR correction, I am not sure that the ethicist would agree, and Judaism may say that humanity created in the image of G-d outweighs curiosity. The suggestion of using different time limits for germ line modifications and research may be admirable, but seems to me unworkable. It could also work both ways – as implied elsewhere in the document, embryo manipulations for the former may take longer than 14 days.

Overall, the comments made in the concluding paragraph of this section – about the differences in embryo status, and about the notion that the present system promotes dialogue about societal respect for life – are very much in keeping with Jewish teachings. Likewise, a balanced combination of scientific progress and public confidence in both research and regulation seems to have been achieved via the 14-day rule, and I would argue for its retention unless there are strong reasons for change.

The main argument for extension of the time limit is that the current system places unjustified constraints on advances in the field. This might be true, but the concluding comments – that it is impossible to determine whether or not this is in fact true – is very apposite. One issue, however, is that fetal research is mentioned specifically. Fetal surgery during pregnancy is already taking place in the UK, and thus research at that level is not as far-fetched as implied, albeit not affecting the core topic addressed here.

The discussion about international context and its implications makes an important point about the impact and status of British regulations. This theme is not unique to the 14-day rule. The case of the mitochondrial donation in Mexico is an example where the regulatory process seems to have been limited. A more sinister instance has been reported recently (post the workshop) from the Ukraine.[1] It is very apparent how issues in this field in general are handled differently between countries and cultures. Not only

ethical approval of research on embryos differs between countries, but also the relative impact of religious law on this topic varies between societies. These factors need to be taken into account. It is very unclear how much impact – if any – the 14-day limit has had or will have on the quality and nature of British research in the field.

These comments are points of nuance and detail; overall I believe that the conclusions reached are thoughtful and sensible and I do not feel that the Jewish community should have any major objections to them.

Note

1 Brannan S, Campbell R, Davies M et al.(2017) Ethics briefing, J Med Ethics 42(12):815-16.

A response to the background paper

David Jones[*]

Background paper

The background paper neglected to ask whether the 14-day rule and the 'moral status' of the embryo are not best understood as rhetorical devices with essentially a political function. For example, how can one argue that "the compromise… was only ever acceptable because the rule it stipulated could not be breached" (paragraph 6). A rule that "could not be breached" is not a "rule", and is certainly not a "compromise". Speed limits are compromises, but a speed limit faster than anyone could drive is not a compromise, nor indeed is it a rule in any meaningful sense. The 14-day 'rule' functions to give reassurance by means of an empty prohibition. It is part of a disingenuous political settlement, as I have argued elsewhere at length.[1]

The word 'compromise' is used repeatedly in the background paper without explaining what positions this 'compromise' reconciles or on what rational basis. The position of acknowledging the full moral status of the human embryo, which might seem an obvious candidate for one pole of this 'compromise', is conspicuous by its absence. Likewise, the 'gradualist' position is not adequately explored. On what basis does status increase? Complexity? Species specific traits? Sentience? Autonomy? The account of 'personhood' prevalent in modern bioethics is a kind of gradualism but would make no distinction between the embryo at 14 days and the foetus at 24 weeks. Neither are 'persons'. If the basis of increasing status is not explicit, then 'gradualism' is an empty concept and effectively another rhetorical device to facilitate aims that have been decided on a utilitarian basis.

In relation to the science, the paper gives no analysis of how much evidence of potential benefit is necessary to justify the sacrifice of a human embryo. At the Progress Educational Trust meeting it was interesting to watch a noted embryologist react to the suggestion that researchers use embryos from primates before working on human embryos.[2] He raised ethical concerns about how the primate embryos could be obtained (i.e. about research on primates). The ethical bar to primate research is raised very high. It must be clear that research cannot be done in another way, and that the potential benefits of the research are urgent, well defined and credible. Furthermore, research on non-human animals should occur within a context of seeking to 'refine, reduce and replace' such research. Where is the equivalent in relation to

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opening new vistas of human embryo research?

The paper also gives no critique of the 'hyping' of research or the harm done by overstating the potential benefits. The alleged benefits of a 28-day rule are justified merely by repeated reference to 'progress' through 'basic research' (paragraph 8). The example of admixed human embryos, used by the background paper (paragraph 46) exemplifies this problem. The public were told repeatedly that admixed embryo research was urgently needed, with no reference to scientific criticisms and no reference to other promising avenues of research. People were therefore unprepared and perplexed when this supposedly urgent research failed to obtain funding and was abandoned. And how are the public to believe scientists the next time? Even on a crude pragmatic measure, the political costs of abandoning the 14-day rule must be offset by concrete research proposals, based on credible research, already shown to be promising in animal models, and unattainable in any other way. Otherwise it will erode public trust.

Some arguments for extending/abandoning the 14-day limit

- The prohibition of research after 14 days was disingenuous empty rhetoric corrosive of public reason. The 14-day rule pretended to protect embryos but functioned to facilitate their destruction. It would be more honest to dispense with it (and with the HFEA).

- The rule reinforces the idea that embryos before this limit are expendable. Since the 1990 Act came into force 2.5 million embryos have been discarded, 50,000 per year (c. 4000 per year in research).

- The rule is difficult to justify by most philosophical approaches (utilitarian, libertarian, natural law). The embryo's moral status changes little, if at all, between ten days and 20 days.

- Abandoning the 14-day rule would probably affect very few embryos; if one is concerned to protect human embryos, one should focus elsewhere (e.g. on the 'reduce and replace' agenda).

Some arguments against extending/abandoning the 14-day limit

- Even if the 14-day rule is hypocrisy, 'hypocrisy is the compliment vice pays to virtue'. Keeping the 14-day rule is a symbolic acknowledgement that there is a virtue in protecting the embryo. Better hypocrisy than shamelessness and casual disregard of embryos.

- The 14-day rule was established for a variety of reasons, in a number of jurisdictions, and has survived for over 30 years. The very act of shifting the rule

weakens the replacement. Who can honestly believe that 28 days would be an 'inflexible limit'?

- Due to twinning, serious philosophers and theologians have regarded 14 days as the beginning of the individual[3] and/or as a moral limit.[4]

- The 14-day rule prevents the sustaining of an embryo in vitro post-implantation. The sustaining of post-implantation embryos is effectively the beginning of ectogenesis.

- There is no argument for the benefit of studying early human development which cannot be extended to eight weeks, 16 weeks or 24 weeks (i.e. the legal limit of elective abortion). This may currently be unachievable, but the first step is culturing the post-implantation embryo.

- The significance of the heartbeat (at around 21 days) and the neural tube (14 to 28 days) are in part symbolic but they make it indisputable that the embryo is a living organism. There is a convergence with other reasons (twinning, implantation).

- Experimentation after 14 days is of limited significance for clinical IVF (in comparison to the first five days) and also faces the problem of how comparable this development will be to the development of the implanted embryo in vivo.

- If embryos can now be cultured to (and possibly beyond) 14 days then the rule has the potential to become a real rule and not an empty piece of political rhetoric as hitherto. On the other hand, to abandon this rule at this point, even before the limit has been reached, would expose the utter moral bankruptcy of the current political settlement.

- Simple prohibitions are preferable morally and politically to systems of licencing or review. They need involve no complicity in the system of embryo experimentation. They can attract widespread support.

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1 Jones DA (2011) The "special status" of the human embryo in the United Kingdom: an exploration of the use of language in public policy *Human reproduction and genetic ethics* **17**: 66-83.

2 The Progress Educational Trust Public Conference 'Rethinking the ethics of embryo research: genome editing, 14 days and beyond', 7 December 2016.

3 Ford NM (1988) *When Did I Begin?: Conception of the Human Individual in History, Philosophy, and Science* (Cambridge: Cambridge University Press); and Anscombe G (1985) Were You a Zygote?, in *Philosophy and Practice*, Griffiths A (Editor) (Cambridge: Cambridge University

Press).

[4] McCormick SRA (1991) Who or what is the preembryo? *Kennedy Institute of Ethics Journal* **1(1)**: 1-15; and Kenny A (2008) The beginning of individual human life *Daedalus* **137(1)**: 15-22.

Moral status and the properties of the embryo

Elselijn Kingma[*]

I offer two substantive comments on the background paper:

1. I offer a consideration against the widespread view that moral status depends on intrinsic properties alone (paragraph 14). My consideration suggests that the location of an embryo – whether it is in a pregnant woman or in a petri-dish – may affect its moral status and/or value.

2. I nuance the discussion of moral status and gradualism presented in the background paper, in order to correct any inference that only 'gradualism' about moral status allows that the moral consideration given to an embryo may vary with its development.

1. Potentiality and extrinsic properties

The background paper notes that it is 'usually accepted that moral status should depend on intrinsic properties' (paragraph 14). I want to offer a contrary consideration that may be important to embryo research.

1. Arguments for the moral status (or *full* moral status) of embryos nearly always rely on some appeal to potentiality. Either having the potential to become that which we all recognise as having full moral status; or being a *potential* human being (see e.g. background paper, paragraph 18).

2. Perhaps only intrinsic characteristics matter where moral status depends on present characteristics. But where moral status is mainly due to having a certain potential, or being a potential entity, this is different. For, when it comes to potentiality, both extrinsic and intrinsic features are relevant.

    a. The stronger claim would be that only a 14-day embryo-implanted-in-a-willing-womb has the potential to become a human being and/or is a potential human being. A 14-day embryo in a petri-dish, by contrast – which has passed the stage of being able to implant in a womb – does not have the potential to become a human being. Just as a spark in the dry season in the Australian bush is a potential fire; a spark on the north-pole is not. If the moral status of the embryo derives from being a potential human then,

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on this strong claim, only the embryo-in-a-willing-womb has moral status. The embryo in the petri-dish, past the possibility of implantation, is not a potential human and therefore lacks moral status.

b. The slightly weaker claim would be that extrinsic characteristics do not determine potentiality and moral status but make a significant moral difference nonetheless. Consider an acorn (or 'oak embryo'). Suppose we all agree that an oak has some value; and that an acorn also has some value (though not as much as an oak) in virtue of being able to become an oak. It seems that there is then still a (moral) difference between picking up and destroying an acorn sitting in your fruit bowl – which is never going to become an oak unless you make the effort of taking it out and burying it in a suitable location – and digging up acorns that are presently lying in suitable soil, and that have an actual chance of becoming oaks if left undisturbed. The acorn in the bowl has negligible potential; the acorn in the soil is a different matter. If the value/status of acorns derives from being a potential oak, then that value should vary not just with intrinsic characteristics that determine that potential but with extrinsic characteristics too.

3. If this is right, then the consequences for embryo research may be:

a. It is not just stage of biological development that is relevant to the moral status/value of an embryo; but whether it is (or will be) placed in a situation that contributes the necessary environment.

b. This means there is (further) good reason for a moral distinction between 'research' embryos and 'reproductive'/implanted embryos.

c. If it is not possible to implant *in vitro* embryos after a certain time, and we are not yet able to raise them outside the human body ('ectogenically'), then such embryos do not in fact have the potential to be a human being/are not potential human beings.

d. This conclusion would change, of course, if ectogenesis did become an option.

2. Moral status and gradual consideration

The background paper contrasts 'absolute concepts of moral status' with 'gradualism'. It then goes on to suggest that gradualism allows for compromises (paragraph 35), and that a gradualist approach to moral status allows for the balancing of the value or interests of the embryo against other considerations (paragraph 35, 39).

I want to add two points. First, the background paper is not consistent on what is meant by gradualism. Second, it would be wrong to infer from the presentation of these two alternatives that *only* gradualism about moral status allows for compromises or the balancing of considerations.

Unclear definition of gradualism

The paper offers two definitions of gradualism: (1) the view that "moral status develops gradually" (paragraph 35) and (2) "a theory of moral status which states that the moral value of embryos increases with their biological development" (paragraph 36).

1. These definitions of gradualism are not equivalent; one posits the gradual development of *moral status*, the other of *moral value*. But moral status and moral value are not the same; something can have moral value without having moral status; i.e. without being considerable *for its own sake*. (See also paragraph 15: "A distinction has been made between moral status and moral value. Moral value is a weaker concept than moral status. That which has moral value need not have moral status").

2. Because of the two non-equivalent definitions it is not clear what the authors mean by gradualism, or which position is being defended. (Inconsistencies about the meaning of gradualism as well as the occasional conflation of moral value and moral status also affect paragraphs 37 and 39, including quotations from the Irish Council on Bioethics. This makes these paragraphs difficult to interpret.)

Moral status and consideration by degree.

The background paper contrasts absolute and gradualist views of moral status, suggesting that the latter allows for degrees of consideration or the balancing of interests where the former does not. But this is false; absolute views of moral status can also allow for degrees of consideration or the balancing of interests.

1. Moral status is a notoriously slippery concept. It roughly means 'moral considerability': to have moral status means that one's needs, interests or well-being must be given consideration for one's own sake or that one is a member of the *moral community* (see also paragraph 12).

2. Moral status can either come by degree, or it can be an all-or-nothing concept.

    a. If moral status comes by degree then something can have more or less moral status. The maximum amount of moral status is often labelled *full* human status. For example, (adult) humans are usually considered to have *full* moral status. A dog, by contrast, may have some moral status, but not *full* moral status. Its interests or wellbeing must be considered – but not as much as that of a human adult.

   b. If moral status is an all-or-nothing concept, then things are either the sort of thing that is not morally considerable at all, or the sort of thing that is morally considerable. A rock, for example, is not morally considerable at all, and therefore does not have moral status. Anything that is morally considerable – where its needs, interests and well-being need to be considered for its own sake – has moral status. Since both adult humans and dogs must be considered for their own sake, both have moral status on an all-or-nothing conception of moral status; neither is not morally considerable at all.

3. The first key point here is that on neither view determining whether something has moral status tells us much about how much consideration it should be given; and therefore that on either view, there is room for variability in degree of consideration.

   a. If moral status comes by degree, then knowing that something has moral status tells us nothing about how much moral status it has; how much it should be considered compared to adult humans.

   b. If moral status is an all-or-nothing concept, then, again, knowing that something has moral status only tells us *that* it should be considered for its own sake; it does not tell us how much consideration it should be given.

4. The second key point is that, on neither view, does determining whether something has moral status tell us *what kind* of consideration it is to be given. This is another source of variability: knowing *that* something's needs, interests and well-being should be considered for its own sake does not tell us *how* they should be considered or what such a consideration looks like. Interests vary with life-form and life-stage; respecting the interests of a cow, an infant and an adult are quite different exercises; autonomy and respect for privacy may be very important for the latter but they are virtually meaningless for the former two (a newborn has few current privacy interests). Embryos are radically different even from human newborns; even if the two have identical moral status, they may have very different needs and interests and therefore respecting their moral status may demand very different things from us.

5. In conclusion: determining whether something has 'moral status' tells us nothing about how much and what kind of consideration it should be given, in the absence of substantial further argument/detail.

   a. It is possible that embryos gradually acquire moral status.

   b. It is also possible that all embryos have moral status but should not be given *that* much consideration; the moral consideration given may depend on the level of development.

c. It is also possible that all embryos have moral status *and* should be given the same consideration as adult humans, but that to respect their interests is still something radically different from respecting the interests of an adult human being and therefore very much dependent on their level of development.

6. The above means that it is not just 'gradualism' about moral status that allows for degrees of consideration or the balancing of interest; the possibility of gradation in the quantity and kind of consideration is compatible with almost any understanding of moral status[1]; it is just located in different places depending on how exactly moral status is to be defined.

Notes

[1] Perhaps the only exception is a view that (1) recognises that moral status comes in degree, but is nonetheless arguing that embryos have 'full moral status' AND (2) does not grant that embryos might have different needs and interests from adult humans. The latter point is implausible (think about newborns); the former is, I think, tough to defend.

The statutory time limit for maintaining human embryos in culture

Katrien Devolder[*]

My personal view is that, from a theoretical ethical perspective, there are good reasons to move the 14-day limit to around 21/28 days after conception. The embryo and early fetus have no significant moral status. They cannot feel pain and do not have agency (e.g. they do not have plans, cannot see themselves as one among others, do not have desires etc.), not even the beginnings of it. There are other reasons for not using embryos or early fetuses for research/therapeutic purposes (e.g. because this may offend those opposed to these practices), but these reasons are outweighed by the expected benefits of using embryos older than 14 days for research and or therapy.

However, we are considering a policy question, not a merely theoretical question, and therefore additional considerations come into play, including possible public and/or political opposition to embryo research in general, and distrust of science and/or scientists (who may be perceived as removing ethical barriers so they can conduct 'their' research freely). Such reactions could have a detrimental effect on scientific progress, which should be avoided.

It has been argued that the 14-day limit was defended as a compromise between scientists who wanted to conduct embryo research (or whose work could benefit from such research) and those opposing all embryo research (thus, it was not adopted for epistemic reasons, i.e. because it reflects some truth about the moral acceptability of research with embryos before and after 14 days of development). But was it really a compromise? It is usually thought that a necessary condition for a compromise is that both sides have to make concessions. Yet, it seems that the adoption of the 14-day limit gave scientists virtually everything they needed at the time. After all, at that point in time, it was not technically possible to culture embryos *in vitro* for longer than seven to nine days. This may create the impression that the 14-day limit was adopted to gain the acceptance of the public and policymakers so that scientists could proceed with their scientific research.

Why is this relevant? If the 14-day limit offered a 'good balance' between two opposing viewpoints, then it might serve as a good starting point for finding a new 'good balance' should it be decided that the 14-day limit is to be moved (perhaps one would only need to show that the expected benefits of culturing embryos for more than 14 days outweigh the moral cost of keeping the embryo alive for, say, seven to 14 days longer). However, if the 14-day limit did not represent a 'good balance' in the first place (as some opponents of embryo research think), then this needs to be taken into account when determining where a new 'good balance' may lie.

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Perhaps the central question is the following: assuming that certain very important research or therapeutic goals can only be achieved through research using embryos older than 14 days, can we move the 14-day limit in a way that is and will remain acceptable to the public and policymakers? (Note that this is different from developing a compromise between two opposing viewpoints, i.e. pro and contra embryo research.) What would need to be done to achieve this?

Here are some initial thoughts:

Scientists would need to explain why they think that the additional benefit of conducting research on embryos/fetuses older than 14 days as compared to conducting research on embryos between seven to 14 days old (which is new terrain too, since it only recently became possible to culture embryos for seven to nine days) is very significant. Is this the right time to extend the limit, or should scientists first conduct research on embryos seven to 14 days old *in vitro*, and then re-evaluate their views?

There may need to be some plausible story about why the limit should be moved to 21/28 days (and not further) (perhaps similar to the 'story' about the moral relevance of the development of the primitive streak). This might be necessary to make the new limit acceptable to society.

The public needs to be convinced that moving the 14-day limit will not automatically initiate a slippery slope towards moving the limit further and further. Here are some preliminary thoughts related to this issue:

a. Will moving the 14-day-limit be seen as evidence of the fact that this and similar limits are not actually firm limits, but will be changed whenever 'the need' for scientists to move the limit arises?

b. If the moral status of the embryo gradually increases in the course of its development (and if a gradual moral status is seen as a useful approach in this debate), and if what matters is 'respect' for the embryo (central to which is the proportionality principle: 'we can only use it for very important purposes'), then one could easily see how some may be concerned about a slippery slope (after all, one could then reason that even if the fetus has a higher moral status than an early embryo, it may be permissible to use it for research, if the expected benefits are highly relevant) and this concern would need to be anticipated and addressed. The fact that the 14-rule has remained in place for more than 25 years does not necessarily show that there is no slippery slope as, in those 25 years, the need to move the limit did not arise; after all, it was not technically possible to culture embryos for longer than seven to nine days.

c. Might it be possible to forestall fear of a slippery slope by allowing a long time to discuss the issue, i.e. by consulting the public and policymakers etc.? I think it is important not to create the impression that moving the 14-day limit is something that can be easily decided by a few individuals. I think the process of decision-making with wide involvement is important.

d. One concern is that the current climate may be such that some people have little trust in scientists, facts and arguments. Is there a risk that politicians and some media outlets will take advantage of the new debate to encourage opposition to embryo research (including research before 14 days) or even to science and scientists in general, and perhaps even to abortion or other related practices where the protection of the embryo is at stake?

e. These are all empirical questions. Before deciding whether to open the debate about whether the 14-day limit should indeed be moved, it would be helpful to get an idea of what people's views on the 14-day limit are, and on the possibility of moving the limit. We also need to think about the extent to which the societal view on moral status matters, given that it may be afflicted by various misconceptions and biases.

Another question derives from the following scenario: suppose it is decided that the 14-day limit should be extended. Should it be explicitly defended and presented as a 'compromise' (if that is what it is), or should it be presented as a 'principled' ethical position to make it acceptable to the public?

Some comments on developmental thresholds and their moral and policy significance

Shaun D. Pattinson[*]

In theory, an embryo could have *moral status* (i.e. intrinsic value as a recipient of direct duties) and/or *vicarious value* (i.e. value to someone or some group with full moral status). There is a manifest divergence of views over whether the developing human is owed direct moral duties with the same weight as those owed to you or me (full status), duties of less weight (limited status) or no direct duties at all (no status). The most popular limited status position holds the embryo's value to be gradualist or proportional to gestational development until it obtains full moral status at birth or beyond.

Variants of the proportional status position appear to best capture the approach of the majority of the Warnock Committee and the current legal position. The Warnock Committee declared that the "embryo of the human species ought to have a special status", albeit not the "same status as a living child or an adult".[1] The Human Fertilisation and Embryology Act 1990 (the 1990 Act) amended the Abortion Act 1967. The result is that English law grants increasing protection to the developing human according to four legally relevant thresholds: preimplantation (currently up to the development of the primitive streak or 14 days, whichever is earlier),[2] implantation to 24 weeks, post-24 weeks, and birth.[3] The basis of this progressively increasing protection is not articulated by the law.

As Hyun *et al*. point out, the 14-day rule is not, and was never intended to be, "a bright line denoting the onset of moral status in embryos".[4] It was first recommended in 1979 by the Ethics Advisory Board of the US Department of Health, Education and Welfare on the basis that it represented "the stage normally associated with completion of implantation".[5] Five years later, the Warnock Committee used 14 days as a precautionary proxy for the development of the primitive streak, which they regarded as a "reference point in the development of the human individual" on the basis that it was the point after which an embryo could no longer split into identical twins.[6] This developmental limit was given legislative force by the 1990 Act and in various other regulatory instruments across the world, including in Canada, China, India and the US.[7]

Revisiting the 14-day rule requires consideration of the weight of the arguments in

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favour of the existing rule and the alternatives. Those alternatives do not reduce to the simple question of keeping the threshold for research at 14 days or moving it to 21 days, 28 days or another factor of 7.

The 14-day rule is regarded as too permissive by those adhering to the full status position and is set far below any plausible threshold for holders of the no status position. According to the proportional status view, the balancing exercise between the rights[8] or interests of an embryo and those with full status becomes more demanding as the embryo develops. Merely tolling the bell of possible benefits from advancing scientific knowledge will only take us so far; how far will depend on the underlying theory or intuition. The need for such a balancing exercise makes any variant of the proportional status position more complex in application than the full or no status positions for which one key factor in the moral evaluation is static. The proportional status camp is further complicated by it encompassing many otherwise divergent positions.

I have, elsewhere and with others, defended a variant of the proportional status position as an application of Gewirth's Principle of Generic Consistency (PGC).[9] This principle requires agents[10] to act in accordance with the rights of all agents to their generic needs (i.e. to what is needed, to at least some degree, to successfully pursue chosen purposes as such). In application, it grants full status to those who are apparently agents and proportional status to those displaying only partial possession of the associated traits and characteristics. Research on embryos, when aimed at addressing the generic needs of apparent agents, requires a multivariable evaluation in which some features can be addressed directly (by deductive application of the PGC), but the overall evaluation will necessitate the indirect application of the PGC (by procedural mechanisms required by its deductive application). The 14-day rule is a potential outcome of the indirect application of the PGC. The comparatively low moral status of the early embryo, however, implies that an exceptionless 14-day threshold should not be regarded as unrevisable irrespective of scientific developments.[11]

Many contemporary conceptions of public reason and public ethics take the appeal to procedure further by rejecting its foundation in, and restraint by, a moral principle of this type and instead requiring all ethical arguments to be translated into shared or agreed values.[12] The rub is that the debate on the limits of permissible embryo research can easily become one over core values, thereby curtailing options for consensus or compromise.

Here, I restrict myself to some general philosophical points. First, any biological structures used to support a regulatory threshold for embryo research will have functional equivalents in (at least some) other species and will therefore support a case for equivalent protection for those other species. Secondly, insofar as the potential of a human embryo to develop further within a suitable uterine environment is relevant, it varies in degree between individual embryos and is subject to

manipulation. Thirdly, where destructive embryo research is supported despite the embryo being recognised as possessing moral status, the knowledge gained from each experiment should be recorded and disseminated with the aim of limiting avoidable replication and maximising the knowledge gained.

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1 Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at paragraph 11.17.

2 Section 3(3)(a) of Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents.

3 See further Pattinson SD (2014) *Medical Law and Ethics, 4th Edition* (London: Sweet and Maxwell), especially chapters 7, 8 and 10.

4 Hyun I, Wilkerson A and Johnston J (2016) Embryology policy: Revisit the 14-day rule *Nature* **533**: 169-71.

5 Ethics Advisory Board, US Department of Health Education and Welfare (1979) *HEW support of research involving human* in vitro *fertilization and embryo transfer* (US Government Printing Office), at page 107.

6 Department of Health & Social Security (1984) *Report of the Committee of Inquiry into Human Fertilisation and Embryology (Cmnd.9384)* (London: HMSO), at paragraphs 11.5 and 11.22.

7 See Pattinson SD (2002) *Influencing traits before birth* (Aldershot: Ashgate), at Appendix 3; and Hyun I, Wilkerson A and Johnston J (2016) Embryology policy: Revisit the 14-day rule *Nature* **533**: 169-71.

8 Such rights would have to accord with the interest conception, rather than the will conception of claim-rights.

9 See Gewirth A (1978) *Reason and morality* (Chicago: Chicago University Press) and the defence of meta-principles for its application in Beyleveld D and Pattinson SD (2000) Precautionary reasoning as a link to moral action, in *Medical Ethics,* M Boylan (Editor) (Upper Saddle River, New Jersey: Prentice-Hall), p39; Pattinson SD (2002) *Influencing traits before birth* (Aldershot: Ashgate); Beyleveld D and Pattinson SD (2010) Defending moral precaution as a solution to the problem of other minds *Ratio Juris* **23**: 258-73; and Capps P and Pattinson SD (Editors) (2017) *Ethical rationalism and the law* (Oxford: Hart), especially chapter 1.

10 Agents are those able to act for their own chosen purposes and, as such, the only intelligible addressors or addressees of moral prescriptions or practical precepts of any kind.

11 See further Pattinson SD (2002) *Influencing traits before birth* (Aldershot: Ashgate), chapter 4, especially pp.99-100.

12 See e.g. Rawls J (1997) The idea of public reason revisited *University of Chicago Law Review* **64**: 765-807.

Reviewing the 14-day limit on human embryo research

Julian Hitchcock[*]

The legislature should consider three essential objectives when considering any proposed life science law. Is it practicable and free from ambiguity (the certainty test)? Does it reasonably anticipate future advances (the progress test)? Above all, is the legislature competent to make such a law (the competence test)? I am confident that, in reviewing the 14-day limit on human embryo research, Parliament can pass the first two tests. However, I doubt that it or the public is yet capable of passing the third.

Ethical consideration without a rigorous understanding of the underlying science is meaningless; indeed unethical in its capacity to mislead. Nevertheless, I believe that an opportunity has arisen to equip Parliament to reform the law appropriately and proportionately. By more than doubling the time available for embryonic study within the current limit, the Zernicka-Goetz extended embryonic culture system provides an opportunity to develop novel scientific bases for informing ethical debate and future legislative proposals. Whilst declaring a personal preference towards a more permissive regime, I believe that no Bill should be presented to Parliament before an expert committee has reported to it on the ethical and legal implications of this new data set, and serious efforts have been made to increase public understanding of human embryology.

The character of life science laws

Life science innovations emerge into a dense legal environment. Most are technical improvements that click neatly into a regulatory framework designed to receive them. Occasionally, however, an advance calls that framework into question. At one extreme, the law may expose people to a new risk; at the other, it may deny them a benefit carrying no risk at all. The legislature has a heavy responsibility to avoid such statutory fossilisation. If the integrity of evidence is fundamental to justice in judicial proceedings, it is more so in legislative proceedings, because statutes based on ‘alternative facts’ guarantee injustice whenever the resulting law is applied.

Parliamentarians must therefore base replacement laws on up-to-the-minute scientific evidence, and be equipped to challenge naive, fraudulent and doctrinal claims robustly. It is not necessary for MPs or peers to mislead Parliament directly or deliberately: statutory injustice arises whenever Parliamentarians use Acts of Parliament to privilege fallacies over empirical facts in order to satisfy a public that believes them. The key to ensuring that any new life science law is both just and democratic is therefore to empower members of the public to assess the issues

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critically despite a mass of false information, enabling them to distinguish fact from doctrine ideology, and, in many cases, headline.

(In passing, I consider it legitimate to argue that, whether or not the embryo suffers, humanity is harmed by a purported 'commodification' of human life. I disagree with this view: without evidence, it is meaningless. Positions should never be privileged by dint of being doctrinal.)

Proxies, practicality and progress

The 14-day rule is a 'proxy' rule. It creates legal certainty by linking a legal effect, prohibition, not to a biological event, but to the time at which that event is assumed to take place: "[…] the primitive streak is taken to have appeared in the embryo not later than the end of the period of 14 days […]".[1] Reference to a specific post-fertilisation (or equivalent) day meets the certainty test, by freeing courts from having to consider detailed questions concerning the state of embryological development: a 19-day proxy limit would be more practicable than a 'neural tube rule', for example. However, even such a revised limit would fail the progress test, because the proxy date stands for a naively characterised biological event of limited ethical significance. It is here that Parliament and the public have most to learn in order to pass the competence test and where the opportunity lies for rules that more honestly reflect scientific reality. In particular, any review should reflect the shift in biological reckoning from the morphological perspective prevalent at the time of the Warnock Committee to one focused on dynamic gene activities within the developing embryo and their phenotypic implications.

Morphological assessments have the practical merit that they do not require researchers to interfere with the object of study. Assessment of genetic events, on the other hand, can only be visualised by means of an intervention, such as the application of a fluorescent marker. Genetic tagging is, however, a standard tool of developmental biology, and as studies establish the range of post-conception times (PCTs) as proxies for specific genetic events, there would be no need to use genetic tags at all. For example, the PCT for specific genetic or histological events (which might, in principle, be determined in hours and not days) may be recruited as a proxy exactly as the 14-day limit currently stands for a morphological event. The challenge is to produce a continuously updated Carnegie stage table, setting out by PCT, not only morphological development, but genetic, histological and systemic activities for each Carnegie stage and inter-stage. These data should be available in a user-friendly format that enables the public to understand the significance of each event in ethical terms.

Two particular instances stand out: the migration of germ cells and the emergence of neural perception. The former might, in principle, inform debate about genomic editing of the embryo, but feels less directly relevant. However, neural perception is obviously pertinent. The prevalence of the myth that the primitive streak establishes the

embryo's central nervous system at least confirms that sentience and the ability to feel harm are key ethical criteria for many people. Ethical discussion, and by extension statutory justice, would be impoverished without reviewing a PCT index of the stages of sensory neural development and physiology.

Even if the embryo were to experience sensations, however, some will ask whether it is a human being that is doing the sensing, or merely a potential one. Early human development may differ little from that of closely related species only in a potential that, subject to cultivation limit, is largely theoretical. Species comparative stage tables might, therefore, inform ethical discussion of exclusively human characteristics.

Finally, it should be emphasised that the statutory purposes for licensing human embryo research are directed towards securing the 'human dignity' of born human beings from the ravages and indignity of disease.[2] Research on post-14-day embryos would further secure 'human dignity'. Placing the dignity of pre-persons above that of actual persons appears not only to be wrong, legally,[3] but unethical too.

Limits on the limit

The 14-day rule implies termination of the embryo's existence. Legally, termination means the point at which the cultured entity ceases to be defined as such under Section 1 of the Human Fertilisation and Embryology Act 1990 (the Act).[4]

> "In this Act […] (a) embryo means a live human embryo […] and (b) references to an embryo include an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo."

Point (a) implies that allowing the embryo to perish will bring it outside the definition. But so, too, would a process that stopped the embryo from being 'human'. This is to beg the question, but scientific reflection can inform it. Certainly, an entity deprived of one or more germ layer (endoderm, ectoderm or mesoderm) cannot be deemed to be any sort of embryo: even if its cells were to be cloned and implanted, they could not give rise to a human being. Similarly, if emergent structures, such as epiblast and trophectoderm, were to be isolated from one another within the first 14 days PCT, no 'human' embryo, and thus no 'embryo' for legal purposes, would remain. The isolated structures could, if technically feasible, be lawfully cultivated for indefinite periods[5] under the existing framework.

Point (b) suggests another approach to the same facts. Parliament's Dolly-prompted revision of a previous definition is a tail-eater: an embryo includes something "that is […] undergoing a process capable of resulting in an embryo". [6] What (aside from the fact that this carelessly captures things that are unlikely to become embryos) does this mean? I suggest that guidance may be found in the decision of the Court of Justice of the European Union, in *International Stem Cell v Comptroller General of Patents, Designs and Trade Marks*,[7] that a parthenote does not constitute a 'human embryo'

under the Biotechnology Directive,[8] if, “in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human being”.

Construing the Act in this way, this would capture our de-constructed embryo. However, it would also be relevant if, instead of surgically dissecting out embryonic structures at day 13, we were to perform an equivalent genetic intervention to prevent the development of mesoderm, trophectoderm or some other fundamental constituent. Not only would the material cease to be a ‘human’ embryo for the reasons outlined above, but it would have no more “inherent capacity of developing into a human being” than a parthenote. On this ground, too, it is not a human embryo for purposes of the Act, and it may be used for research purposes beyond 14 days under the present law.[9]

No doubt the ability to culture individual structures would provide a useful basis for experimentation. However, as the very point of such isolation is to destroy the coherence of the former embryo, it may be of limited utility. However, coherence could be maintained by editing the embryo’s genome so as to bring it outside the human genome. Although a human embryo that has been altered by the introduction of ‘animal DNA’ is regulated as a ‘human admixed embryo’,[10] the Act fails to contemplate the effect of introducing plant, microbial or viral DNA, or even just DNA, or of otherwise editing it.[11] Is an embryo with a non-human genome ‘human’? In what circumstances should it be deemed so? In which should it not? Who is competent to decide? These issues, which require us to reflect more deeply on the genetic identity of human beings, should be explored in any review of the current limit.

We should also consider the reverse situation: in which a synthetic entity with embryo-like features (SEEF) is constructed from constituent stem cells. This was achieved using a mouse model shortly after the first draft of this note, in a way that, had it been made of human cells, would not have enabled it to pass the suggested International Stem Cell (ICT) test[12] (i.e. it would not be a “human embryo” in law). Suppose, however, that 16 to 20 human stem cells were to be assembled into a synthetic morula that would pass our ICT test. Theoretically, the Act ought to permit cultivation to a point equivalent to day 18 PCT, because, although the 14-day limit begins “with the day on which the process of creating the embryo began”,[13] the morula would ordinarily arise at day four PCT. In principle, if not necessarily in practice, studies could involve deconstructing and then re-assembling embryos in some manner. If ‘human’ at that point, the clock would start running again and would end at gastrulation. Such attempts, if justified, would only represent an abuse of the present law if conducted for a non-statutory purpose or were contrary to the deemed intentions of Parliament.

In summary, important research may be undertaken under licence without extending the statutory limit. This work will help to populate the canonical Carnegie stage table with data that, aside from its biomedical value, should inform any ethical and legislative review.

The Act provides a clear framework for amending the 14-day rule and licensing therapeutic editing of mitochondrial and, perhaps in future, nuclear DNA.[14] These conditions may converge: for example, if therapeutic intervention on the embryo is plausible within 14-days PCT,[15] could circumstances arise in which *in vitro* intervention becomes more justifiable after 14-days? Finally, however, any review of ethical bases and regulatory design must consider the position of human SEEFs ('SHEEFs'),[16] entities which, by existing outside the canonical stages, expose the weakness of regulating conduct according to canonical proxies. Pending such a review, I would ask the HFEA to adopt a constructive and unrestrictive approach to all such matters, taking care to stay firmly within its statutory remit.

Notes

1 Section 3(4) of Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, ('the Act') – my emphasis. If a primitive streak were to appear at e.g. eight days, the limit would arise automatically.

2 As these comprise an assault on bodily integrity, efforts to resist them are consistent with the right of integrity under Article 3(1) of the EU Charter of Fundamental Rights and Freedoms: "everyone has the right to respect for his or her physical and mental integrity". The Charter is deemed to restate existing UK law, so any UK departure from the EU should be immaterial here.

3 There is no legal basis for privileging the supposed dignity of entities that cannot be born over the actual dignity of those that have been. All human rights laws that refer to 'human dignity', starting with the United Nations Declaration on Human Rights 1948, refer to the dignity of human 'persons' who have, by definition, been born. The opening of the Declaration, "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood", repeats the answer ("Men are born and remain free and equal in rights […]" (Declaration on the Rights of Man and of the Citizen, Assemblée Nationale Constituante, Paris, 26 August 1789)) to Rousseau's Social Contract: "Man was born free, and is everywhere in chains.**"**

4 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, as amended by the Human Fertilisation and Embryology Act 2008.

5 Without any obligation to deposit equivalent structures at the UK Stem Cell Bank.

6 Embryo means embryo.

7 *International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks* (Case C-364/13) (2013) O.J.E.U. C-260.

8 Official Journal of the European Communities, (1998) *Directive 98/44/EC on the legal protection of biotechnological inventions*, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:HTML.

9 Subject to a licence.

10 Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, as amended by the Human Fertilisation and Embryology Act 2008, at section 4A(6).

11 Any of which stands a far greater chance of falling outside the class of organisms imbued with the human genome.

12 See Harrison SE, Sozen B, Christodoulou N, Kyprianou C and Zernicka-Goetz M (2017) Assembly of embryonic and extraembryonic stem cells to mimic embryogenesis in vitro *Science* **356(6334)**: eaal1810.

[13] Legislation.gov.uk (2017) *Human Fertilisation and Embryology Act 1990*, available at: http://www.legislation.gov.uk/ukpga/1990/37/contents, as amended by the Human Fertilisation and Embryology Act 2008, at section 3(4). The embryo would still have to be 'human', and have (in my view) "the inherent capacity of developing into a human being".

[14] Under a new Act of Parliament to permit a genetic alteration other than one made by mitochondrial transfer under Legislation.gov.uk (2015) *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*, available at: http://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents.

[15] Provided no cells are added to it from another source. Ibid, at Section 3ZA(4).

[16] See Aach J, Lunshof J, Iyer E and Church GM (2017) Addressing the ethical issues raised by synthetic human entities with embryo-like features *eLife* **6**: e20674

Compromises, fudges and thresholds

Dave Archard[*]

The Warnock Report sought to ensure (and to reassure the general public) that certain things could not and would not be done to the human embryo. One way it did this was to characterise the human embryo as having a 'special' status. This characterisation has frequently been described as a 'fudge' or a 'muddle'.[1] Philosophers were also unhappy with the Committee's recommendations seeing them as merely endorsements of what was, at the time, 'roughly acceptable' rather than morally defensible positions.[2]

The selection of the 14-day threshold is seen as part of this putatively indefensible approach. I think, however, that it can be defended. In the first place, it is obvious that law and regulatory regimes do need thresholds. These are many and varied. In the context of artificial reproduction alone, one can think of several: the number of families a single gamete donor can be permitted to create; the age limit for the provision of assistance with artificial reproduction; the number of embryos created *ex utero* that it is permitted to put back.

Thresholds are open to two importantly different kinds of criticism: first, that thresholds as such are a bad thing and are not needed (one could, for instance, use other criteria for making the relevant decisions); and, second, that the selection of a particular threshold is unjustified. In turn, the second criticism can be one of *arbitrariness* (why is *any* particular threshold justifiably preferable to some other?) or one of *misidentification* (why is *this* particular threshold the right one?). Compare the case of picking a voting age. Whatever age is selected, the charge can (and will) be made that some other age would do just as well, so why is 18 picked out as the one; or it will be said that the age which is picked is inferior to some other at which the relevant distinction is more reliably picked out, so why is someone at 18 qualified to vote whereas someone at 17 is seen as disqualified.

No one thinks that there should be no upper time limit in respect of embryo cultivation for research. Moreover, time limits (measured in discrete days or weeks) may be counted a generally reliable (but not invariant and necessary) correlate of developmental stages. In this sense, a particular time is a *proxy* for the achievement of certain developmental milestones. In short, criticism of the 14-day rule is most likely to be about the choice of 14 rather than about the use of a number of days *per se*.

In her autobiographical account of her policy roles, Mary Warnock identified as one of the two issues on which her Committee could not agree and as that which "was

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fundamental to the whole enterprise" the question of whether embryo research was permissible, and, if so, should be subject to mandatory regulation. The impossibility of agreement arose from a dispute as to the status of the embryo. It was between those who saw the embryo from the outset as a human person, and those who saw it as 'not yet' a human person. Warnock identifies 11.9 as "the most crucial" paragraph of the Report. It identifies this disagreement, and affirms the precept that an answer to the question of what status ought to be accorded to the embryo "must necessarily be in terms of ethical or moral principles".

Yet the choice of a developmental threshold for permissible research did not provide an answer to that question exclusively in terms of moral principles. This is because, as Warnock also acknowledges, "an absolutely central consideration" in the work of her Committee was "the difference between what […] was sensible, or even morally right, and what is most likely to be acceptable as a matter of public policy".

In effect, the threshold of 14 days was supported by what she terms an "*amalgam of arguments*". These fall into quite distinct categories. There are, first, independently of and outside policy considerations, metaphysical and moral reasons supporting the particular threshold chosen. In the case of 14 days, these were the thought that beyond but not before that point there is a single identifiable human being and, further, a being that can experience pain.

Second, the threshold chosen is an acceptable compromise between the positions identified in Paragraph 11.9. A compromise is a set of mutually agreeable concessions by parties to otherwise incompatible positions who prefer such concessions to continued disagreement.[3] Think, for instance, of an agreed policy on abortion as a compromise between the 'clash of absolutes' (pro-life and pro-choice) that is managed by fixing a time limit and/or circumstances under which a termination is legally permitted (e.g. for health of mother; rape; severe fetal abnormality).

Third, the use of the threshold can be argued to prevent a problematic slide down a *slippery slope*. Following Bernard Williams and others, the crucial slide is not an argumentative or logical one but an empirical one ("Allowing P – that may be tolerable – will, as a matter of fact, lead to tolerance of Q, R and S – that is intolerable").[4] The slope is not one of logical entailment (a belief in the permissibility of P commits one to a belief in the permissibility of S) but rather of certain or probable developments if P is allowed. We should immediately add that a slippery slope may, as a matter of fact, be unlikely but nevertheless be one that is plausibly and generally feared. In other words, the public may believe that a slide down the slope is likely even if it is not imminent or probable.

Fourth, the threshold ought to be a *clear, determinate and precise* one. In this vein Warnock favoured a time specified one rather than the achievement of a developmental stage. There is a vagueness and indeterminacy about the latter given the variation between embryos in developmental progress and because the question

of when exactly a stage has been reached may be unclear. By contrast, this is not the case for a limit defined as a specific number of days.

Fifth, a regulatory scheme that uses the threshold should be *feasible*. The scheme can be enforced in a manner that all relevant parties can readily see is transparent and as such can be conformed with. Everyone knows what they have to do and must not do.

Sixth, the use of the threshold chosen permits research that will (probably) yield significant (sufficient) good. These parenthesised qualifications make a difference for reasons that I will return to.

Warnock was, in my view, absolutely right to think that a threshold in this area of policy making is supported by an amalgam of arguments and ones of the kind that she indicates. She did not sacrifice the integrity of philosophical argument to simple considerations of pragmatic success. Rather she sought to support her conclusions with different but mutually reinforcing reasons.

Hence, the following points need to be made:

- First, making successful policy on this matter is not straightforwardly a matter of winning a philosophical argument on an issue such as moral status and the nature of personhood.

- Second, the different arguments within the amalgam must be carefully weighed and balanced against one another. Nevertheless, the difficulty of doing so should be openly acknowledged. This difficulty is directly attributable to the very different nature of each argument and reason.

- Third, compromises that have been made can also be unmade and re-made. They are essentially unstable and contingent responses to particular conflicts of viewpoint, interest and preference. They crucially depend on the balance of positions, and on the strength of the different parties' commitment to them. These can all change over time. One party to a compromise may relinquish or alter their view. Parties may also be in a stronger position than previously and less willing to maintain the existing compromise; or, conversely, in a weaker position and unable to sustain their prior contribution to a particular compromise.

- Fourth, Warnock calculated that the threshold chosen would permit significant research to be done. However, there is a crucial difference between the certainty of future research outcomes, and their probability. There are also differences in the kinds of research, and the value of their respective outcomes. In consequence, there are different valuations to be made of the permissions granted to various kinds of research. What is guaranteed and what is only probable may also change over time; equally what is and is not valuable is not fixed.

In sum, the recommendation of the 14-day rule was not an intellectually indefensible fudge, mess or simple compromise. It was warranted by several important considerations. Times may have changed to a point where some of the considerations in its favour no longer have the force they once did. That does not show that they did not have force at the time; nor that the *kind* of consideration that formed a part of the amalgam should not still be taken seriously.

Notes

1 See, inter alia, Fox M (2000) Pre-persons, commodities or cyborgs: the legal construction and representation of the embryo *Health Care Analysis* **8(2)**: 171-88, at pp 171–181; Brazier M (1999) Regulating the reproduction business? *Medical Law Review* **7(2)**: 166-93.

2 Hare R (1993) In vitro *fertilization and the Warnock report*, in Essays on bioethics, Hare R (Oxford: Clarendon Press); Lockwood M (1985) The Warnock report: A philosophical appraisal, in Moral dilemmas in modern medicine, Lockwood M (Editor) (Oxford: Oxford University Press), pp155–186.

3 See, for example, Benjamin M (1990) Splitting the difference: compromise and integrity in ethics and politics (Lawrence, Kansas: University of Kansas Press), at chapter 1; and Golding M (1979) The nature of compromise: a preliminary inquiry, in Compromise in ethics, law, and politics, Pennock J, and Chapman J (Editors) (New York: New York University Press), pp 3-25.

4 Williams B (1985) Which slopes are slippery?, in Moral dilemmas in modern medicine, Lockwood M (Editor) (Oxford: Oxford University Press), pp26-37.

Appendix

Workshop agenda

NUFFIELD COUNCIL ON BIOETHICS

Workshop:

STATUTORY TIME LIMIT FOR MAINTAINING HUMAN EMBRYOS IN CULTURE

The Nuffield Foundation, 28 Bedford Square, London, WC1B 3JS
Friday 16 December 2016 at 10.00 am

AGENDA

1 **Welcome and introductions**
Jonathan Montgomery (Nuffield Council on Bioethics)

2 **Setting the scene – challenges and opportunities**
Sheelagh McGuinness (University of Bristol)

3 **What has the current limit achieved?**
Invited interventions followed by plenary discussion

4 **How might scientific opportunities change if the limit were redrawn?**
Invited interventions followed by plenary discussion

* Lunch *

5 **Developmental thresholds and their moral and policy significance**
Invited interventions followed by plenary discussion

6 **International context and implications**
Invited interventions followed by plenary discussion

7 **Review of interests engaged**
Chaired discussion

8 **Conclusions and representations**
Jonathan Montgomery (Nuffield Council on Bioethics)

Workshop attendees

Jonathan Montgomery (Chair), Professor of Health Care Law, University College London; Chair of the Nuffield Council on Bioethics (2012-2017)

Sam Alvis, Policy Officer, Wellcome

Dave Archard, Professor of Philosophy, Queen's University Belfast

Liz Bohm, Senior Policy Advisor, Royal Society

Sheny Chen, Senior Portfolio Developer, Wellcome

Andrew Chisholm, Head of Cellular and Developmental Sciences, Wellcome

Katrien Devolder, Marie Curie Fellow, Oxford Uehiro Centre for Practical Ethics, University of Oxford

Charlotte Elves, DPhil Candidate, Faculty of Law, University of Oxford

Grace Gottlieb, Senior Public Affairs and Policy Officer, Medical Research Council

Andy Greenfield, Programme Leader in Developmental Genetics, Medical Research Council's Harwell Institute and member of the Nuffield Council on Bioethics

Joyce Harper, Professor in Human Genetics, University College London

Julian Hitchcock, Counsel, Denoon Legal LLP (now Marriott Harrison LLP)

Elselijn Kingma, Professor of Philosophy, University of Southampton

Tom Livermore, Science Policy Officer, Royal Society of Biology

Sheelagh McGuinness, Senior Lecturer, University of Bristol Law School

Pete Mills, Assistant Director, Nuffield Council on Bioethics

Kathy Niakan, Researcher, The Francis Crick Institute (pm only)

Shaun D. Pattinson, Professor of Medical Law and Ethics, Durham University and

member of the Nuffield Council on Bioethics

Sandy Starr, Communications Officer, Progress Educational Trust

Mehrunisha Suleman, Centre of Islamic Studies, University of Cambridge

Hugh Whittall, Director, Nuffield Council on Bioethics

Magdalena Zernicka-Goetz, Professor and Director of Mammalian Development and Stem Cell Research, University of Cambridge

The event was also attended by **Matthew Hill** (Health Correspondent for BBC in the West) and **Deborah Cohen** (BBC Radio Science Editor). It was subsequently featured in the two-part BBC Radio 4 programme 'Revisiting the 14-day rule', broadcast in January 2017 (Episode 1 on 17 and 23 January and Episode 2 on 24 and 30 January), available at: http://www.bbc.co.uk/programmes/b08cj7w8. The programme included interviews with Jonathan Montgomery and Magdalena Zernicka-Goetz.

Nuffield Council on Bioethics staff Ranveig Svenning Berg and Bettina Schmietow provided additional assistance and support with the meeting arrangements; Catherine Joynson, Ranveig Svenning Berg and Shaun Griffin also assisted with the preparation and publication of the final report.