The ethics of embryo research and the 14-day rule

Grant Castelyn

Bachelor of Arts, Philosophy

Department of Philosophy, Faculty of Arts

Macquarie University

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Summary

Recent advances in the field of developmental biology have enabled the culturing of embryos for 13 days, significantly longer than the previous record. Any further culturing is restricted by a widespread regulation on embryo research known as the '14-day rule'. Following the announcement of the advances in *in vitro* culturing, there have been several calls from scientists and philosophers to revisit the rule, with many suggesting that an extension is appropriate.

Arguments for an extension typically claim that research into later periods of embryonic development would lead to significant beneficial applications, easing the suffering and extending the lives of many. However, embryo research is still a contentious issue; concerns about the harms of embryo research which have been raised in the past, are being reiterated in response to the proposed extension.

In this thesis, I consider the appropriateness of an extension. My analysis begins with an ethical evaluation of the grounds and justifications for the existing 14-day limit on embryo research. I then examine arguments for an extension and, in the final part of the thesis, consider some new developments in the field of embryo research which pose potential challenges for its regulation. I argue that there are strong reasons to support an extension to the current 14-day limit and outline an alternative criterion on which an amendment could justifiably be based.

Candidate Statement

I certify that this thesis entitled "The ethics of embryo research and the 14-day rule" is an original piece of research that has been completed by me. It has not previously been submitted for a higher degree to any other university or institution.

The information used in this research has been obtained from a variety of published sources, including journal articles, books, reports, legislation, podcasts, and online publications. The use of these information sources has been appropriately indicated in the thesis. Any assistance that I have received has also been acknowledged.

This research did not require Ethics Committee approval.

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Introduction

There has been a longstanding controversy regarding the permissibility of embryo research, with polarization between those emphasizing the potential benefits and those alleging the mistreatment of embryos. Recent advances in the field of developmental biology have reignited this debate, raising new questions about the current research restrictions. In this thesis, I will investigate the ethical implications of an amendment to current embryo research regulations.

Human embryo research is currently regulated by a guideline known as the '14-day rule', which prohibits the culturing of human embryos beyond 14 days of development. In May 2016, two teams published the results of related experiments in which human embryos were cultured *in vitro* for up to 13 days (Deglincerti et al., 2016; Shahbazi et al., 2016). The duration in which the embryos were sustained is a significant extension to what has previously been achieved (Carver et al., 2003). It is therefore the first time that the 14-day rule has served as a practical restriction to research. This increase in *in vitro* embryo viability has prompted calls for an extension to the 14-day limit on embryo research.

The ethical issues relating to the proposed extension of the limit are similar to those that motivated the initial regulation of embryo research: namely, whether research should be allowed because of the potential benefits; or whether it should be prohibited because of concerns relating to the mistreatment of the embryo. The 14-day rule aims to resolve this conflict by specifying a point after which research would entail the misuse or mistreatment of the embryo. Justification regarding the moral significance of 14 days is necessary to support this claim. Some have regarded the 14-day limitation not as the result of a substantive settling of the moral questions, but rather as the result of a more

pragmatic decision regarding a way to move forward – an attempted compromise between conflicting moral concerns, regarded as necessary to provide an acceptable basis for legislation. (Hyun, Wilkerson, & Johnston, 2016; Hyun, 2016; Chan, 2017; Cavaliere, 2017; Elves & McGuinness, 2017).

In this thesis, I examine the reasons supporting the setting of this limit at 14 days. I claim that the same reasons that underpinned the original proposal for the 14-day limit are relevant to determining whether it should be extended. As such, an assessment of the moral significance of the 14-day limit, and the ethical justifications for an extension, is necessary. I maintain that the success of extension arguments will, in part, depend on the strength of the justifications supporting the 14-day limit. I argue that the ethical considerations that have supported the 14-day rule speak more strongly for an extension than the maintenance of the current limit.

Embryo research in Australia is currently regulated by the Licensing Committee of the National Health and Medical Research Council (the NHMRC Licensing Committee). This Committee was established by the Research Involving Human Embryos Act (2002), which prohibits the culturing of human embryos beyond 14 days of development ("Embryo Research Licensing Committee", 2017). While my investigation does not focus on a specific regulation, but rather the 14-day rule in general, it is important to note that my analysis and its conclusions will, if accepted, have implications for local embryo research regulations.

In Chapter One, I provide an overview of the background information relevant to the extension debate. I start by summarising the early stages of embryo development. I outline the embryo research dilemma, presenting an overview of conflicting values and concerns surrounding embryo research. Following this, I discuss the current state of the

14-day rule and the details concerning its formulation. I conclude the chapter by describing the recent scientific advances that have motivated the calls for an extension.

In Chapter Two, I assess the strength of the justifications for the 14-day limit. I identify two major justifications for the limit of 14 days – namely, that it represents a point beyond which individuation and neural development reach certain milestones. From a critical analysis of the arguments in support of these justifications, I show that neither provide a convincing basis for the limit being where it currently is. I go on to highlight how the 14-day rule currently enables early embryo research and that if the rule is invalid such research might be rendered either impermissible or, alternatively, unrestricted. I resist these conclusions by proposing that the identification of certain key precursors to sentience can provide a convincing criterion for protection of the embryo, and if accepted would provide support for an extension of the rule.

In Chapter Three, I attend directly to the arguments for an extension to the current limit. I assess the most prevalent reasons for extending the limit – namely, technical feasibility and beneficence – and conclude that they provide strong reasons for extending the limit. I then consider a possible alternative limit on research. On the basis of this analysis I contend that there is no relevant *moral* difference between a 14-day embryo and a 28-day embryo, and therefore that the additional benefits that would be afforded by research into this later period, support an extension.

In Chapter Four, I discuss specific challenges that may arise from a revision of the current embryo research regulation. I begin by considering arguments opposing an extension that appeal to possible resulting harms. I show that while there are practical difficulties associated with an extension, they can nevertheless be mitigated through a careful and considered amendment process. I then go on to discuss the challenges raised

by recent advances in synthetic biology, assessing the various problems that arise from the creation of synthetic embryo-like entities. These developments highlight an important feature of the 14-day rule as a regulation that is based on biological markers that preempt rather than directly trigger morally significant features. I argue that a concern for sentience can justify an extension to 'natural' embryo research while at the same time successfully addressing the new challenges posed by 'synthetic embryos'.

In assessing several key aspects relevant to the current embryo research debate, my thesis presents a constructive argument in support of an extension to the current research regulations. It is constructive in the sense that it not only endorses an extension to embryo research, but also addresses and responds to potential difficulties and future challenges. The value of such a proposal is that it would provide a practical and durable means by which to enable a wide range of research that may lead to the development of many therapeutic applications, potentially benefiting countless individuals.

Chapter 1: Embryo research

Since the beginning of embryo research there has been disagreement regarding its acceptability. As the field has progressed and greater insights have been made possible, the controversy surrounding the practice has intensified. The source of the contention arises from the conflict between the benefits and harms associated with embryo research. In this chapter, I provide an overview of the issues pertinent to the debate. I summarise the relevant period of embryo development and discuss the methods and outcomes of embryo research. This discussion highlights the conflict that has motivated the opposing views. I describe how the formulation of the current research regulations have attempted to resolve or address this conflict. The chapter concludes with a discussion of the recent scientific developments that have motivated the calls to extend the current limit.

Embryo development

Embryo research involves the use of organisms during the embryonic period of development. In humans, this period covers the first eight weeks (56 days) of development (Moore, Persaud, & Torchia, 2015; M.A. Hill, 2017). In this section, I will summarise the major developmental changes that occur during the first four weeks (1-28 days) of human development. The relevance of this period is that it covers the current period of allowable research (up to 14 days) and a proposed extended period (to 28 days). Development of the human organism is extremely complex and involves changes at many different levels. I will limit my summary to major changes, only mentioning details at the molecular and cellular level if they are relevant to questions regarding the moral considerability of the embryo.

The development of a human organism begins with fertilisation. This is a complex process (normally occurring in the fallopian tube) in which maternal and paternal DNA are combined through the merging of sperm and oocyte. The entire process takes approximately 24 hours, giving rise to what is known as the zygote. The first week of development continues with the zygote beginning a series of cell divisions ('cleavage') as it travels along the fallopian tube towards the uterus. Once the zygote reaches the uterus (2-3 days), it will consist of over 12 cells (blastomeres) and is referred to as a 'morula'. Midway through the first week (4-5 days), the morula begins a differentiation process in which the cells transform into the inner cell mass (ICM or 'embryoblast') – which will go on to form the embryo proper – and a surrounding outer cell layer ('trophoblast') – that will form the extra-embryonic structures. Towards the end of the first week, the embryo (now called a 'blastocyst') will hatch from the protective covering originating from the ovum (zona pellucida) and attach to the surface of the uterine wall (endometrium) in preparation for implantation (Moore et al., 2015; M.A. Hill, 2017).

Implantation continues into the second week of development, normally completing at approximately 10 days after fertilisation. After attaching to the uterine wall, the trophoblast differentiates into two distinct layers[1], after which (at approximately 7-8 days) the blastocyst begins to merge into the connective tissue of the uterine wall. During implantation, the blastocyst and uterus undergo many cellular and molecular changes that will enable the transfer of nutrients and hormones to the developing embryo. During the implantation process (around 8-9 days) the cells of the blastocyst

[1] The syncytiotrophoblast and cytotrophoblast, which play a role in the implantation process and go on to form some of the extra-embryonic structures.

undergo further internal developmental changes. A cavity (that will later become the amniotic cavity) begins to appear within the ICM as it differentiates into the epiblast and hypoblast[2], forming what is known as the bilaminar disc. At the end of the second week, a pregnancy can be detected by testing for a hormone that is produced by the embryo (Moore et al., 2015; M.A. Hill 2017).[3]

By the beginning of the third week (14-21 days) of development, the implantation of the embryo into the uterine wall is complete (Moore et al., 2015; M.A. Hill, 2017). This period of development is marked by the appearance of the so-called 'primitive streak', at around 15-16 days (Moore et al., 2015; M.A. Hill, 2017). The primitive streak – a thickened linear band on the epiblast that is formed by cell growth and migration – signals the beginning of gastrulation, a process in which the body plan of the embryo is formed. The emergence of the primitive streak is believed to represent the last point at which the embryo can successfully split into monozygotic twins (Smith & Brogaard, 2003). Gastrulation involves the differentiation of epiblast cells into the three germ layers of the ectoderm, mesoderm, and endoderm. The ectoderm will form skin cells and neurons; the mesoderm will form cardiac, skeletal, and muscle cells; and the endoderm will give rise to the gastrointestinal and respiratory tracts. The hypoblast will also undergo further differentiation, eventually forming the extra-embryonic mesoderm and yolk sac (Moore et al., 2015; M.A. Hill, 2017). After 18-19 days, development of what will eventually become the adult nervous system begins through a process known as 'neurulation'. This process involves a series of cell migrations and folding, which subsequently form the neural plate, neural groove, and eventually the

[2] These go on to form the three germ layers and yolk sac.

[3] Human Chorionic Gonadotropin (hCG)

neural tube – which will go on to eventually form the brain and spinal cord. Neural development continues throughout the rest of the embryonic and foetal periods and even after birth. Closure of the neural tube continues into the fourth week, normally completing at around 30 days of development. (Moore et al., 2015; ; M.A. Hill, 2017; Smith & Brogaard, 2003; Chen & Chisholm, 2017). During this time, the primitive heart tube forms and the first formation of blood cells begins (approximately 19 days) (Chen & Chisholm, 2017).

During the fourth week (21-28 days) the embryo forms a number of body segments ('somites') and at this time the heart normally begins to beat (22-25 days). Although, recent evidence suggests that this may occur as early as 16 days (Tyser et al., 2016). Neural development continues with the emergence of early brain structures known as 'primary vesicles'. These are very basic structures which, after the formation of the secondary vesicles in the fifth week of development, will eventually go on to form the structures of the adult brain. During the fourth week and even into the fifth week, the synaptic nerve connections and parts of the brain that are necessary for sensation have not yet begun to form. (Moore et al., 2015; M.A. Hill, 2017; Chen & Chisholm, 2017)

The embryo research debate

The significance of the embryonic period (particularly the early stages outlined above) is that it involves fundamental developmental changes which can have major effects on later stages of prenatal development and throughout the adult life of the organism (Fischbach & Fischbach, 2004; McGee, Philpott, Kuhn, Robertson-Kraft, & Patrizio, 2005; Monahan, 2016). A detailed understanding of the processes that drive these early stages of development is not only of theoretical interest, but can also lead to many beneficial scientific and therapeutic applications. It is these potential benefits that

arguments for the importance and even necessity of embryo research are based on. The potential for beneficial therapeutic applications has led to an increase in both the amount and scope of research currently being conducted using human embryos.

However, the use of human embryos as research subjects raises some challenging moral questions. The concern that embryos may be mistreated has led to strong opposition to embryo research. In the remainder of this section, I outline the implications of embryo research, which inform the opposing positions of the embryo research debate. I start by summarising the proposed benefits of embryo research.

Benefits of embryo research

The contribution to applied scientific knowledge that research using human embryos enables, is considered to be of great importance. One of the most notable therapeutic applications of embryo research is the development of assisted reproductive technologies (ARTs), such as *in vitro* fertilisation (IVF). IVF has made it possible for many infertile individuals to have genetically related children, alleviating the psychological and social consequences that often accompany the inability to produce a child (Cousineau & Domar, 2007). Ongoing embryo research has resulted in dramatic increases in IVF success rates, avoiding distress and benefiting millions of individuals (Horsey, 2006), and has led to various diagnostic and therapeutic applications such as preimplantation genetic diagnosis (PGD) and mitochondrial replacement (MR) techniques.

PGD is a method of early prenatal diagnosis in which cells from *in vitro* embryos are biopsied for high risk genetic diseases, such as cystic fibrosis and Huntington's disease, or for chromosomal abnormalities that may reduce the chances of a successful IVF

pregnancy.[4] Embryos that indicate a lower risk for disease or that exhibit fewer abnormalities are selected for transfer (Sermon, Steirteghem, & Liebaers, 2004; Roberston, 2003). The lower quality or higher risk embryos may either be destroyed or frozen for future use. Early forms of PGD focused on sex-linked genetic diseases by identifying embryo chromosomes. While PGD techniques are now far more advanced, the procedure is still used for the practice of sex selection for medical reasons (Williams & Wainwright, 2014). There has been some criticism regarding the use of PGD. These objections are generally concerned with social issues that relate to attitudes towards disabilities, and concerns about eugenics and 'designer babies' (Williams & Wainwright, 2014). While these ethical objections are of serious concern, the use of PGD has nevertheless brought significant benefits (Sermon et al., 2004; Roberston, 2003; Gavaghan, 2006). There is substantial evidence that PGD has enabled increases in successful IVF pregnancies, provided an alternative to pregnancy termination, and reduced instances of genetic diseases in children.

Much like PGD, MR techniques are used to avoid pregnancies with embryos that have certain diseases and conditions. The target of MR techniques are mitochondrial DNA diseases (mtDNA diseases) that result from abnormalities in maternal mitochondrial genes. These abnormalities can have significantly detrimental consequences for the affected embryo, often resulting in conditions such as Leigh Syndrome (Thorburn, Rahman, & Rahman, 2003; Ciafaloni, et al. 1993) and Mitochondrial DNA Depletion Syndrome (Millichap, 2002) which typically entail substantial suffering and reduced life expectancy. MR techniques avoid mtDNA disease by substituting the abnormal mitochondria from the mother with healthy mitochondria from a donor. The resulting

[4] Embryo biopsy is only one method for PGD.

embryo contains genetic material from three individuals: the mother, father, and the mitochondrial donor, hence the label 'three parent babies' (Torjesen, 2013). Concerns have been raised about the unknown long-term effects of MR techniques (Baylis, 2013) and about the social implications that may result from the novel number of progenitors (Scully, 2017). However, regardless of these concerns, MR techniques can allow women with abnormal mtDNA to have genetically related offspring free from the detrimental effects of mtDNA disease.

While these diagnostic and therapeutic applications have had a significant impact in alleviating infertility and avoiding instances of genetic disease, arguably the most remarkable breakthrough resulting from embryo research is the discovery of human embryonic stem cells (hESCs) (McGee et al., 2005). hESCs are undifferentiated cells that make up the early embryo. Depending on the stage of development hESCs can be totipotent or pluripotent. Totipotent cells can become any cell type of the human organism, including the extra-embryonic support structures (e.g. placenta, umbilical cord). Pluripotent cells are still able to differentiate into almost any cell type of the adult human organism, but are no longer able to form the extra-embryonic structures.

Research on hESCs can provide insight into the mechanisms that drive the differentiation processes vital to the development of the embryo and that play an ongoing role in the adult life of the organism. Greater knowledge of these developmental mechanisms may enable the prevention and treatment of congenital conditions and developmental abnormalities (e.g. birth defects and miscarriage) (Devolder, 2015; Cowan et al., 2004; Reubinoff, Pera, Fong, Trounson, & Bongso, 2000).

A sufficient understanding of the properties that underpin the potency of hESCs and the mechanisms that direct the differentiation process may also enable vast therapeutic applications, not only for reproductive purposes such as the health and wellbeing of the embryo, but also for the treatment of a great number of diseases and conditions that can occur throughout the human lifespan. By creating stem cell lines that can proliferate indefinitely, and by uncovering the molecular triggers necessary to direct cell differentiation, stem cells may be used to create cells and tissue of almost any type (Reubinoff et al., 2000). This possibility has several significant applications. For example, such cells and tissues have the potential to aid in the development and testing of new drugs (Fischbach & Fischbach, 2004; Cowan et al., 2004; Reubinoff et al., 2000) and can serve as models for testing the effects of various toxins (Betts, 2010). Of even greater possible benefit is the potential for hESCs to repair damaged tissue. Conditions such as diabetes may be treated by creating insulin-producing pancreatic cells (Fujikawa et al., 2005; Kimbrel & Lanza, 2015). There is also evidence that suggests hESCs can regenerate damaged neurons and spinal cord cells, which may lead to treatments for Parkinson's Disease (Kim et al., 2002; Kimbrel & Lanza, 2015) and spinal cord injuries (Keirstead et al., 2005; Kimbrel & Lanza, 2015). Success in any one of these areas would greatly reduce the suffering and/or increase the life expectancy of an innumerable number of individuals (Fischbach & Fischbach, 2004).

It is evident that research involving human embryos has given rise to several diagnostic and therapeutic applications. While these applications are not without risks and critics, they nevertheless have many clear and substantial benefits, including the treatment of infertility, the prevention of suffering and premature death, and the avoidance of the social and emotional harms associated with these unfortunate conditions. These significant possible benefits are appealed to by human embryo research advocates to

justify the ongoing practice of embryo research. However, the research practices necessary to produce these benefits are considered by some to be problematic. In the following section, I will outline the alleged problems associated with embryo research and their relevance and role in arguments that oppose embryo research.

Problems with embryo research

Of perhaps greatest significance are the concerns raised about the necessary and unavoidable destruction associated with all embryo research. This concern has prompted many to question the morality of the practice.[5]

Firstly, traditional methods of deriving hESCs, a practice vital to stem cell research, are intrinsically destructive: embryo destruction is a foreseen and ineliminable feature of the research. This derivation process involves the extraction of pluripotent cells from the ICM of the blastocyst. By separating the ICM from the trophoblast the embryo is destroyed. The development of the remaining trophoblast cells cannot continue as there is no ICM to form the embryo proper, nor can the development of extracted ICM continue, because the cells of the extracted ICM are used to develop stem cell lines (Chung et al., 2008; Reubinoff et al., 2000).[6] However, a biopsy technique like that used in PGD can be employed to derive hESCs without destroying the embryo (Chung et al., 2008). Nevertheless, even embryo research that is not intrinsically damaging involves

[5] There are other criticisms of embryo research, including feminist critiques concerned with harm and problems with consent relating to women as oocyte donors (Ewing, 1989; Warren, 1990). These are serious concerns that must be considered when formulating any regulation of embryo research. This type of concern is particularly relevant in investigations considering the permissibility of embryo research. As the focus of my research will be the consideration of an extension to the current limit, I will not consider these types of objections as they are not necessarily exacerbated by an extension to current research practices.

[6] There has recently been evidence that embryo-like structures can be created from trophoblast stem cells from mice (Harrison, Sozen, Christodoulou, Kyprianou, & Zernicka-Goetz, 2017). However, this research is only made possible by use of additional mouse embryonic stem cells. Hence it still involves the destruction associated with traditional stem cell deviation. Furthermore, it is not clear whether this procedure would be possible using human material.

the destruction of at least some embryos. Observational and therapeutic research (such as IVF and PGD) entail the destruction of embryos as a technical consequence. These applications have only been made possible through years of slow and complicated preliminary research, involving significant embryo loss. Even now with major advances since the early days of research, many embryos are not successfully cultured, fail to successfully implant, and are discarded in favour of higher quality specimens (Khalaf & Grace, 2014).

If these current technical limitations were overcome and only viable embryos were created, some destruction would still be morally necessary. If research resulted in permanent alterations that may be detrimental to the resulting child, then it would be unethical to transfer the embryo into a uterus to be carried to term, as the resulting fetus/child may suffer. Even if an alteration would not result in any specific identifiable harm or suffering, the permanence of certain interventions is a further reason why some oppose the transfer and birth of such an embryo. Germ line gene editing is such an example. By editing the genes of gametes or embryos, alterations will be passed down to subsequent generations, raising two potential concerns amongst critics. Firstly, the long-term effects of these alterations are unknown. They may result in unforeseen harm to future generations (Lanphier et al., 2015). Secondly, there is an alleged problem with consent, in that the initially altered entity and all subsequent entities are not able to consent to the alteration of their genome (Collins, 2015).[7] Although this problem may be contested, it could be argued that any embryo that was subjected to this type of research may have to be destroyed at an appropriate time, either before it developed into

[7] There are various grounds on which this problem may be contested. One specific example is to question why consent is vital for germ line gene editing, but not for other modifications (e.g. the development of communications technologies) to future generations (Gyngell, Douglas, & Savulescu, 2017).

an entity capable of suffering from the alteration or harm, or before it developed autonomy.

To sum up, embryo research poses a moral dilemma. One is faced with a choice between the therapeutic and scientific benefits that result from embryo research, or the protection of the embryo from destruction, and therefore the foregoing of those significant potential research benefits. (Devolder, 2015).

The 14-day rule

Various attempts have been made to address this dilemma and, as already indicated, research involving human embryos is now currently regulated by 'the 14-day rule'. This rule permits the use of human embryos for research, but only up to 14 days after fertilisation. The founding of the 14-day rule is commonly attributed to the Committee of Inquiry into Human Fertilisation and Embryology (Warnock Committee).[8] This government committee, chaired by Mary Warnock, was established in the United Kingdom in 1982 to investigate the ethical issues surrounding developments in human fertilisation and embryology.[9] The Committee was made up of another fifteen professionals and academics from a variety of backgrounds, including science, philosophy, medicine, social work, theology, psychology, and law. The recommendations of the Committee, which were outlined in the 1984 '*Warnock Report'*, served as the foundation for the Human Fertilisation and Embryology Act (1990) (Lovell-Badge, 2008; Hare, 1993; Lockwood, 1988; Theodosiou & Johnson, 2011). This legislation led to the creation of the Human Fertilisation and Embryology

[8] The earliest mention of a 14-day limit on embryo research is found in a 1979 U.S. report. Although, due to various political reasons the recommendation was never given the opportunity to be properly reviewed (Hyun, 2016; Webster, 2016).

[9] Several other issues were also considered by the Committee.

Authority (HFEA), which is now responsible for regulating all embryo research in the United Kingdom**.** This regulation includes the licencing of research and monitoring of experiments to ensure accordance with the restrictions set out in the legislation.

The central concern of the Committee was with settling the question of whether embryo research should be permitted. Rather than trying to determine the point at which life begins or when the embryo becomes a 'person' (questions to which the Committee believed there are no completely objective answers), the Committee set themselves the task of determining "how it is right to treat the embryo" (Department of Health and Social Security 1984, p. 60). The process of the investigation involved deliberation of evidence obtained independently and via submission from a substantial number of professional organisations, interest groups, and members of the public (Wilson, 2014). In addition to the scientific details regarding the benefits and problems associated with embryo research, the Committee also considered several moral, religious, and personal views. The final recommendation of the Committee was informed by the examination of the most common arguments for and against embryo research. I will outline these arguments below.

The Committee acknowledged what it considered to be the most prevalent objection to the use of the embryo for research. According to this objection, the embryo demands the same moral consideration as other humans (i.e. children and adults) because of its potential for human life. These arguments claim that moral concern for the embryo outweighs any potential benefits that may result from research (Department of Health and Social Security 1984). The primary concern underpinning this objection relates to the embryo's right to life. Expressed formally, it is argued that:

(1) Every human being has the right to life;
(2) The human embryo is a (potential) human being;
(3) Therefore, the human embryo has a right to life (Kuhse & Singer 1990, p. 69).

Embryo research is thus opposed because embryos that are used for research are not able to fulfil their potential for life (Department of Health and Social Security 1984). The Warnock Report also considered what it calls "instinctive opposition" to embryo research, in which certain research practices are seen as corrosive of our respect for the sanctity of human life. The Warnock Report claimed that there is widespread fear that scientists may interfere with the process of reproduction to engage in eugenic practices or the creation of hybrid organisms (Department of Health and Social Security 1984, p. 61-62).

In response to the above objections, a variety of arguments supporting embryo research have been proposed. The Committee discussed what it considered to be the most widespread view, which claims that the embryo has some moral status (and specifically, moral status higher than that to be accorded to other non-human entities). However, according to this view, the respect that this degree of moral status entails is not absolute and can, therefore, be weighed against benefits that would result from research. The Committee claimed that while research using non-human embryos can provide some beneficial outcomes for humans, there are nevertheless some areas in which there is no substitute for human embryos. In these cases, the Committee suggested that if the benefit is significant, it would then be permissible to use human embryos for the necessary research (Department of Health and Social Security, 1984).

From a consideration of the above arguments and an investigation into the legal status of the embryo, the Committee concluded that the human embryo should be accorded a special status to ensure its protection (although not to the same extent as infants or

adults) but that, because of the value and benefits of embryo research, a total prohibition was undesirable. It was, therefore, determined that while embryo research may be permissible, certain regulations would be vital to protect against the frivolous or unnecessary use of human embryos. It was proposed that an authority (the HFEA) be established to prevent the unnecessary and irresponsible use of human embryos for research. It was suggested that the authority should be responsible for ensuring that the use of embryos as research subjects is warranted and for overseeing the time that human embryos can be kept alive *in vitro*. In considering a limit on embryo research, the Committee concluded that as each developmental stage is of equal importance in forming a continuous process that is vital for ongoing development, there is therefore no single and determinate biological point beyond which the embryo should not be kept alive. However, it was considered that a clear limit on *in vitro* culturing was necessary to alleviate public concern. After considering several suggestions for a limit on embryo research, the Committee selected a limit of 14 days.[10] It was intended that this would provide the necessary protection of later stage embryos while still allowing beneficial research before 14 days (Department of Health and Social Security, 1984).

This 14-day limit on embryo research has been enacted as law in twelve countries, including the United Kingdom, Australia, New Zealand, and Canada. It also forms the basis for institutional and scientific guidelines in five further countries, including the United States, China, and India (Hyun et al., 2016). In addition, there are international guidelines, such as the International Society for Stem Cell Research (ISSCR), which have some influence in countries with no regulations (Hyun, 2016). There is, thus, an

[10] Three dissenting members of the committee expresses an alternative view that all embryo research should be prohibited (Department of Health and Social Security 1984, pp. 90-93).

almost international agreement concerning the 14-day rule (Hyun, 2016).[11] It is thought that the widespread adoption of the 14-day rule is due to the clear and unambiguous limit proposed by the rule. As such it is regulation considered by many to be successful and appropriate. (Hyun et al., 2016; Hyun, 2016; Chan, 2017; Cavaliere, 2017).

However, the success of the rule may be due in part to technical limitations of post-14-day embryo culturing, rather than the merit of the limit itself. Since the infancy of embryo research, *in vitro* culturing had not advanced significantly beyond 7 days (Carver et al., 2003). It is understandable that a limit of 14 days could be seen as a purely theoretical (therefore passive) restriction rather than an active practical constraint on research, which might explain its widespread acceptance (Hyun et al., 2016; Chan, 2017).

Recent scientific advances

As noted earlier, the purely technical limitations of embryo culturing persisted until May 2016, at which time two research teams in the U.K. and U.S. successfully cultured human embryos *in vitro* for up to 13 days (Deglincerti et al., 2016; Shahbazi et al., 2016). Researchers were able to apply techniques previously developed for culturing mouse embryos through implantation, to human embryos. The experiments involved the culturing of blastocysts using a collagen coated substrate (as an attachment point for the embryo), higher than normal oxygen levels, and a specific time-based exposure to a modified culture medium, to successfully grow the embryos up to implantation. The experiments were terminated at 13 days in accordance with the 14-day rule.

[11] There are some regulations that use a different limit (i.e. Switzerland at 7 days) and others that do not appeal to a limit but rather prohibit any research (e.g. the U.S. prohibits the use of federal funds for embryo research).

These experiments have yielded significant insights into the development and implantation process of the human embryo. The previous culturing techniques had been successful up to the pre-implantation stage (1-5/6 days). This is the stage at which IVF embryos are normally transferred, and is therefore adequate to facilitate IVF. However, because embryos could not be cultured *in vitro* much longer than 7 days and because the *in vivo* embryo is unobservable once it implants into the uterine wall, the next stage of development (6/7-14 days) remained inaccessible to researchers. The new ability to observe the developmental period up to 14 days has led to a number of important discoveries, including the self-organising properties of the human embryo, the correspondence between *in vitro* and *in vivo* development, and important species differences in development (Deglincerti et al., 2016; Shahbazi et al., 2016; Morris, 2017). Each of these insights have the potential for significant therapeutic applications. Since these advances in culturing there have been calls for a revision of the 14-day rule. A particularly widespread view is that the current limit should be extended, with some suggesting that an alternative limit of 21 or 28 days may be appropriate (Harris, 2016; Connor, 2016). I will discuss the further potential benefits of embryo research and consider the argument for an extension in Chapter Three.

Conclusion

It is clear that research involving human embryos has proven beneficial. However, the unavoidable and necessary destruction of embryos is seen by some as morally problematic and therefore, challenges the appeal to beneficence as a supporting justification for embryo research. As I have explained, the current limit on embryo research has somewhat eased the conflict surrounding embryo research and has proven useful in establishing regulations.

The recent scientific developments in embryo culturing raise challenging questions. As research progresses there is the potential for even greater discoveries, the implications of which have prompted calls for the re-evaluation of the current guidelines. In order to investigate the proposed re-evaluation, it will be necessary to assess both the justifications for the current limit and the arguments for revising it. In the next chapter, I will analyse the appropriateness of the current 14-day limit. This will involve a discussion of the reasoning behind it as well as the criticisms and objections raised against it.

Chapter 2: The 14-day limit

As discussed in Chapter One, the 14-day rule was proposed as a way to alleviate public concern for the embryo, affording it some protection while leaving open the possibility for the development of beneficial applications, by permitting some research. This compromise was achieved by designating a clear temporal limit on embryo research. The justifiability of this compromise cannot be determined solely on the basis of what it has achieved, but will also require an assessment of the reasons supporting its selection. This determination will serve to inform the appropriateness of an extension to the current limit.

In this chapter, I will conduct such an assessment, arguing that the current restriction to 14-days is not supported. Although an exhaustive analysis of the reasoning behind the current limit on embryo research is outside the scope of this thesis, my discussion will show that the most prominent justifications presented in support of the 14-day rule are unconvincing. I will therefore argue that there is no strong reason why the 14-day rule cannot be amended and consequently, that an extension may be considered. Following this assessment, I discuss the implications for embryo research that result from a rejection of the argument supporting the 14-day limit. Importantly, I avoid supporting either a prohibition or unrestricted research by presenting an alternative criterion for determining the limit for permissible embryo research.

Why 14-days?

The reasoning behind the selection of 14 days as the limit on research is that it (roughly) corresponds with a certain set of biological processes and properties that are considered relevant for the protection of the embryo. The temporal limit of 14 days serves as a place holder for these biological markers, which are claimed to precede the morally

significant embryonic features. The idea is that it is only once these features arise that the embryo has a degree of moral considerability that would rightfully preclude its use in research. The rationale underpinning the original formulation of the rule is indicated in the following passage from the 'Warnock Report'.

> *"…the objection to using human embryos in research is that each one is a potential human being. One reference point in the development of the human individual is the formation of the primitive streak. Most authorities put this at about fifteen days after fertilisation. This marks the beginning of individual development of the embryo. Taking such a time limit is consonant with the views of those who favour the end of the implantation stage as a limit. We have therefore regarded an earlier date than this as a desirable end-point for research. We accordingly recommend that no live human embryo derived from in vitro fertilisation, whether frozen or unfrozen, may be kept alive, if not transferred to a woman, beyond fourteen days after fertilisation, nor may it be used as a research subject beyond fourteen days after fertilisation."*
> (Department of Health and Social Security 1984, p. 66).

As this statement makes clear, the potential for human life is acknowledged as a justification for the protection of the embryo, and the limit on research is based on the beginning of individual development as marked by the appearance of the primitive streak and the completion of implantation.[12]

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[12] In the introduction to a 1985 publication of the Warnock Report, Mary Warnock has offered a contradicting position, stating that: *"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 consideration of what the embryo was at a particular time immediately after fertilisation."* (Warnock 1985, p. xv). Michael Lockwood (1988) has proposed two possible ways in which the apparent contradiction may be resolved. The first is that the mention of the potential of the embryo to become a human

Appeals to potentiality as grounds for the protection of the embryo typically regard the embryo as having the potential for human life, and the associated moral considerability, from fertilisation (Singer & Dawson, 1990; Buckle, 1990). At the most basic level, the embryo is accorded moral consideration on the basis of its potential to become a specific entity which has moral status (e.g. human being, person, etc.). A common form of this argument, and one that appears to be acknowledged in the passage from the Warnock Report, is that human beings have moral status and embryos are potential human beings. Therefore, embryos have moral status. As research involving human embryos violates this moral status it should, therefore, be prohibited.

To avoid the resulting prohibition of research, the Committee proposed that the formation of the primitive streak and the completion of implantation are most relevant for the protection of the embryo. Several arguments, which aim to demonstrate the relevance of each of these biological processes for the protection of the embryo, have been presented in support of the 14-day limit. These include claims which focus on the significance of implantation as the point at which embryo viability and developmental potential greatly increases (Fischbach & Fischbach, 2004; Pera, 2017).[13]

However, the most prevalent argument in support of the 14-day limit concerns the relevance of the primitive streak. As indicated in the above passage from the Warnock

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being in the Warnock Report is an acknowledgment and dismissal of the common argument for protection. The second is that in the 1985 introduction, Mary Warnock is suggesting that the majority of the committee only rejected the significance of potentiality immediately after fertilisation, and not at some later point. Lockwood does not consider either to be plausible and suggests that the mention of potential may be somewhat unintended (1988, p. 211).

[13] Prior to implantation there are higher rates of spontaneous abortion. It has been claimed that this indicates that implantation is a vital enabling condition for developmental potential (Singer & Dawson, 1990). It has also been argued that if opposition to embryo research is based on the destruction of embryos, it would be inconsistent not to oppose natural reproduction (and the high rate of pre-implantation embryo loss) on the same grounds (Harris, 2007).

Report, the primitive streak is said to mark the beginning of the individual development of the embryo (Lockwood, 1988; Warnock, 2007; Pera et al., 2015, Chan, 2017). It is claimed that a particular (potential) human life is only present once individuality is fixed (Kuhse & Singer, 1990). It has also been argued that the appearance of the primitive streak – and the limit of 14 days – has been selected because it marks the beginning of neural development (Lockwood, 1988; Warnock, 2007; Pera et al., 2015, Chan, 2017) – the idea being that research must be prohibited before neural development commences as this will ensure that there is no possibility of embryo suffering.

Because of the emphasis given in the Warnock Report and its prevalence in subsequent justifications for the 14-day limit, my analysis will focus on the claim that the emergence of the primitive streak marks the biological individuation of the embryo. I will analyse this claim, arguing that it does not provide convincing support for a 14-day restriction on embryo research. Following this I will consider the claim that the primitive streak was selected as a precursor to neural development, and will argue that this justification also fails to provide convincing support for the limit of 14 days.

The relevance of the primitive streak

Individuation

The most prevalent argument in support of the 14-day limit emphasises the importance of individuality in justifying the protection of the embryo. Specifically, this argument claims that research prior to 14 days is permissible by appealing to the non-individuality of the pre-14-day embryo. The non-individuality of the pre-14-day embryo is premised on the idea that prior to the formation of the primitive streak (roughly around 14 days) it is possible for the embryo to undergo segmentation; that is, the process by which an

embryo can split into two, forming monozygotic twins; or two embryos can fuse into one, forming a chimera. The most common form of the non-individuality argument focuses on the possibility that the embryo may twin.[14] Difficulties in classifying or accounting for the fate of an embryo that splits into two has led some to suggest that the pre-14-day embryo is not an individual with moral standing (Kuhse & Singer, 1990; Devolder & Harris, 2007). It is claimed that moral status must attach to an individual and that if it is possible for an entity to divide, then it cannot be regarded to be an individual organism. The upshot is that the pre-14-day embryo is not an individual organism and as a result does not have moral considerability (Oderberg, 2008; Harris, 1990; Napier, 2010; Dawson, 1990b; DeGrazia, 2006; Guenin, 2006; Munthe, 2001).

When considered more closely we can see that this argument is based on a number of possible supporting claims: an *empirical* claim, that twinning is possible up to 14-days from fertilisation (Napier, 2010); a *metaphysical* claim, that the possibility of twinning makes indeterminate the identity of the embryo – individuality only becoming fixed once twinning is no longer possible (Napier, 2010); and a *moral* claim that identity is necessary for moral status or protection. While each of these claims is open to criticism, my analysis will focus on what I believe to be the strongest objections to the non-individuality argument. These objections concern the metaphysical claim – that the possibility of twinning undermines the individuality of the embryo – and the empirical claim – that twinning is possible up to 14-days from fertilisation. I begin with the empirical claim.

It has been suggested that the empirical claim, that twinning is possible up to 14 days

[14] There are other non-individuation arguments that appeal to the lack of distinction between embryoblast and trophoblast, and to the totipotency of blastomeres. However, these face similar problems (see for example Oderberg, 2008).

from fertilisation, may be incorrect. The scientific literature on segmentation suggests that there is a range of 6-21 days in which segmentation is possible (Dawson, 1990b, pp. 55-57). Dawson contends that proposals claiming segmentation can occur at an earlier stage of development are based on terminological confusion, whereby segmentation is taken to mean 'cleavage' – that is, the process of cell division – rather than 'division into parts more or less similar' – as in the case of twinning. Individuation arguments are used to defend the concept of individual continuity as the determinant for moral status in response to the discontinuity posed by monozygotic twinning. To respond to the difficulties posed by the discontinuity of twinning, segmentation must be taken to mean 'division into parts more or less similar'. If segmentation is considered as cleavage, twinning would still pose a problem for claims that individual continuity is the determinant of moral status. For this reason, I agree with Dawson's suggestion that proposals that locate irreversible individuality at the earlier stage of development (e.g. 6 days) can be dismissed (1990, pp. 56-57).

At the other end of the spectrum are claims that segmentation may occur up until 21 days. If this is true, this would present a significant challenge to the 'individuality' basis for the 14-day rule. The possibility and the occurrence of twinning beyond 14 days has been extensively discussed (see for example Hall, 2003). While post-14-day cases of twinning are rare and generally result in abnormal development, such as conjoined twins and *fetus-in-fetu*, they may nevertheless be relevant to concerns regarding individuality.[15] Individuation arguments are concerned with the classification of human individuals for the purposes of acknowledging the potential for developing into a human being. As such, the relevance of twinning is not that it results in two individual

[15] Fetus-in-fetu is a condition in which one twin develops inside the other twin (Dawson, 1990b, p. 57)

organisms/entities, but rather two potential human beings (Oderberg, 2008; Dawson, 1990b). If research is permissible during the period of non-individuality because of the possibility for the embryo to still split into two human beings, then this period of non-individuality should be extended up to the point at which there is no longer any possibility for twinning, and it does not seem obviously relevant how normal or abnormal the emerging individuals may be.

The possibility for twinning after the formation of the primitive streak is a serious problem for the individuation argument as a justification for the limit of 14 days. It should be noted, however, that in addition to the above empirical objection, the individuation argument faces a further problem.

The metaphysical claim of the individuation argument states that if it is possible for the embryo to divide, then it is not an individual organism. The problem I would raise, however, is that if the pre-twinned embryo is not an individual organism, then what is it? Napier (2010) has claimed that "[t]winning presupposes an organism that undergoes twinning: it is certainly identifiable as that organism which will undergo twinning." (p. 790). That is, the very process of twinning or splitting requires *an individual organism* that can be split. One would be hard pressed to explain the processes of twinning, and similarly the origin of twins, without an appeal to some individual organism that exists prior to twinning. David S. Oderberg (2008) makes a similar point when describing how a pre-twinned embryo, even if it will split, easily satisfies the requirements for being an individual. He states that "[i]n respect of a woman only one of whose ova has been fertilized, the answer to the question posed within fourteen days of conception, 'How many embryos is she carrying?,' is 'One.'"(1997, p. 274). From this it seems quite apparent that, at least prior to any twinning, there is an individual entity present.

However, the question as to whether the possibility for twinning changes that way that the pre-twinned embryo should be regarded, is still open (Oderberg, 2008; Smith & Brogaard, 2003). The argument appears to suggest that a possible future event can affect the present status of an entity (Oderberg, 2008). I suggest that this proposal is problematic. For example, if for some reason there is a possibility that I may undergo the process of fission – that is, split into two identical versions of myself – sometime in the next two weeks, it is unclear why my moral considerability would be altered at any point prior to the fission. To regard me differently just because of the mere possibility that I may split in two, would be quite strange. While this example may be dismissed as farfetched, there are in fact several real-world parallels. Amoeba, plants, flatworms, bacteria, and cells can all be divided into descendants of the same kind; it seems implausible and incorrect to regard these progenitor entities to be of a different kind (with a different status) than their 'progeny', just because of the ability to divide. Why should the embryo, which rarely divides, be any different? (Oderberg, 2008, p. 269). If this is correct, then the possibility for twinning should have no bearing on the status of the pre-twinned embryo.

As we have seen, the appeal to individuation as a metaphysical requirement for the embryo to be a potential human being, is commonly used to justify the research limit of 14 days. From my analysis, I have argued that the metaphysical claim that individuation is a necessary requirement for a recognition of the human potentiality of the embryo, and for any resulting moral considerability, is not convincing. Furthermore, the claim that it is the possibility of twinning that sets the point of irreversible individuality at 14 days appears to be incorrect.

Neural development

If the individuation argument does not clearly support 14 days as the cut-off point for embryo research, are there other grounds offered that can do so? Some have suggested that the 14-day limit on research was selected to protect against the possibility for suffering, by designating the emergence of the primitive streak as a precursor to neural development and the possibility for pain sensation (Lockwood, 1988; Warnock, 2007; Pera et al., 2015; Aach et al., 2017; Chan, 2017).

Although there is no explicit appeal to neural development or suffering in the formulation of the 14-day rule, the Warnock Report did consider an argument (termed the "strictly utilitarian view") that research should be restricted once the embryo was capable of feeling pain (Department of Health and Social Security 1984, p. 65). It was claimed that two possible limits could apply as a result of this reasoning: specifically, either once the central nervous system (CNS) begins to emerge; or when functional activity begins.[16] The report placed the emergence of the CNS at 22-23 days, and stated that the exact timing of functional activity was not known, but is believed to occur much later in development than the emergence of the CNS.

Current knowledge regarding the timing of the anatomical and functional development of the CNS supports the periods outlined in the Warnock Report. The earliest anatomical structures associated with the CNS arise at the beginning of the third week of development (roughly 19-23 days) (Moore et al., 2015) and functional activity of the pathways necessary for pain sensation may occur around 23-30 weeks (Lee et al., 2005;

[16] Although it is not made clear in the Warnock Report, I consider that 'functional activity' refers to the development of active neural circuits. This would require, at a minimum, the differentiation of electrophysiologically active neurons and synapse formation (Johnson et al., 2007; Zhang & Poo., 2001).

Derbyshire, 2006; Lowery et al., 2007). As both of these processes occur beyond 14 days they provide little support for the 14-day limit. Even if, as is proposed in the Warnock Report, a few days were subtracted from the earliest development of the CNS to ensure that there was no possibility of the embryo sensing pain (Department of Health and Social Security 1984, p. 65), the resulting limit (roughly 17-20 days) would still be later than 14 days. While I find the concern for pain sensation to be a convincing criterion for the protection of the embryo, I maintain that it is does not provide sound justification for the 14-day limit specifically.

To the extent that support for the 14-day limitation rests on the success of these claims, then, it lacks adequate foundation. If the current limit lacks the necessary evidentiary and conceptual support, the possibility arises that research permission *beyond* 14 days may be justifiable. The alternative, however, is that no research is justified, and instead what is morally required is a total prohibition on embryo research. I want to now consider both these possible outcomes, starting with the total prohibition position.

Can a limit on research be preserved?

Clearly the 14-day rule both restricts and permits research. As such, a lack of support for the existing limit opens two possible responses, one of which would be to deny that research at any stage of development is justifiable. This would result in a total prohibition on embryo research. As did the Warnock Committee, I consider this to be an undesirable and unwarranted outcome, on the grounds that significant benefits would be foregone. To avoid a total prohibition one must reject the arguments for the outright protection of the embryo and instead provide an alternative, defensible criterion for moral considerability, to which a research limitation can be attached.

Arguments supporting a complete restriction on research typically accord the embryo with a degree of moral considerability that requires protection right from the point of fertilisation. There are a variety of claims used to support the protection of the embryo from the point of fertilisation (e.g. species membership, genetic identity, numerical identity, and the continuity of development) most of which face significant opposition (Dawson, 1990a). I will limit my critique to what I consider to be the most important argument, that of potentiality.[17] As outlined above, the argument from potentiality accords moral considerability (and protection) to the embryo because of its potential to become a morally considerable entity (e.g. human being, person, etc.) (Stier & Schoene-Seifert, 2013; Harris, 2007). This argument faces two common challenges, concerning the logic and scope of the concept.

First, it is unclear how potential could be sufficient to grant the embryo *full* moral status (Stier & Schoene-Seifert, 2013; Harris, 2007). The claim is that it is unclear how, or why, one should treat a merely *potential* thing as if it were the *actual* thing. Just because the embryo can undergo changes necessary to become a human being, that is not a reason for treating it as a human being.[18] Second, it seems that this argument may entail protection for *all* potential human beings. The *reductio ad absurdum* objection to the view claims that if it is the potential for human life that grounds moral status, then many other entities would require similar protection (McGee, 2014; Harris, 2007; Sagan & Singer, 2007). Entities such as germ cells and even somatic cells also have a potential for human life. According to the potentiality argument, these entities should then be accorded the same moral consideration as human embryos. It is claimed that the only

[17] Because it is specifically acknowledged in the Warnock Report as the grounds for the protection of the embryo.

[18] For example, a prince is a potential king but does not have the rights of an actual king (Stier & Schoene-Seifert, 2013, p. 20).

way to avoid this conclusion – which many would find absurd – is to abandon potentiality as the criterion for moral status (Stier & Schoene-Seifert, 2013).

Even if these problems with potentiality arguments can be resolved there is a further difficulty with the appeal to potentiality as a protection criterion for the *in vitro* research embryo. It is clear that research embryos (whether specifically created for research or surplus IVF embryos) have the same intrinsic potential as 'procreative embryos'. Namely, the natural ability (that non-human animal embryos lack) to develop into a human being.[19] However, there is an important difference in the capacity to actualize this potential. There is a good chance that a procreative embryo will realize its potential and become a human being, as all the necessary factors required for the development of this potential are present. That is, the procreative embryo is currently, or eventually will be, in a uterus and will be nurtured until it develops into a human being. Conversely, the research embryo will not at any point be transferred to a uterus; nor will it be nurtured through development. As such, there is a clear sense in which it has no genuine chance (at least with current technology) of developing into a full-fledged human being (Singer and Dawson, 1990; Sagan and Singer, 2007; Hyun, 2013).

Therefore, even if potentiality was a convincing criterion for moral considerability, it would entail that only the procreative and not the research embryo was afforded protection. From this it would appear to follow that no restriction of *in vitro* embryo research was warranted. However, I disagree with this outcome, on the grounds that I find potentiality to be an unconvincing criterion for the protection of the embryo. Instead I argue that concern for the avoidance of pain and suffering provides sufficient

[19] I use the term 'procreative embryo' to refer to *in vitro* and *in vivo* embryos that are part of a procreative project. Namely, those that are intended for gestation and eventual birth.

justification for the protection of both research and procreative embryos.

More specifically, I argue that in a general sense it is sentience rather than potentiality that should serve as the appropriate reference point for restricting research. Such a restriction would be consistent with research regulations concerned with the welfare of adults, infants, and non-human animals as research subjects; and would function in a similar way to the current restriction, by protecting and respecting the embryo, while still allowing some research.

Sentience as a criterion of moral considerability is generally defined as the capacity to feel pleasure or pain (Kuhse and Singer, 1990; Warren, 1997). However, there is some ambiguity concerning the concept, particularly regarding the aspect of 'feeling'. Interpretations of sentience range from the rudimentary capacity to respond to external stimuli, to self-conscious awareness (van Bogaert, 2004; Bortolotti & Harris, 2005). My use of 'sentience' will refer to 'pain sensation', a capacity that sits somewhere between these two extremes. Specifically I am referring to a capacity for the (conscious) sensation of pain that is more complex than a simple reflex response, yet does not involve any higher level self-conscious pain awareness.

If sentience is to serve as the basis for a restriction on embryo research by preventing the possibly of suffering, it will be necessary to determine the precise point at which the capacity emerges. However, because neural development – much like all embryogenesis – proceeds along a continuum, it is difficult to determine the exact point at which an embryo has the capacity for pain sensation. The selection of an incorrect limit would have two problematic outcomes. An overly cautious limit – selected to ensure that there is no possibility for suffering – may substantially restrict research opportunities limiting potential therapeutic benefits. On the other hand, an attempt to maximise research

opportunities may result in a limit that is too late, potentially leading to the suffering of the embryo. In order to avoid these outcomes, I suggest that rather than basing the limit on the emergence of sentience, the restriction on embryo research should be determined by the presence of *key sentience precursors* (what I will refer to henceforth as *'key S-precursors'*): namely, properties or features of the embryo that contribute to, but do not constitute, the capacity for pain sensation.[20]

To explain a little further, pain sensation requires a variety of components, some of which are also utilised in more rudimentary spinal reflex responses (Lowery et al., 2007). These components arise at different points in development, with the more basic reflex structures generally emerging prior to higher level components necessary for the sensation and awareness of pain (Lowery et al., 2007; Derbyshire, 2006). A specific set of these shared rudimentary structures could be defined as key S-precursors. If research was restricted once these emerged, it would avoid the further development of more complex structures necessary for pain sensation, thereby protecting the embryo against the possibility of suffering.

To be clear, the above is merely an example of possible key S-precursors and how they may function, and is by no means meant to serve as a recommendation for the basis of a specific limit on embryo research. In order to determine which components are appropriate key S-precursors that should inform the corresponding research limit, further research is necessary. Key for the purposes of my investigation, however, is that both the literature on embryogenesis and recent advances in embryo culturing clearly indicate that neural development only begins *after* 14 days. Furthermore, it is quite clear

[20] This is my own term, used to designate the types of properties or features relevant for my proposed criterion. Thanks to Mianna Lotz for her help in coming up with a suitable shorthand.

that the capacity for sentience occurs much later in development, with the establishment of the first functional reflex responses and sensory capacity occurring at approximately 7 weeks and pain sensation arising with thalamocortical connections (fibers connecting the thalamus and cortex) anywhere from 23-30 weeks (Lee et al., 2005; Derbyshire, 2006; Lowery et al., 2007). Therefore, if pain or suffering is the key relevant concern when it comes to determining morally acceptable treatment of the embryo, the limit of 14 days turns out to be overly restrictive (Kuhse & Singer, 1990).

Conclusion

From its investigation, the Warnock Committee concluded that there are conflicting views regarding the value of embryo research, on the one hand, and concern for the embryo as a potential human being, on the other. To accommodate the tension between these views the 14-day limit was designed to alleviate public concern by protecting the embryo beyond a certain stage of development, while allowing for valuable research to occur prior to that stage. The rule achieved this compromise by claiming that the embryo only requires protection after 14 days of development. I have discussed the most compelling arguments justifying the selection of 14 days and have shown them to be unconvincing. If the 14-day limit is unsupported the possibility arises that research should be either prohibited or unrestricted.

I have considered potentiality arguments as the most prevalent justification for the prohibition of embryo research. I have argued that in addition to common objections (relating to the logic and scope of the concept) potentiality does not provide convincing justification for the protection of research embryos. This raises the possibility that the use of research embryos may be unrestricted. I dismiss this conclusion, suggesting that the possibility for sentience is a convincing reason for the protection of both research

and procreative embryos.

However, I have also argued that due to the continuum of embryo development, the accurate determination of the onset of sentience remains difficult. As an alternative, I claim that identification of key S-precursors would provide a more acceptable limit on embryo research. The fact that key S-precursors emerge much later that 14 days, provides support for an extension of the 14-day rule. In the following chapter I will further investigate the appropriateness of an extension.

Chapter 3: Extending the limit

The discussion in Chapter Two led us to the conclusion that the proposed justifications underpinning a 14-day limit on embryo research do not actually succeed in establishing 14 days as the morally required cut-off point. I have also argued that the development of what I have referred to as key S-precursors is a more convincing criterion for the protection of the embryo than the emergence of the primitive streak; and, moreover, that the point at which key S-precursors emerge is much later than 14 days. I have therefore suggested that the current limit may be inappropriate and overly restrictive. However, neither of these conclusions establish conclusively that the current limit should be extended; they merely suggest that an extension may be permissible. In order to determine whether an extension is in fact justified, an assessment of the supporting arguments is necessary.

In this chapter, I will assess these supporting arguments and in turn the proposal for an extension, arguing that there are strong reasons to consider an extension. The most persuasive extension argument depends on an appeal to technical feasibility and beneficence. While each of these defenses raise some concerns, when considered together they provide strong support for an extension. To further assess the appropriateness of an extension, an alternative limit of 28 days will be considered. This assessment will confirm that no significant concern for embryo welfare is raised during this later period of development.

Arguments for an extension

The arguments for extending the current 14-day rule typically appeal to the consequentialist justification for research, namely that an extension of the current limit is warranted because it would result in significant scientific and therapeutic benefits

(Harris, 2016; Connor, 2016). Katrien Devolder and Julian Savulescu (2006) have taken the standard consequentialist justification for research a step further, arguing that there is a moral *imperative* to conduct beneficial research. They claim that it is morally impermissible to delay or deny the opportunity for research that could potentially save lives or ease suffering, suggesting furthermore that those responsible for a delay or denial are also responsible for any resulting harms (i.e. death or suffering). This reasoning has been used to argue that cloning (Devolder & Savulescu, 2006) and human embryonic stem cell research (Devolder & Harris, 2007) should be actively supported. If we accept their argument, this would seem to suggest that an extension to the current limit may not only be justified but even required.

The standard appeal to beneficence is similar to the arguments presented in support of permitting embryo research during the initial debate. However, a key difference is that the current appeal is supported by claims that an extension is now technically feasible. In this section, I will analyse what I consider to be the most compelling argument for extending the current 14-day limit. This argument claims that many significant benefits would be made possible by research using embryos beyond 14 days. Because the culturing of embryos beyond 14 days is now possible, restrictions should be amended to allow research beyond the current limit. As mentioned, this argument depends on two appeals, namely to the alleged technical feasibility of post-14-day embryo culturing, and to the potential benefits that research in to this period would enable. To provide a rigorous and accurate assessment of the argument for an extension I will consider each appeal individually, and will argue that while each faces some individual difficulties, when combined they provide strong support for an extension.

The argument from technical feasibility

In its strongest form the argument from technical feasibility claims that the technical ability to go beyond 14 days is a reason to extend it (Cavaliere, 2017, p. 6). However, there is little evidence that this argument has been used in the current debate. Instead, most arguments merely suggest or assume that it is, or will be, possible to culture embryos beyond 14 days. Prior to May 2016, technical limitations prevented the culturing of embryos beyond 9 days. During that time, an extension of the 14-day limit would have had no practical research implications. However, now that embryos have been cultured for up to 14 days, it is implied that the only thing preventing beneficial research beyond that point is the current restriction. A number of challenges have been raised against the argument from technical feasibility.

Firstly, there is actually relatively little evidence given to support the central claim. That is, it is unclear whether extending embryo research beyond 14 days is in fact technically feasible. To date the longest period in which human embryos have been cultured *in vitro* is 13 days (Deglincerti et al., 2016; Shahbazi et al., 2016). While these experiments were intentionally terminated, the possibility that embryos could be cultured longer is not a certainty (Pera, 2017). Furthermore, the researchers involved in these experiments have suggested that the current culture medium may not be able to provide hormones and nutrients (normally delivered via the uterus) that would be necessary for continued development (Reardon, 2016). However, I would argue that while this uncertainty weakens the position, the dramatic advances in the culturing of human embryos, as well as recent progress in the development of artificial wombs for non-human animals (Partridge et al., 2017), suggest that the capacity to go beyond 14 days in the near future is probably more likely than not.

A second challenge that has been raised against the argument from technical feasibility relates to the so-called 'is-ought' problem, also known as the 'naturalistic fallacy' (Cavaliere, 2017). This is an objection which argues that normative claims cannot be derived from factual claims (Hume, 1986; Moore, 1993). Applied to the current question, the argument from technical feasibility appears to be making a normative claim – namely that embryo research *ought* to be extended – on the basis of a purely factual claim – that extending embryo research *is* possible. The point of the naturalistic fallacy is that appeals to nature or facts do not translate automatically to normative conclusions. However, the argument from technical feasibility is not used to make any normative claims. Instead it is used to support the claim that an extension to the current limit would have beneficial outcomes, by highlighting that the opportunity for the research necessary for these benefits may be available.

I find neither of these criticisms of the argument from technical feasibility to be convincing. Questions about the actual feasibility of extending embryo research are certainly relevant in deciding if an extension is appropriate. However, recent advances in research abilities, and the fact that *in vitro* culturing of embryos is currently restrained by regulations and not demonstrated technical inability, indicate that scepticism concerning an extension is unsubstantiated. Furthermore, the normative claim that research should be extended is derived from the argument from beneficence. The argument from technical feasibility is only used to support the beneficence claim by suggesting that an extension (and the associated benefits) is possible. As such, I believe that the argument from technical feasibility provides support for the consideration of an extension to the current limit. If such an amendment would be beneficial, an extension may be justified. In the next section I will consider this possibility.

The argument from beneficence

The argument from beneficence claims that embryo research is justified and perhaps even necessary because of the substantial benefits it will provide to human wellbeing. This appeal as an argument for extending the current limit is based on claims of the significantly greater benefits that will arise if research beyond 14 days is allowed (Harris, 2016; Connor, 2016; Cavaliere, 2017).

Very little is known about embryonic development during the period of 14-28 days. In fact, it is commonly referred to as the 'black box' of development (Connor, 2016). This black box period previously stretched from 7 through to 28 days. However, since the recent advances in embryo culturing, significantly greater insight into days 7- 14 has now become possible. The little that is known about the remaining period of 14-28 days has been pieced together from animal models of embryogenesis and embryos from the Carnegie Collection (an extensive reserve of embryo and foetus specimens) (M.A. Hill, 2017; Elves & McGuinness, 2017). If the culturing of embryos was permitted beyond 14 days, a more complete and precise picture of early human development would become possible.

In addition to increases to theoretical knowledge, it has also been suggested that research into the developmental period beyond 14 days will have beneficial implications for the treatment and prevention of several conditions. The first major process that occurs within the period after 14 days of embryonic development is the completion of implantation. As mentioned in Chapter Two, this is a significant milestone in development as it represents one of the major hurdles in embryo viability. Failure to implant is one of the most common problems with IVF (30-70% of cases fail to implant) (Zernicka-Goetz, 2017). Greater insight into the mechanisms involved in this process may lead to increased implantation rates (Zernicka-Goetz 2017; Connor,

2016). During the weeks following implantation, the embryo is very sensitive to teratogens. It has been suggested that research into this period could improve the understanding of environmental causes of birth defects (Chen & Chisholm, 2017; Connor, 2016). This period also involves processes that are important for the development of the heart and nervous system: defects that affect these systems are among the most common congenital abnormalities (Chen & Chisholm, 2017).

Despite the importance of the post-14-day period of development, the specificity and certainty of the applications that an extension in research would provide is not clear. It has therefore been suggested that the argument from beneficence for a rule extension relies on an overly optimistic view of scientific progress, which overemphasises the benefits and capabilities of research (Cavaliere, 2017). In response to this concern, Johnathan Montgomery (quoted in M. Hill, 2017) has stated that in this kind of experimental research any specification of research outcomes is unwarranted and speculative. A such, it is common practice for researchers to proceed with caution, making only educated guesses based on the probability of outcomes.

While the inherent uncertainty of future research outcomes is understandable, it may nevertheless weaken the position based on the argument from beneficence. However, as was outlined in Chapter One, significant insights have already been gained from research into the period of embryo development between 7 and 14 days. For example, the research has highlighted previously unknown differences in embryo development between humans and mice (Deglincerti et al., 2016; Shahbazi et al., 2016). This has significant implications, since much of our knowledge of early human development is informed by mouse embryogenesis (Pera et al., 2015; Zernicka-Goetz, 2017). If research was extended beyond 14 days, the full extent of the differences between human and mouse development would become apparent. There are also clear benefits that an

extension to research will have for preclinical work. For example, allowing research beyond 14 days may provide a far more effective method than traditional techniques use to assess mitochondrial replacement and gene editing research. Currently this work involves performing an adjustment (i.e. mitochondrial transfer or gene edit), establishing a cell line, and then analysing the quality of the stem cells and derived tissue. The opportunity to perform a mitochondrial transfer or edit genes of an embryo and then culture it to gastrulation would allow researchers to analyse the viability of the embryo and to see the impact of the edited genes on the body plan (Hyun, 2016; Connor, 2016). While it may not be possible to specify definite therapeutic applications, the contribution to our understanding of human development and the implications for the preclinical work just discussed, highlight clear and probable theoretical and practical benefits of an extension.

A second criticism that has been raised against the argument from beneficence relates to the consequentialist calculus. The beneficence argument to extend the current limit on research either assumes that the embryo would not be harmed through extended research, or that any harm to the embryo would be outweighed by the resulting benefits. However, it is claimed that this does not accurately reflect the correct balancing of the costs and benefits from an extension to the current research limit (Cavaliere, 2017). Of particular relevance is the fact that the harm resulting from research affects the embryos being used as research subjects, but these embryos receive none of the benefits. Research embryos thus incur all the cost, while current and future members of society reap all the benefits. This is regarded as unacceptable because the consequentialist appeal to beneficence claims that research harms are outweighed by resulting benefits and if the embryo does not benefit from research it is not apparent how the harms they may suffer can be outweighed. However, consequentialist reasoning is typically

concerned with *overall* benefits and harms (Sinnott-Armstrong, 2015). As such, it appears that the objection is not unique to the case of embryo research, but rather to consequentialist reasoning in general.

Regardless, this weighting problem is not considered a challenge by those who deny that research harms the embryo. Such proponents may accept that the research embryo does not receive any of the resulting benefits, but would reject the claim that the embryo incurs a disproportionate share of the costs, because the early embryo is not an entity that can be harmed.[21] However, this dismissal of possible harm to the embryo has been criticized. Cavaliere (2017, p. 7) has suggested that because the status of the embryo has not been settled, claims that the embryo is not an entity that can be harmed, or that even if it is, that harm is outweighed by the potential research benefits, may be unfounded. While I accept that there is no consensus regarding the status of the embryo, I argue that because of this uncertainty, the initial criticism – that the embryo endures a disproportionate share of the costs/harms of research – may also be unsupported. The problem seems to lead to the question of which argument has the burden of proof regarding the status of the embryo.[22]

A final concern with the argument from beneficence is whether the proposed outcomes of extended research are straightforwardly beneficial. For example, improvements in

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[21] This is only one possible response to this objection. For example, Julian Savulaescu (2002) has argued that in some circumstances embryo destruction may be justified even if embryos are considered persons.

[22] A further reply is that harms may result from the fact that various attitudes, beliefs and feelings exist within society concerning the status of embryos. Those who hold views in opposition to an extension may be harmed because they feel alienated or devalued by society (Cavaliere, 2017). Cavaliere acknowledges that those advocating for an extension on utilitarian grounds are likely to accept the possibility of this kind of harm, yet still consider it insignificant when compared to the benefits that would result from an extension. These comparisons of harm are difficult to resolve. However, I believe that it would be more controversial to claim that harms like social alienation outweigh the potential therapeutic benefits from extending research, than the reverse.

IVF rates have been presented as a reason for permitting research beyond 14 days (see for example Connor, 2016; and McKie, 2016b). While greater IVF success would certainly have some benefits (e.g. reducing financial, psychological, and social costs associated with infertility), it may result in overall negative outcomes. The relevant point here is that the assumption that an increase in birth rates is a good thing, is not universally shared. There are a variety of anti-natalist positions concerned with the problems associated with procreation.[23] However, the arguments most relevant to the questions regarding the presupposition that increased IVF success rates are inherently beneficial, are objections that highlight the costs to existing individuals. It could be argued that resources spent on IVF (i.e. research and clinical costs) should be more effectively used to ease the suffering of existing individuals (Rachels, 2014). In addition, by enabling infertile individuals to have biologically related children, other child rearing options are not explored. This could mean that many existing children who are in need of stable and permanent care and who might ordinarily be adopted, may be overlooked in favour of IVF (Søbirk Petersen, 2002; Rulli, 2014).[24]

The possibilities raised by these arguments are by no means uncontroversial. Furthermore, the comparison of harms is a difficult and complicated matter. As such, I will not attempt to discuss these issues further here, but simply note, in addition, that increased IVF rates are not the only benefit that may result from an extension to the 14-day limit. There are many therapeutic benefits that may be possible from researching gastrulation and stem cell differentiation, that would not lead to increased birth rates. As

[23] Examples include claims that procreation results in harm to those brought into existence (Benatar, 1997; Brake & Millum, 2016), and that increases in population can have detrimental environmental and social impacts (Brake & Millum, 2016; Young, 2001; MacIver, 2015; Kates, 2004).

[24] See Levy & Lotz (2005) for a related argument concerning reproductive cloning.

such, the problems raised are therefore not sufficient on their own to preclude further embryo research altogether. However, if improvements in IVF success rates are presented in support of an extension all the implications need to be considered in order to correctly assess the argument.

From my discussion above I have shown that while the specific therapeutic applications of an extension are somewhat uncertain, there are nevertheless clear scientific benefits and preclinical applications. I have also argued that the problems relating to the unequal weighting of benefits rely heavily on claims about the status of the embryo. However, this is an unresolved and complicated issue, and without a defense of these claims the objection is unconvincing. Furthermore, while there are questions as to whether research outcomes are straightforwardly beneficial, these questions do not apply to all embryo research. Each of these problems illustrate the complexity of the consequentialist reasoning, but none of them at this point raise insurmountable difficulties for the argument from beneficence. As such, I maintain that the appeal to both technical feasibility and beneficence provide convincing grounds for extending the current limit on embryo research. In the remainder of the chapter I will further assess the appropriateness of an extension to the current limit by considering a current proposal for an alternative research limit.

A 28-day limit?

Although there is significant contention as to whether the limit on embryo research should be extended at all, two possible alternative limits have been proposed: 21 and 28 days (Harris, 2016; Connor, 2016). Because the greater limit raises the possibility for the greatest opportunities and challenges, I will focus my consideration on the proposal for a 28-day limit.

Extending the analysis conducted in the previous chapter, I will proceed with the claim that the most convincing criterion for the restriction of embryo research is the emergence of key S-precursors. In order to determine whether the embryo satisfies this criterion before 28 days, I will review the known biological differences that occur up to this point. From this analysis, I will argue that none of the processes or features that occur during 28 days of development provide adequate reason for prohibiting research during this extended period. Furthermore, I will argue that the significance of the potential benefits that can be achieved between 14 and 28 days, provides sufficient reason to permit extended research.

As explained, the third week (14-21 days) of development involves a number of major processes that have served as the basis for the current 14-day restriction, including the completion of implantation, the formation of the primitive streak (and gastrulation), and the beginning of neurulation (Moore et al., 2015; M.A. Hill, 2017). It is claimed that these processes signify the emergence of morally significant features, such as potentiality, individuation, and the capacity for suffering. However, as I have shown, the relationship between these biological processes and morally significant features is unconvincing. I have further argued that potentiality and individuation are not convincing criteria for the protection of the embryo. As such, research during this period (i.e. 14-21 days) does not raise any specific moral concerns.

During the fourth week (21-28 days) the embryo undergoes several major changes which mainly comprise morphological developments, such as the beginnings of many organ systems (Moore et al., 2015; M.A. Hill, 2017). While some of these developments – such as the first heart beats – may have emotional connotations, the moral significance of these (early) organ structures have been questioned (John Harris quoted in Sample, 2016; Johnathan Montgomery quoted in M. Hill, 2017). I have

argued that sentience should serve as the reference point for restricting research. As such, the continuation of neural development during this period warrants attention. However, as I have previously outlined, the earliest structures that may serve as key S-precursors appear significantly later than 28 days. It is not until the seventh week that the first reflex responses begin to function. The nervous system is therefore not functional, nor is there any potential for sensory capacity until the at least the seventh week of development (Derbyshire, 2006; Chen & Chisholm, 2017). It is therefore clear that there is no possibility for sentience at least up to 28 days of development.

While many important changes occur during the period from 14-28 days, I maintain that none of the occurring process or resulting features raise specific moral concerns. As such, the restriction of research during this period is unsupported. Furthermore, as has previously been mentioned, this period offers a great opportunity for research that would contribute to our theoretical understanding of human development and may also have the potential for many therapeutic applications. Because research up to 28 days of development does not raise any specific moral concerns for the embryo, and because significant benefits may result from the potential therapeutic applications, the proposal to extend the embryo research limit to 28 days appears to be well supported.

Conclusion

In light of concerns about the justifiability of the 14-day rule, discussed in the previous chapter, this chapter has considered the arguments in support of an extension to the current limit. I have outlined and assessed the most persuasive argument for an extension, namely the consequentialist argument from beneficence supported by an argument from technical feasibility, arguing that they present a strong case for an extension to the current 14-day limit.

I then considered the implications of a possible alternative limit of 28 days. I have determined that research concerning the developmental stages that occur within this period has the potential to provide significant scientific and therapeutic benefits. Furthermore, as there is no possibility that the embryo may experience pain sensation as a result of research experimentation up to 28 days of development, an extension to this period does not raise any significant concerns for embryo welfare.

Having shown that the 14-day rule can be extended and that the arguments for an extension are convincing, I contend that there is a good reason to extend the current limit. However, the appropriateness of an extension does not only depend on the strength of the arguments considered so far. Some further practical issues must also be considered; these will be the focus of the next and final chapter.

Chapter 4: Further considerations

Any amendment to embryo research regulations, no matter how justified, is likely to face significant criticism. In response to the type of amendment that I have supported, there are a number of further challenges that must be considered if an extension is to be pursued. A revision of the current limit has been objected to on the grounds that it would give rise to various social harms. From an analysis of these objections, I will claim that the supposed harmful consequences of a revision are both uncertain and, moreover, preventable. As such, I suggest that if a revision of the current limit is conducted through a careful and appropriate process, any negative social and political effects will be minimised or avoided. In addition, developments in the field of synthetic biology, challenge the 14-day rule with the possibility of creating 'embryo-like entities' that do not fall within the scope of the current regulations. This possibility has led to suggestions that any regulation that is based on the current format (even if it is extended beyond 14 days) will be unable to effectively regulate research involving these novel kinds of entities. Let us consider these challenges now.

Arguments against a revision

To conduct a comprehensive assessment of the appropriateness of an extension, it is necessary to consider whether a revision of the current limit may present any practical difficulties. In this section I will consider two of the main reasons that have been presented in opposition to the revision of the 14-day rule: first, that it will undermine public trust; and second, that it may lead to undesirable outcomes.

The most prevalent objection relates to the role of the current limit as a means to foster public confidence. It has been suggested that any extension to the rule, particularly now that it serves as a practical restriction to research, may undermine the confidence the

public has in the government's ability to effectively formulate and enforce regulations, and in the scientific community's adherence to the restrictions (Cavaliere, 2017). This objection is typically supported by a slippery slope argument. This argument claims that an extension to current restrictions will eventually lead to more relaxed research practices, until eventually scientists may begin "culturing babies outside the womb" (David Jones quoted in Johnson, 2016, para. 37). This argument is premised on the idea that engaging in or allowing a certain practice, will inexorably lead to activities that are considered to be objectionable. The concern is that if the current limit is extended because it now poses an actual constraint to scientific research, then further extensions will be made when other limits become inconvenient.

Here as elsewhere, slippery slope arguments face a number of criticisms, including a lack of empirical evidence for the decline into undesirable practices; the disregard of the potential capacity for regulatory power to protect against the 'slide' by maintaining effective restrictions and oversight; and the presupposition that the relevant postulated resulting research practices will indeed be morally problematic (see for example Resnik, 1994). In the case of embryo research there is good reason to reject the claim that an extension will result in further extensions. Cell biologists Azim Surani (quoted in Connor, 2016) and Robin Lovell-Badge (quoted in McKie, 2016a) have suggested that there are other research methods, such as the use of tissue from aborted foetuses or ectopic pregnancies, which can be used to study the period beyond 28 days. If correct, this provides a good reason to doubt the claim that an extension to the current limit will inevitably lead to research on foetuses or neonates. However, just as there are uncertainties surrounding the claimed research benefits that would result from an extension to the current limit, it seems quite reasonable to assume that there is also uncertainty surrounding the interests and purposes of future research and the

developmental stages and processes necessary to achieve these purposes. That is, while there may indeed be no current reason to culture embryos beyond 28 days, it is currently not possible to state with certainty that there will never be a strong reason to conduct research on human embryos beyond that point. This leaves open the possibility, however unlikely, that extending the current limit may lead to a slippery slope towards research on later term embryos or foetuses. Indeed, some have suggested that even a short extension to the current limit will be seen by those who oppose embryo research (or an extension to the current limit) as confirmation of the slippery slope predictions (Harris, 2016; Cavaliere, 2017).

However, there are other examples in which limits similar to those relating to embryo research have been altered, yet has not lead to a loss of public trust or a slide down the slope (thus far). Regulations relating to gene editing, surrogacy, human/non-human animal chimeras, and human cloning have been amended in response to scientific advances (Hyun, 2016). It is certainly not clear that public trust in the regulation of scientific research has been undermined as a result of each of these amendments. The preservation of public trust in these cases is most likely a result of the thorough methods by which these amendments were pursued and implemented. Furthermore, as a result of well-established regulations, there is no sign that research involving human foetuses or neonates is on the horizon. Through an adequate review process, like those involved in the regulatory amendments just discussed, it is likely that many of the concerns outlined above can be avoided or alleviated. In addition, if a firm criterion for moral considerability can be stipulated (e.g. key S-precursors as I have proposed), it would enable the development of clear and effective regulations that would protect against any slippery slope.

It is interesting to note that a poll was recently carried out in the U.K. regarding an extension of the limit on embryo research to 28 days. The survey, conducted by YouGov[25], showed that only 19% of the 1740 respondents wanted to keep the current 14-day limit (Leida, 2017). When combined with those who wanted an outright ban on research (10%), it represents a minority who may be troubled by an extension, especially when compared with the 48% who were in favour of an extension. While these results provide some indication that an extension may currently be the most preferred option, because the remaining 23% were undecided, a shift in attitudes is a possibility. As such, these results do not provide conclusive evidence regarding public opinion and the likely impact of an extension.

This possible shift in attitudes is the focus of a pragmatic concern that has also been raised against a revision of the current limit, namely that it might be counterproductive in the sense of leading to more rather than less restrictive regulations (Warnock, 2017; Powell, 2016). There is still opposition to embryo research in general (Jones, 2016). It has been suggested that a potential risk in reviewing the current rule is that more conservative, 'prohibitionist' views will be revisited and their proponents will have a public platform to voice their position. These views may in turn influence the public and lawmakers, possibly resulting in a reduction or total restriction on embryo research (Warnock 2017; Powell, 2016). As Mary Warnock has warned "[w]e should note that every time the law about embryo research has been changed or amended the opposition has rallied its forces, and I think it would do so again if we try to get the 14-day rule extended. The risk is that all the progress we have made since 1990 would be lost." (McKie, 2016b, para. 34). This would obviously be an undesirable outcome for those

[25] yougov.co.uk (for research methodology see: https://yougov.co.uk/about/panel-methodology/)

advocating for an extension. The possible risk of such an outcome must therefore be taken into account and weighed against the potential benefits motivating call for an extension. Moreover, many who hold this view emphasise that a hasty amendment – one that foregoes sufficient deliberation and discussion – would increase this possibility. To avoid this, it has been suggested that any revision should mimic the 'Warnock Process' (Sample, 2016; Warnock, 2007). That is, it should be a slow and deliberate process in which the public is involved in an informed deliberation of the relevant issues and concerns (Warnock, 2017; Hyun, 2016). However, even if there is a conscientious and open debate about extending the current limit, there remains the possibility that more conservative regulations may result. It is important to note that the pragmatic concern regarding conservative regulations may apply more to regulations that involve an open and public revision process, such as that involved in legislative change. Other types of regulations, such as institutional policies and scientific guidelines, may have more internal review procedures, which may minimise external influence.[26]

A clear example of the potential influence of conservative views can be drawn from the original consideration of embryo research. In response to the publication of the Warnock Report, a Private Members Bill – the *Unborn Children (Protection) Bill 1985* – was introduced to prevent the use of human embryos for research (Lovell-Badge, 2008; Hare, 1993; Lockwood, 1988). At the time of its introduction this Bill had significant Parliamentary support. However, there was a shift in the recommendations of the Warnock Report and the *Human Fertilisation and Embryology Bill* was eventually passed in 1990 (Lovell-Badge, 2008; Hare, 1993; Lockwood, 1988;

[26] Of course, even with reduced external influence, the revision of current scientific and institutional regulations may lead to more restrictive guidelines because of shifts in internal ideologies.

Theodosiou & Johnson, 2011). This change in support has been attributed to the increased involvement from the scientific community, which served to educate the public and politicians, enabling a better understanding of the value and problems associated with embryo research. This example emphasises the importance of adequate scientific, legal, and ethical engagement to ensure that those involved in the debate, and any policy revisions, are sufficiently informed.

Furthermore, avoiding a revision of the current limit out of fear that a conflicting view may prevail, seems to disregard some of the central concerns that originally motivated the 14-day rule (i.e. alleviating public anxiety and accommodating diverse values about the embryo) (Department of Health and Social Security, 1984; Warnock, 1985; Hyun et al., 2016). These issues are still central to many of the discussions concerning an amendment to the current limit (Hyun et al., 2016; Chan, 2017; Cavaliere, 2017). This pragmatic objection would be problematic for those who emphasise the importance of respect for pluralistic values in developing public policy.

To summarise, it is certainly possible that a revision of the current 14-day limit may undermine public trust or result in more restrictive regulations. However, these outcomes are not logical or practical certainties, nor has there yet been provided persuasive evidence in support of these as objections to reviewing the rule. Furthermore, as I have shown, a consideration of similar amendments suggests that an appropriately careful and considered revision process would avoid or mitigate the possible problems that may arise from an extension. However, even if these social and political problems can be avoided, there are other challenges raised by a potential extension to the limit on embryo research. In the next section I will discuss these rather more novel challenges and suggest a possible approach to responding to them.

The challenge posed by synthetic biology and embryo-like structures

A number of recent stem cell-related discoveries potentially pose serious challenges for the current regulations on embryo research. These challenges have motivated calls for a revision of the 14-day limit and have also led some to question the appropriateness of an extension as a solution.

Specifically, ongoing research investigating the differentiation and organisation of stem cells has led to techniques for engineering several types of functional human tissue that resemble primitive human organs, called 'organoids' (Lancaster & Knoblich, 2014). Organoids can be derived from either organ progenitors or pluripotent stem cells, which self-organise to both resemble the structure and replicate a specific function of a particular organ (Lancaster & Knoblich, 2014). These organoids are very useful in modelling human diseases and development (Lancaster et al., 2013). As engineering techniques advance, these entities may become more complex (Kelava & Lancaster, 2016; Quadrato et al., 2017). If these entities are able to more closely resemble complete human structures (e.g. brains), certain ethical questions may arise (Bae & Walsh, 2013; Munsie, Hyun, & Sugarman, 2017). Of particular relevance to the regulation of embryo research is the creation of entities that resemble structures of the early embryo, called 'gastruloids' (Pera et al., 2015). Gastruloids differ from organoids in that they replicate a developmental process (i.e. gastrulation), rather than the structure and function of particular organs (Munsie, Hyun, & Sugarman, 2017). In one case, gastruloids have developed cell structures that resemble the primitive streak and three germ layers (Warmflash et al., 2014). Importantly, because these gastruloids are not intact embryos (as they lack certain features and correct structure), they are not subject to the current embryo research regulations (which commonly refer to IVF embryos (Hyun, 2016)). As such they provide unique opportunities for research that would

ordinarily be prohibited using real embryos (Pera et al., 2015). While at present these gastruloids are structurally rudimentary, there have been suggestions that with time it will be possible to engineer more advanced and complete 'synthetic embryos'[27] (Aach et al., 2017). The creation of such entities would allow for more accurate and far reaching research outcomes. However, as these entities become more similar to 'natural' embryos the distinction between non-synthetic and synthetic will become less clear and they may eventually fall under the current regulations.[28] Aach et al (2017, p. 2) have claimed that in order to accurately determine whether current regulations would apply to these synthetic embryos, research on natural embryos beyond the currently permitted limit of 14 days would be necessary to ascertain the extent of the similarities. This, they argue, provides a reason for the revision of the current embryo research regulations.

In addition to these practical challenges, Aach et al. (2017) suggest that synthetic embryos highlight more fundamental problems with the current regulation and any amendment that would follow the same format. They claim synthetic embryos would not be captured by the current 14-day rule because they may be able to bypass certain stages of standard embryogenesis. Assuming that the 14-day limit functions by referring to certain biological features (i.e. the emergence of the primitive streak) which preempt various morally significant properties or characteristics (i.e. neurulation which is associated with sentience), Aach et al. have described how, through the use of specific culturing methods and 3D printing, synthetic embryos may be created that commence

[27] Also referred to as 'Synthetic Human Entities with Embryo-like Features' (SHEEFs) (Aach et al., 2017).

[28] I will use the term 'natural embryo' to refer to non-synthetic intact human embryos.

neurulation without developing a primitive streak.[29] They suggest that research on these entities would be permissible beyond 14 days as they have not exhibited the features that trigger the restriction (i.e. the primitive streak). They further argue that any amendment to the current regulation which appealed to alternative biological markers that preempt morally significant features would face the same difficulty, as synthetic embryos could also bypass these markers. For example, it may be possible that combinations of cerebral organoids could create entities that are capable of suffering without going through standard stages of development.

A restriction based solely on biological markers that preempt morally significant properties is indeed likely to be ineffective in regulating research on the kinds of the entities that may result from developments in synthetic biology, since the absence of those biological markers prevents those entities from coming within the scope of the regulation. However, I disagree with the emphasis given to the formation of the primitive streak. While the emphasis on a temporal limit of 14 days is ubiquitous across current regulations, only a few instances include a reference to the primitive streak.[30] In fact, the selection of a temporal limit as opposed to a biological marker, was designed to simplify the restriction, avoiding uncertainty regarding developmental timing and the identification of specific features. As Warnock stated, "[i]f the limit is in terms of days, … [it] is a simple matter of counting, and there can be no dispute" (1985, p .xvi). Assuming the synthetic embryos can be classified as embryos, and therefore captured by the current regulations, their use beyond 14 days of development would be prohibited, even without a primitive streak.

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[29] Aach et al. (2017) characterise the format of the 14-day rule as 'preemptive'. While I agree with the characterisation, I am not certain that the term 'preemptive' accurately captures the idea. However, for reasons of consistency I have decided to adopt their terminology.

[30] That is, all regulations that are based on the 14-day rule. (i.e. not those in Switzerland) (Hyun et al., 2016).

However, the developmental plasticity of synthetic embryos raises a further concern. While it appears that the 14-day rule would still restrict research using synthetic embryos that lack certain biological markers, it may only do so somewhat ineffectively. In skipping certain developmental stages, synthetic embryos may also have a faster developmental progression. In that case, the 14-day limit may restrict research only after the synthetic embryo has developed morally significant features. For example, it has been suggested that it might be possible for a synthetic embryo (or composite of cerebral organoids) to become sentient before 14 days of development (Aach et al. 2017, p. 14).

This has led some to suggest that the only solution to this potential problem would be to base any research restriction directly on biological markers or properties that trigger moral concern, rather than those that preempt it (Aach et al, 2017). For example, if the capacity for pain sensation is taken as the basis for limiting research, then research should be restricted when the required biological conditions first appear (namely, neural substrates and relevant functionalities), rather than at the appearance of a stage or property that immediately precedes them. It is claimed that this would avoid the problems that arise from bypassing, because the restriction is not dependant on a particular sequence of development (Aach et al., 2017). To achieve this, it would be necessary to first determine which properties or characteristics of the embryo are morally significant, and then to identify the biological conditions that underpin these features. Aach et al. are careful to note that regulations for natural embryo research need not mirror the novel regulations required for research involving synthetic embryos. They acknowledge that certain morally significant features that apply only to natural embryos (e.g. potentiality) may arise before the restriction criterion relevant to synthetic embryos (e.g. neural substrates).

However, as I have argued in the preceding chapters, I find sentience to be the only convincing criterion for moral considerability. I suggest that such a criterion applies equally to the procreative embryo, the research embryo, and the synthetic embryo. As such it seems a strong candidate on which to base a restriction marker. As previously discussed, the determinants of sentience would most certainly be biological in nature. While there is some consensus as to what these biological properties are (Lee et al., 2005; Derbyshire, 2006; Lowery et al., 2007), there are still uncertainties regarding their functionality and structure (Aach et al., 2017). As I have highlighted, this uncertainty is problematic, as an error in selecting the appropriate trigger could lead to an ineffective restriction (i.e. one that prevents beneficial research or that fails to prevent suffering).

Aach et al. have proposed a solution similar to mine regarding the identification of key S-precursors; namely, that research should be restricted once properties are present that contribute to, but do not enable, sentience. Aach et al. (2017, p. 12) suggest one possible option would be to permit research only where the two types of neurons necessary for the connection from sensory nerve input to cortex, are absent or non-functional. They suggest that the absence of these two key biological properties would serve as a safeguard to protect against the unforeseen emergence of pain sensation.

Conclusion

There are convincing reasons to extend the current limit on embryo research. However, a revision of the 14-day rule is not ethically straightforward and may present a number of challenges and risks. As I have indicated these include the possibility that it will undermine public trust or lead to more conservative regulations. While I do accept that the arguments raised against an extension highlight some relevant concerns, I maintain that these concerns can be successfully addressed. Certainly it is clear that a thorough

analysis of reasons, and an open and rational debate, will be essential for ensuring an appropriate and acceptable outcome to deliberations. As such, I maintain that while the arguments against a revision highlight important issues that must be considered and addressed, they do not at this point provide decisive reason to oppose extension of the current limit.

In addition, synthetic embryos raise challenging questions for any embryo research regulations. While I disagree with the current emphasis given to the relevance of the primitive streak as a restriction criterion, it is clear that the 14-day rule, and any amendment to it, may be ineffective in protecting synthetic embryos from possible suffering. I maintain that what I have referred to as key S-precursors are a convincing candidate for a restriction criterion for all types of embryo research, and would serve as an effective solution to the challenge posed by synthetic embryos. However, uncertainty regarding the key determinants of pain sensation make the accurate identification of what the key S-precursors are, somewhat challenging. Although I have outlined some possible responses to these questions, they are by no means conclusive. Further research is necessary to appropriately consider and address these problems.

Conclusions and future directions

The aim of this thesis has been to conduct an ethical evaluation of the grounds and justifications for the existing 14-day limit on embryo research. Recent scientific advances in embryo culturing have indicated that it may be technically feasible to sustain human embryos *in vitro* beyond 14 days. Research beyond 14 days would allow for significant insights into a variety of important stages of development. An understanding of the mechanisms involved in these developmental processes may be useful in developing many potentially beneficial applications. The possibility of sustaining and researching embryos beyond 14 days of development, and the potential benefits that such research would afford, have prompted proposals to extend the current 14-day limit on embryo research. I have assessed those proposals, considering the grounds for the current limit as well as the strength of the extension arguments, and have concluded on the basis of that assessment that an extension to the current limit on embryo research would be justified. Before making some final remarks about directions for future research, let me briefly review the overall structure and progression of my argument in this thesis.

In Chapter One I presented an overview of aspects relating to current embryo research and the current extension debate. I outlined the details of the tension between embryo research benefits and harms, and the formulation of the research regulations. Following this I demonstrated the motivations behind the 14-day rule as an attempted compromise between the need for research and concern for the embryo.

In Chapter Two I assessed the grounds underpinning the existing 14-day limit. I outlined the key arguments in support of the current limit, ultimately coming to the conclusion that none of these are convincing as grounds for prohibiting embryo research

beyond the 14-day mark. I acknowledged that the implications of this assessment may prima facie leave open the possibility either that no embryo research is morally acceptable, or that no restriction is appropriate. However, I found neither of these conclusions to be warranted, arguing instead that a concern for possible sentience and, specifically, the identification of relevant key S-precursors, would provide a superior basis on which to protect the embryo.

In Chapter Three I considered the arguments for an extension to the embryo research cut-off point, discussing the argument from the technical feasibility of culturing embryos beyond 14 days, and the argument from the beneficence of research into this period. I found that while each argument is open to some criticism, they nevertheless provide strong support for an extension to the 14-day limit. Moreover, as I argued in this chapter, an extension to 28 days would provide significant benefits to understanding and improving embryonic and therefore human well-being without raising any further significant moral concerns.

In Chapter Four I moved on to consider the possible practical consequences of extending the period of permissible embryo research into the 14–28-day phase of embryonic development. I acknowledged that an amendment to the current limit may lead to community or public anxiety about the relaxation of regulations, and potentially undermine the merit of any alternative limits. I also considered the pragmatic concern that the hasty revision of the current rule could result in undesirably conservative restrictions. However, I argued that these considerations, while important to take in to account, ultimately do not provide sufficiently strong reason to oppose an extension. That is because, as I have explained, the specific problems being referred to can be avoided or alleviated through appropriately thorough and rigorous revision and regulatory processes. I also discussed possible responses to challenges for embryo

research regulations that have emerged due to developments in synthetic biology.

Based on my analysis, I have arrived at the conclusion that the current limit on embryo research ought to be revised. I have suggested that an extension to the limit, rather than a reduction, is justified. I have also argued that key S-precursors not only provide an ethically appropriate criterion for the protection of the embryo, but also avoid a number of further challenges for regulating embryo research. As conservative estimations place the emergence of key S-precursors at around 7 weeks, with some suggestions that it may even be as late as 30 weeks, if key S-precursors are used as the criterion for restricting embryo research, then it is possible that research will be morally permissible beyond 28 days. Because of this, some may consider that a consequence of my argument is the permissibility of foetal research and that my account is problematic on that ground. While I accept this consequence, and believe that under certain conditions (e.g. appropriate benefits, oversight, public acceptance, and certainty regarding the effects to the embryo/foetus) certain research beyond 28 days may indeed be morally permissible, I offer here no argument that the current limit should be extended to this period. I have only considered a proposed alternative limit of 28 days, and have argued that there are strong and convincing reasons for research using human embryos to be permitted up until this time.

The analysis I have provided is by no means exhaustive. The aim of my assessment has only been to determine whether an extension to the current 14-day limit would be ethically permissible. As such, my suggestion that the current 14-day limit on embryo research should be extended is only a preliminary determination. A substantive decision regarding an extension to the current limit will have to be supported by a deeper analysis. Such an analysis would include an exhaustive consideration of the related benefits and harms (e.g. those to animals, society, women, patients, embryos, etc.), a

thorough philosophical analysis of the metaphysical issues (of which I have only mentioned a few), and a complete consideration of the social and political issues. This level of analysis has not been possible due to space limitations.

Nevertheless, by clarifying the conceptual and moral basis for revisiting the question of an ethically appropriate limit on embryo research, my analysis has contributing to the grounds for reviewing the current limit and to urging a fuller consideration of an extension to the current limit. I have also outlined several reasons that support an alternative limit of 28 days and have provided an alternative criterion on which amended research limits may be based.

The revision of the current regulations is by no means urgent. As I have stressed, a careful review process is necessary to ensure that any amendment is appropriately grounded and implemented. Research up to 14 days of development has only just begun. As research into this period progresses there are likely to be insights that further inform the consideration of an extension. As such, an important direction for future research will be ongoing analysis to ensure that these emerging developments and key challenges are properly evaluated.

In addition, the capacity of general embryo research regulations to incorporate and adequately regulate research involving synthetic embryos, must be carefully examined. This thesis has highlighted several issues that such an investigation must examine, such as the detailed analysis of required triggers for moral considerability (including possible precursors to sentience). As such, I hope to have contributed to clarifying the direction in which further research should proceed in this increasingly complex field.

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