The 14-day rule in the Dutch Embryo Act

To: the Minister of Health, Welfare and Sport
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Health Council of the Netherlands

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summary

Scientific research with human embryos

Scientific research with human embryos can yield knowledge that is of great importance to preventing diseases and treating infertility. For that reason, this type of research is permitted in the Netherlands, under certain conditions. The embryos used for this research are spare embryos that remain after IVF procedures and have been donated to science.

The conditions are laid down in the Dutch Embryo Act (Embryowet).

The purpose of this Act is to balance the interests of research with the need to protect human life in its early stages.

Should the 14-day rule be extended?

Under the Dutch Embryo Act, it is not permitted to allow embryos to develop outside the human body for longer than 14 days. This is known as the 14-day rule. In addition, embryo research must always be reviewed in advance to establish whether it serves a need: does it contribute to medical science, and is there no other way in which the research objective can be obtained?

When the Dutch Embryo Act – and with it the 14-day limit – was introduced, it was technically not possible to sustain embryos in vitro for longer than a week. Therefore, the 14-day rule effectively did not restrict medical research at the time. New technological developments have since made it possible to cultivate embryos outside the human body up to 14 days, which has also extended the possibilities for embryo research. As a result, one question raised during the most recent evaluation of the Dutch Embryo Act was whether there are reasons to extend the 14-day rule, for example to 28 days. The Minister of Health, Welfare and Sport asked the Health Council of the Netherlands to answer this question.

The Minister also wishes to know whether there should be a comparable developmental limit for so-called embryo-like structures. To address these questions, the Health Council of the Netherlands established a committee of experts.

Consideration of three elements

To determine an acceptable limit for research, the committee has considered three elements:

1. the embryo’s worthiness of protection
2. the importance of research beyond the 14-day limit
3. the societal perspective.

1 The embryo's worthiness of protection

An embryo is considered an early form of human life, that is worthy of a certain degree of protection. Worthy of protection means that embryos deserve respectful treatment, even if – in the case of spare embryos following IVF procedures – they are left to perish. For moral reasons, there are restrictions on the ways in which a human embryo may be used. An embryo may be worthy of protection for its own sake, but also for extrinsic reasons, such as its relational and symbolic value. In this context, 'relational value' means that society derives value from a biological or social relationship with human embryos. Embryos also have a certain symbolic value, because they represent what society considers to be meaningful. This includes the beginning of life and all associated traditions.

The embryo's worthiness of protection is both progressive and relative. This means that the embryo's worthiness increases during successive developmental stages, but also that it can be outweighed by more compelling interests. The committee has presumed that in a pluralistic society, a range of views will exist on the moral worth of human embryos. To do justice to the ideal of a pluralistic society, it is therefore important to identify overlapping consensus among citizens' views. In this advisory report, the committee will discuss criteria that, in principle, can rely on a broad level of support in a secular society. The committee ultimately questioned whether there is a timepoint in the development of the human embryo at which it is hard to imagine that a research interest would outweigh the embryo's moral worth. It is difficult to determine any such moment precisely. One example, in any case, according to the committee, is when awareness and the ability to experience pain (*sentience*) arise – which is not until much later in human embryonic development. Several moments in the development of an embryo have moral significance, such as when monozygotic twinning becomes impossible or when blood circulation or brain functions start. However, according to the committee these moments do not point to a well-defined limit for research. The same applies to the relational and symbolic values of an embryo. While they do account for the embryo's increasing worthiness of protection, such timepoints are not compelling enough for an unambiguous legal limit for embryo research.

The embryo's worthiness of protection

It is impossible to pinpoint a moment in time beyond which research involving the use of embryos becomes ethically unacceptable, except in a late stage of embryonic development.

2 The importance of scientific research

Knowledge on embryonic development is important to help understand the causes of developmental disorders. This knowledge can provide clues as to how such disorders or other diseases can be prevented or treated, and how fertility problems can be treated more effectively. Much of the

knowledge gained to date was obtained through studies using animals or human cells. However, as the insights resulting from such studies cannot be applied directly to human beings, research on embryos will remain necessary. All stages of embryonic development are relevant to scientific research. Even so, the committee believes that at the moment, the scientific importance of research with embryos is greatest between day 14 and day 28. At present, there is practically no knowledge about the development of the human embryo after day 14, when crucial processes are taking place. During the third and fourth weeks of embryonic development the body axes are formed and organ development begins. Research in the third and fourth weeks could improve understanding of how congenital cardiac abnormalities and neural tube defects (anencephaly or spina bifida) occur. Such disorders are common among newborns. Knowledge about embryonic development beyond day 28 may be obtained through existing research practices, such as research on foetal tissue from abortions. From 28 days onwards, foetal tissue obtained from abortions is suitable and available for research. While for research into embryonic development foetal tissue tends to be inferior (as it is not always intact), it does reduce the scientific need for research with embryos beyond 28 days.

Knowlegde gap between 14 and 28 days

This relates to, among others, crucial knowlegde on organ formation, developmental disorders, prevention of diseases and fertility treatments. Foetal tissue from abortions is available for research from 28 days after conception.

3 Societal perspective

Embryo research is a sensitive issue. Views on the subject vary widely from person to person. It is important for the legislator to deal with all those views carefully. Insufficient regard for the societal perspective could potentially result in diminished public confidence in embryo research, and might even erode public trust in science altogether. In contrast, support for embryo research among the general public could increase the moral legitimacy of political decisions, including a decision to adapt the 14-day rule. Additionally, acceptance of a new rule would depend on the government's transparency as to its reasons for changing the rule, should it decide to do so. The committee is of the opinion that scientific research after day 14 should serve a clear, evident and justifiable interest.

Societal perspective

To ensure societal acceptance of embryo research and public trust in science, it is essential that the scientific benefits of research with embryos can be sufficiently articulated. Moreover, it must be impossible to obtain those significant scientific insights in any other way.

Recommendation: extend the limit for embryo research to 28 days

After considering the three aforementioned elements, the committee recommends that the 14-day limit for embryo research be extended to a 28-day limit. Purely reasoning from arguments of moral status, the committee holds that it is not possible to identify a specific moment when research with embryos becomes unacceptable, other than in a late stage of embryonic development. Before that, there is a period during which the need to protect (early) human life may, in principle, be weighed against research interests. Nevertheless, an important reason for the committee to propose an unambiguous legal limit at day 28 is the societal perspective, which is closely tied to the public interests that embryo research serves. Research up to day 28 in the development of an embryo can yield valuable knowledge that may be used to prevent developmental disorders and treat fertility problems. That knowledge is currently out of reach and cannot be obtained in any other way. Presently, the interest served by research with embryos after day 28 is less evident. From a societal perspective the need for setting a limit beyond day 28 would therefore be less compelling.

Recommendation: also apply the 28-day limit to non-conventional embryos

Embryos formed by the fusion of a human egg cell and a sperm cell are referred to as ‘classic embryos’. Additionally, it is possible to manipulate stem cells to enable them to recapitulate some, or all aspects of embryonic development in vitro. The resulting entities are called ‘embryo-like structures’ (ELS). Some ELS can even represent all aspects of the integrated development of an entire embryo, but others cannot (for example, because they can only form a single organ). According to the committee, ELS that represent entire embryos (integrated ELS) also qualify for protection under the Dutch Embryo Act, because it cannot be ruled out that they have the potential to become a person. The committee refers to this category of embryos as ‘non-conventional embryos’. Even though they are created differently than via the process of fertilisation (hence ‘non-conventional’), according to the committee they still qualify as embryos. The committee is of the opinion that ELS that are not intended to represent the integrated development of the entire embryos (non-integrated ELS) do not require legal protection under the Dutch Embryo Act.

In determining a research limit for non-conventional embryos, the committee considered the same three elements it considered in the case of classic embryos. According to the committee, non-conventional embryos are equally worthy of protection as classic embryos, because the

two categories are morally equivalent. At present, little is known about public opinion on non-conventional embryos. As a result, it is impossible to determine the exact extent to which their relational value and symbolic value differ from those of classic embryos. However, according to the committee non-conventional embryos have at least some relational and symbolic value, and that value can be weighed against the research interest involved. In the committee's view, the scientific importance of research on non-conventional embryos is the same as that of research involving classic embryos. Hence, the committee also recommends a limit for non-conventional embryos that corresponds to the developmental stage of a classic embryo at day 28.

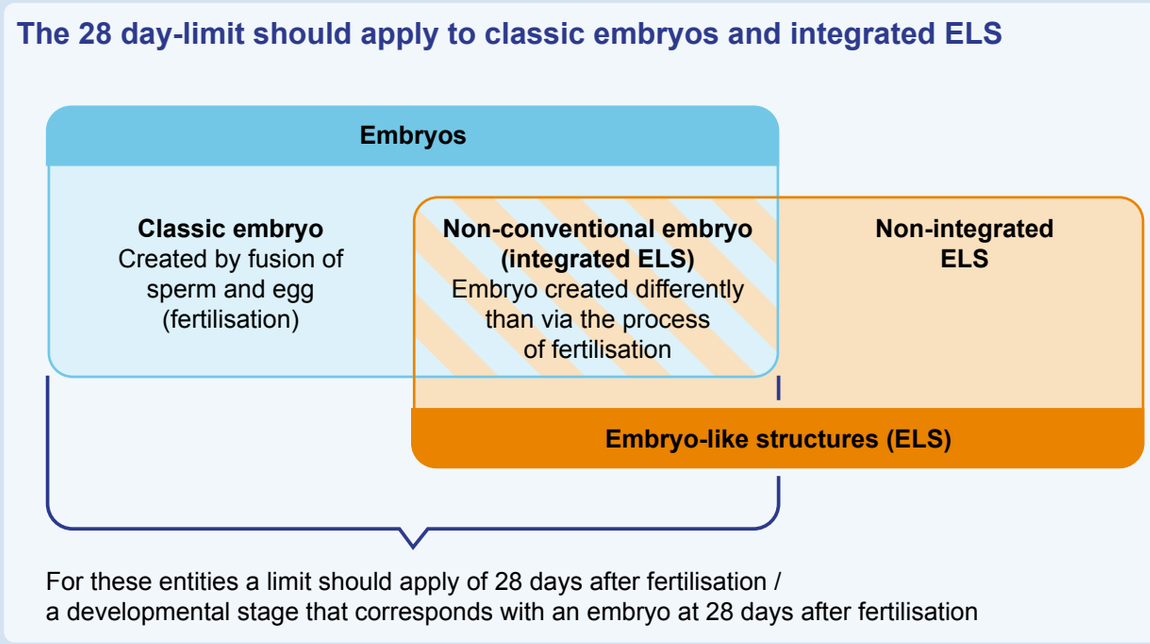

Figure 1 Schematic representation of the relation between embryos and embryo-like structures

Thorough review by the CCMO

While the committee believes that a 28-day limit is acceptable, it is not to say that the embryo is not worthy of protection until that time. It is up to the Central Committee on Research involving Human Subjects (CCMO) to weigh the research interest against the need to protect the embryo, for every proposed study. In current practice the CCMO already thoroughly reviews whether embryos may be used for research, by examining the extent to which the study concerned can be expected to yield important new scientific insights and, if so, whether those insights could not be obtained in a less invasive manner. The committee believes it is important to maintain this review by the CCMO.

Final remark

The committee does not rule out the possibility that the legal limit for scientific research on embryos may be brought up for discussion again at some point in the future. This might occur when the limit is again found to restrict scientific developments with a huge potential for preventing disease and treating infertility, or when views in society on embryo research change. In such a case, the committee believes that the balance between the embryo's worthiness of protection, the scientific importance and the societal perspective should be reconsidered.

01 introduction

1.1 Background

The Dutch Embryo Act imposes conditions on medical interventions on embryos and research involving human gametes, embryos and foetuses. The main objective of the Act is to guard the balance between respect for (early) human life on the one hand, and the importance of curing diseases and promoting the welfare of couples dealing with fertility issues.[1] In the Netherlands, a central oversight committee reviews all research protocols involving human embryos. Conditions are that the research interest should justify the use of human embryos (proportionality) and that there is no other means for obtaining the knowledge (subsidiarity). Key provision of the Embryo Act is the ban on allowing an embryo to develop outside the human body (in vitro) for more than 14 days. In daily practice this is known as the 14-day rule. The 14-day rule has been incorporated in normative frameworks around the world.[2] However, due to new technological developments in embryo research the 14-day rule has been brought up for discussion. One of the developments that is relevant to this discussion is the possibility of using stem cells to create embryo-like structures (ELS). It is still unclear whether or not ELS qualify for protection under the Act. ELS are self-organising structures derived from pluripotent stem cells. ELS are intended to represent the (non-)integrated development of the fertilised embryo.

1.2 Request for advice

The Minister of Health, Welfare and Sport (VWS) intends to amend some components of the Dutch Embryo Act. In line with the recommendations arising from the third evaluation of the Act, the Minister asked the Health Council of the Netherlands to issue advice on the desirability and acceptability of extending the 14-day rule for research with human embryos in vitro. In addition, the Minister asked the Health Council for advice on how to establish a developmental limit for embryo-like structures (ELS) that is in line with the limit for human embryos.

The Health Council established a temporary Committee to answer the request for advice. This committee consists of experts on human embryo research, bioethics, philosophy of law, health law, and science and technology studies. A list of the committee's members can be found at the end of this advisory report. The request for advice can be found at www.gezondheidsraad.nl.

1.3 Terminology and definitions

The use of the concept 'embryo' in this advice

In terms of the scope of application of the Dutch Embryo Act, it is important to define the term 'embryo'. In the Act, an 'embryo' is defined as: 'a cell or connected system of cells that has the capacity to develop into a human being'. Evaluations of legislation conducted since the introduction of the Dutch Embryo Act have revealed that the current legal definition of

'embryo' may be inadequate.[3-5] For example, it excludes non-viable embryos as these do not have the capacity to develop into a human being. As such, they are not protected under the Embryo Act, which appears to be at odds with its purpose. Moreover, according to the evaluations, the current definition provides insufficient scope for determining, from a legal perspective, what should and should not be regarded as an embryo in new areas of research (e.g. research into or involving ELS).[5]

The most recent evaluation of the Dutch Embryo Act proposes a different definition of the term 'embryo'. In October 2022, the Minister informed the Lower House of Dutch Parliament of his intention to amend the definition in the Embryo Act, as has been set out in the Coalition Agreement. The idea is to opt for a definition that is based on the embryo's origin, rather than on its potential to become a human being. According to the Minister, any new definition of the human embryo will refer to the classic scenario: a biological entity resulting from the fusion of a human egg cell and a human sperm cell, in all stages of embryonic development.[6] It is yet unclear whether entities formed by a process other than fertilisation, such as the abovementioned ELS, fall within the scope of protection under the Dutch Embryo Act. One question pertinent to this is whether such entities have the same biological and/or morally relevant features as classic human embryos, based on which they should enjoy the same level of legal protection.

In this advisory report, the committee will use the term 'classic embryos' when referring to embryos formed via a process of fertilisation, i.e. the fusion of a human egg cell and a human sperm cell. The committee will use the term 'non-conventional embryo' to refer to biological entities with a (largely) human genome that were created by a different process but contain the relevant embryonic and extra-embryonic structures to represent the integrated development of an entire embryo.

References to embryos in this advisory report always concern human embryos, unless stated otherwise.

'Embryo' versus 'foetus'

Within the meaning of the Dutch Embryo Act, an embryo is a foetus as soon as it finds itself within the human body. This legal definition differs from common medical usage in the case of a pregnancy, where an embryo is not referred to as a foetus until the third month of gestation. Up until the third month, the developing entity is still called an embryo. Since this advice report does not deal with the topic of research concerning pregnancy, the legal definitions will be maintained. This also means that, in a hypothetical sense, the term 'embryonic development' in vitro can be used to refer to stages that would be identified as being part of the foetal development in in vivo settings.

Counting in days after fertilisation

This advisory report predominantly refers to the period of development since the moment of fertilisation, unless stated otherwise. For embryos in vitro, it is common practice to start counting from fertilisation. The period of development (in vitro) and gestational age (in vivo) are not synchronous. Gestational age is calculated from the first day of the last menstruation. In practice, the difference between gestational age and developmental age is two weeks. An embryo in vitro with a developmental age of 14 days following fertilisation equals a pregnancy term of 4 weeks.

1.4 Methods

This advice is based on a range of sources relevant to this topic, including the Dutch Embryo Act, Parliamentary Papers, EU case law and evaluations of legislation, scientifical medical and ethical literature, and research reports. In addition, the committee consulted the Health Council's permanent Committee on Ethics and Law, on two occasions. The Committee on Ethics and Law contributed points of attention and suggestions and is not responsible for the content of this advisory report. The committee also consulted external experts about the past and current state of political debate and decision-making outside of the Netherlands. Finally, the advisory report was reviewed by the Health Council's Standing Committee.

1.5 Reading guide

In chapter 2, the committee presents the legal framework and describes the background and considerations underlying the 14-day rule in the Dutch Embryo Act. The chapter also discusses specific laws and regulations in other countries and the scientific studies involving embryos that are already being conducted today. Chapter 3 focuses on reconsideration of the 14-day rule. Here, the committee discusses the human embryo's worthiness of being protected, societal considerations and the importance of scientific research. Subsequently, in chapter 4 the committee explores the various types of ELS and the extent to which a developmental limit should apply. In chapter 5, the committee formulates its recommendations.

The advisory report is accompanied by a background document that presents an overview of the most significant changes to the embryo in week 3 and week 4 of its development. There is also a comparative overview of alternatives to embryo research.

02
the 14-day rule for research with embryos

There is international consensus on the importance of maintaining a balance between protecting (early) human life on the one hand, and allowing scientific research with embryos on the other. In this context, many countries allow embryo research until 14 days after fertilisation. The committee observes that the existing opportunities to gather knowledge about the early stages of embryonic development are limited. It has now been shown to be possible to cultivate embryos for a longer period of time. International laws and regulations allow for the 14-day rule to be extended.

2.1 Relative and progressive legal protection

The protection of early human life is regarded by society as an important value. This is why embryos, in our society, have a certain status that entitles them to (legal) protection. Prevailing health law doctrine identifies two types of protection to which an embryo may be entitled: a relative and a progressive worthiness of being protected.[7-10] Progressive worthiness of being protected means that as the embryo develops, it becomes more worthy of protection. For example, an embryo that has not yet implanted in the uterus qualifies for a lower level of protection than an embryo that has. And an implanted embryo, in turn, is not as highly protected as a viable foetus.[11] While the embryo's or foetus' worthiness of being protected increases over the course of its development, it is not regarded as absolute in legal practice. Due to the relative nature of the embryo's worthiness of being protected, it may be outweighed by other, more compelling interests.[8,12,13]

The doctrine of the relative and progressive worthiness of being protected is reflected in the law, in the form of an overall legal framework for procedures on and protection of the embryo, which in many cases requires a further balancing of interests. Of particular note in this regard is the Dutch Embryo Act, in which such considerations are made at the level of the law, or through self-regulation (Model Regulations on Dutch Embryo Act).[10]

2.1.1 Arguments concerning the 14-day rule in the Dutch Embryo Act

The Dutch Embryo Act came into force in 2002 and is based on the general principle of respect for human dignity and for (early) human life. Pursuant to the Dutch Embryo Act, this is understood as a call for restraint in procedures involving embryos, including in vitro procedures on embryos at an early stage of their development.[7] Already in the 1980s and 1990s, developments in reproductive technology sparked debate about the acceptability of using embryos in vitro for scientific research. Such research could potentially advance important collective interests, including the well-being of future children, the prevention and cure of diseases and the welfare of couples with fertility issues. The Dutch Embryo Act aims to maintain the balance between these collective

interests and the principle of respect for (early) human life and human dignity. Several provisions of the Act aim to maintain this balance, such as:

- *The ban on creating embryos for research purposes (Section 24, letter a, of the Dutch Embryo Act):*
  The embryos discussed in this advice are embryos that remain after in vitro fertilisation (IVF) treatments. Couples can consent to the use of their embryos for scientific research. As long as the research has not yet been carried out, they are free to withdraw their consent at any moment. Couples can also record their wish that research can be conducted only after they have been informed about the purpose and nature of that research and have explicitly granted their consent. If an embryo is not donated for research and the couple do not wish to preserve it any longer, the embryo will perish.[1]
- *Assessment by the Central Committee for Research involving Human Subjects, of protocols for research involving embryos and foetuses (CCMO, Section 3 of the Dutch Embryo Act)*:
  The CCMO conducts a priori assessments to establish whether research can reasonably be expected to yield knowledge that is important for medical science and whether the research question cannot be addressed by other means (without using embryos).
- *The 14-day rule for research with embryos (Section 24, letter e, of the Dutch Embryo Act)*:
  It is prohibited to allow 'an embryo to develop outside the human body for longer than 14 days'. After that 14-day limit, the embryos will perish. In the explanatory memorandum, the legislator acknowledged that there may be a scientific interest in sustaining embryos in vitro for as long as possible, for example to enable research into the early stages of embryonic development. At the same time, the legislator pointed to the need for a clear limit, referring to national and international consensus as its primary argument in favour of setting a development limit of 14 days.

In 1979, the US Ethics Advisory Board (EAB) was the first to argue in favour of limiting experimental IVF technology so as to eliminate concerns about potential abuse. There were concerns in particular about genetic manipulation, frivolous experimentation on embryos and the creation of genetic hybrids (human-animal combinations). The US had no embryo legislation at the time, but it did have legislation on research involving foetuses. That legislation defined a foetus as 'an embryo from the moment of its implantation' (unlike the definition in the Dutch Embryo Act, which identifies every embryo inside the human body as a foetus, even before implantation). The EAB therefore decided to set the limit for embryo research at 'the stage normally associated with the completion of implantation (14 days after fertilisation)'.[14]

In 1984, the UK Committee of Inquiry into Human Fertilisation and Embryology (also known as the Warnock Committee) proposed a similar

limit on research involving embryos, in response to societal concerns. The Warnock Committee argued that in principle, all stages are equally important to the development of an embryo and that it was difficult to identify a single stage in the development of the embryo beyond which the embryo should not be cultivated. However, the Committee agreed that an exact limit had to be set in order to allay public disquiet. In the end, the proposed limit was the sum of a range of considerations. One was based on the argument that the benefit should outweigh the harm: pleasure over pain. It was argued that, as long as the embryo feels no pain, in vitro research should be permitted. Pain is associated with functional activity of the central nervous system. According to the Warnock Committee, since the first features of the central nervous system appear (in the process known as neurulation) on day 22 or 23 after fertilisation, embryo research could be permitted until approximately 22 days. The Warnock Committee also took the first signs of functional activity of the central nervous system into account. While it was impossible at the time to identify the exact moment those signs appear, researchers knew – as they do now – that they occurred in a much later stage of embryonic development.
The Warnock Committee also considered drawing the line at an even earlier stage of neural development, when the neural plate appears, around day 17. In the end, the Warnock Committee set the limit for embryo research at 14 days after fertilisation. Internationally, this is also known as the Warnock rule. The principal arguments in favour of the 14-day rule were the fact that several medical associations called for the limit to be set at completion of implantation (14 days after fertilisation) and that the formation of the primitive streak is an important point of reference in the individuation process. Up until around 14 days after fertilisation, there is still a possibility that two primitive streaks develop, resulting in identical twins. In this context, the primitive streak is a sign of individuation.[15]

Similarly, in 1986, the Health Council of the Netherlands recommended setting a 14-day limit for embryo research. The Council had been asked for advice on artificial reproduction in the form of in vitro fertilisation (IVF), artificial insemination using donor semen, and surrogacy. The views of the Health Council were in line with those of the Warnock Committee and the EAB. Key arguments for the Health Council were individuation after 14 days and international consensus on the 14-day rule.[16]

As a second argument in favour of incorporating the 14-day rule in the Dutch Embryo Act, the legislator stated that the cells from which the future individual is going to develop can be distinguished from those serving as the basis for tissues supporting pregnancy (membranes, umbilical cord and placenta) at the end of the second week of embryonic development (day 14 after fertilisation).[1] Even though the completion of the embryo's implantation in the uterus (in vivo) is legally regarded as a transition that implies a higher level of protection for the embryo, in the evaluations of

the Dutch Embryo Act it did not result in the conclusion that an embryo in vitro should likewise be prevented from developing beyond day 14.[4,5]

2.1.2 The 14-day rule from an international perspective

European Court of Human Rights

Despite the consensus, no common international normative basis for research involving embryos has ever been formulated. To date, the European Court of Human Rights ('the European Court' below) has not adopted an unambiguous standpoint on the question of whether embryos fall within the scope of the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR). The European Court merely noted that the embryo and the foetus, given their potential to develop into a human being, should enjoy a certain level of protection on the basis of human dignity, but did so without assigning them the status of a person with the right to live.[17] The European Court left it to the discretionary power of the member States to decide how this protection should be effected. Those states have a wide margin of appreciation, as is customary in connection with "sensitive moral and ethical issues against a background of fast-moving medical and scientific developments that touch on areas where there is no clear common ground amongst member States". According to the European Court, embryo research is one of those sensitive issues on which there is no consensus, meaning that it is up to the member States to decide whether or not to regulate it in their national legislation.[18]

The Convention on Human Rights and Biomedicine, also known as the Oviedo Convention, expressly mentions research involving embryos. The Netherlands has signed but not ratified the Oviedo Convention. At the time, preparations for the Dutch Embryo Act had just begun and several provisions of that Act are not in line with the contents of the Convention. Therefore, it is at those points that the Netherlands expressed reservations when signing the Convention.[19] For example, the Netherlands wanted it to remain possible for embryos to be created for the purposes of scientific research (which is currently subject to a temporary ban).[20] Under Article 18 of the Oviedo Convention, member States that allow embryo research are obliged by law to ensure adequate protection of those embryos. The article explicitly prohibits the creation of embryos for research purposes. Since the Netherlands has not ratified the Oviedo Convention, its provisions cannot be invoked in Dutch courts.[21] Incidentally, the European Court regularly refers to the Oviedo Convention in its decisions, irrespective of whether the accused Member State has ratified the Convention.[22]

International Society for Stem Cell Research

The guidelines of the International Society for Stem Cell Research (ISSCR) constitute another normative framework for embryo research. The ISSCR guidelines are an international standard for ethical behaviour, diligence and transparency in stem cell research.[23] In 2021, the ISSCR adapted its guidelines for stem cell research, also with regard to the

14-day rule. In the new guidelines, the ISSCR highlights the technological progress made in cultivating embryos, and the potential of embryo research to improve human health and well-being. The ISSCR is calling for public conversations on the scientific importance of embryo research and the ethical questions it raises. According to the ISSCR, research with embryos cultured beyond 14 days could be allowed, provided there is broad public support within the jurisdiction and it is permitted by local policies and regulations. This does require a specialized scientific and ethical oversight process for weighing whether the research is necessary and the scientific objective justifies cultivating embryos in vitro beyond day 14.[24]

Laws and regulations in other countries

Matthews and Moralí have shown that policies on embryo research differ from country to country.[2] They studied laws and regulations on the issue of embryo research in the US, China, Japan, Germany, South-Korea, France, India, the UK, Russia, Brazil, Taiwan, Italy, Canada, Spain, Turkey, Australia, Switzerland, The Netherlands, Sweden, Israel, Belgium and Austria. The researchers found that the policies in these 22 countries could be divided into four categories: countries with a total ban on embryo research, countries without any limit for embryo research, countries that apply the 14-day rule and countries that apply a different type of limit. Most countries have incorporated the 14-day rule or a similar limit in their laws and regulations. Switzerland is the only country to impose a legal research limit of 7 days after fertilisation. However, that limit only applies to embryos used to harvest embryonic stem cells. All other types of research involving embryos are prohibited in Switzerland. Russia, Italy, Turkey, Austria and Germany all prohibit embryo research. In Brazil and Israel there is no legal limit for embryo research. The US does not have a limit for embryo research either, although no federal funding is available for research involving the creation or destruction of human embryos.[25,26] Further regulation on this issue is a matter for individual states.

Even though the European Court and the ISSCR leave the door open for embryo research, so far no country has abandoned the 14-day limit. In the United Kingdom, the Nuffield Council on Bioethics held a workshop in 2016 to discuss whether there were persuasive reasons to reconsider the 14-day rule for embryo research. The conclusion was that at the time insufficient political and societal support existed to reconsider the 14-day rule limit. For any reopening of the debate, the benefits of research beyond the 14-day limit would first need to be made more plausible. Also, if the legal limit would be changed it was deemed that an alternative regulatory scheme would be required. The Nuffield Council at that time considered that the scientific benefits that would be achievable by extending the limit beyond 14 days could not be sufficiently specified. In addition, it seemed unlikely that an alternative regulatory scheme could be devised for which broad societal support would exist. As long as these issues are not clarified, the risk of loss of public trust would be too great.

Since then, the political debate on the 14-day rule in the United Kingdom has not yet been reopened but the issue has been kept under review by the regulator, the Human Fertilisation and Embryology Authority (HFEA).[27]

Likewise, France has seen a debate on the introduction of a new limit. While there was no legal limit for embryo research in France, a 7-day limit was applied in practice. The debate specifically addressed the question of whether a legislative amendment should impose a limit of 7, 14 or 21 days. The French government proposed a 14-day limit. The Parliament agreed, but the Senate did not and argued for a 21-day limit.[28] In the end, the Senate did agree to a limit for research on day 14, largely on pragmatic and political grounds. The law was amended in 2021 to include a 14-day limit.[29]

2.2 Scientific research with embryos

2.2.1 Current embryo research up to day 14

When the 14-day rule was introduced, it did not result in an actual restriction of scientific research, since it was not possible at the time to cultivate an embryo in vitro for longer than a week.[30] This is why most discoveries made using embryo research concern the first seven days after fertilisation (the pre-implantation period). It is also practically impossible to study embryonic development in vivo beyond day 7, because after implantation in the uterus (in vivo) the embryo disappears from view, as it were.[31] Even so, research involving human embryos has yielded a great many insights thus far, in particular fundamental knowledge about human development. Additionally, embryo research has been used in the development of fertility treatments, such as IVF.[32] Embryo research is still being used in efforts to further improve such treatments.[33]

It is legally prohibited in the Netherlands to create embryos specially for research purposes. The practice of embryo research in this country has therefore been limited to questions that can be answered using extra embryos that remained after IVF procedures and have been donated to science.

In 2016, researchers from two research groups in the UK and the US made significant progress in research involving human embryos. They managed to cultivate embryos for longer than seven days after fertilisation. The researchers cultivated embryos up until day 14 in vitro, and discovered that those embryos had created the same environment as embryos do in the uterus.[34,35] This discovery has created the potential to study the development of human embryos beyond day 14. Since 2016, another research group has managed to cultivate embryos of primates (macaques) and sustain them up to 20 days after fertilisation.[36] This suggests that it should also be technically possible to sustain cultivated human embryos in vitro beyond the 14-day limit.[31]

2.2.2 Knowledge gaps

The introduction of IVF procedures and the – albeit limited – possibilities for in vitro embryo research have expanded our knowledge of the early development of the embryo, including processes that are difficult to study in foetal tissue obtained from abortions, such as physiological, molecular and genetic processes. Nevertheless, the development of the human embryo beyond day 14 remains largely obscure. Current knowledge of the human post-implantation embryo comes from a variety of sources: animal models, stem cell research, research with foetal tissue from abortions, and scientific collections (see Background Document, Table 1).

With regard to the scientific collections, those of the Carnegie Institute in Washington and the Congenital Anomaly Research Center in Kyoto are scientifically renowned. Since the early 20th century, these two institutes have collected human embryos for the purpose of studying them. The embryos were obtained from abortions or found in hysterectomies.[27,37] These collections have provided a great deal of insight into the early stages of embryonic development. However, since the scientific collections exclusively consist of static images, the information is limited to morphological changes.

In addition, knowledge about embryonic development has been obtained from research with animal embryos, including mice, cows and, to a limited extent, monkeys. Such animal models are often used as an alternative to research involving human embryos. However, animal models will never be able to fully replace the use of human embryos for research purposes, as it will always remain necessary to verify the extent to which the findings from animal models are representative for human embryonic development. For example, findings from research using mouse embryos cannot be adopted directly as a model for human embryonic development. While several factors and genes that bring about changes in the physical characteristics of mouse embryos also appear to be found in human embryos, those factors often play a different role in human embryos and are expressed in different locations and at different moments.[38,39] And while human embryos prior to implantation develop similar to mouse embryos in terms of their physical characteristics, there are considerable differences in the speed of embryonic development and the timing of specific processes in that development.[40]

Stem cell research has also contributed a great deal of knowledge. Stem cell research is a suitable alternative to embryo research for many applications. For example, stem cell research is used to improve our understanding of the formation of various cell types. Stem cells also provide a relatively easy way to test different research conditions, and to subject cells to genetic manipulation and then carefully study them. As two-dimensional stem cells behave differently from real organs, researchers are increasingly using 3D stem cell models. These models, known as organoids, represent part of the complexity and functionality of

specific organs and tissues, due to cells communicating with each other and regulating and organising themselves in spatial structures. Organoids and 2D stem cell models are suitable for research on the formation of specific cell types and organ functions. So while it is true that in some types of research stem cells are a good alternative to embryos, organoids lack the capacity of actually assuming the shape of the organ they represent - for example because the models concerned do not always account for the formation of the body axes. The three body axes (anteroposterior, left-right and dorsoventral) are formed in the third week of embryonic development. Specific genes should be expressed in specific sites along those axes, resulting in the development of specific organs in those sites.

Foetal tissue from abortions is another alternative to research with human embryos. Foetal tissue can be used if the person who carried the foetus has consented and the partner does not object (Section 3 of the Foetal Tissue Act (*Wet foetaal weefsel)*). However, one limitation is that, since foetal tissue from abortions is not complete, its utility for studying the regulation of embryonic development is limited. While foetal tissue from abortions is technically available from day 28 after the onset of the last menstruation (day 14 of embryonic development), it is very rare for an embryo to be identified in the amniotic sac that early.[41] Foetal tissue from abortions is usually suitable for research from day 28 of the development of the embryo.

There are very few, if any, adequate alternatives to using embryos for research into the very early stages of embryonic development, until approximately day 28. All these factors lead to the conclusion that there is a knowledge gap regarding the early stages of embryonic development.

03 reconsideration of the 14-day rule for classic embryos

According to the committee, it is impossible to pinpoint a moment in time beyond which research involving the use of embryos becomes ethically unacceptable, except in a late stage of embryonic development. Before that, there is a period during which research interests may, in principle, be weighed against the need to protect (early) human life. For a long time, it was technically impossible to cultivate embryos for more than 14 days, indicating there was no need to allow research with embryos beyond day 14. As technological possibilities are increasing, the committee cannot see any compelling ethical argument in favour of maintaining the 14-day rule. According to the committee, a 28-day limit is justifiable specially in view of the societal perspective and, tied to that, the current impossibility to study embryonic development between day 14 and day 28, and the valuable information that may be obtained from studying this period.

3.1 The human embryo's worthiness of protection

There is consensus regarding the notion that from the moment they come into being, embryos are worthy of at least a limited degree of protection. This is confirmed in the Dutch Embryo Act. In this context, worthy of protection means that embryos deserve respectful treatment, even if – in the case of leftover embryos from IVF procedures – they are left to perish. This worthiness of being protected is based on the value of the embryo: its intrinsic value, also known as moral status, or its extrinsic value.

An entity has moral status if, on account of specific intrinsic properties, that entity matters for its own sake. As such, the entity has an intrinsic, non-instrumental value. Moral status means that in the treatment of such an entity we are morally obliged to give weight in our deliberations to its needs, interest or well-being.[42]

Alternatively, an embryo's worthiness of being protected can also be based on its extrinsic value. In such a case, the embryo deserves to be protected not for its own sake, but for the sake of its significance within the community. This value is also referred to as the relational and symbolic value of the embryo.

In addition, the human embryo's worthiness of being protected is widely assumed to be gradual, progressive in time and relative.[7-10,39,43]

- Gradual means that moral status comes in degrees: entities can be ranked from 'no moral status at all' to 'full moral status', based on their intrinsic characteristics. The higher an entity's moral status, the stronger the moral obligations of those who deal with it.
- Progressive means that the moral status of a human embryo, and its worthiness of being protected, are often assumed to increase as the embryo develops (see also chapter 2). The Health Council itself also expressed this view in previous recommendations on the progressive moral worth of embryos and foetuses.[39]
- Relative means that other interests may be at stake that are more

substantial, from a moral perspective, than the need to protect (early) human life.[39] For example, this perspective is reflected in legislation that, subject to certain conditions, permits scientific research involving leftover embryos, and in Dutch legislation on abortion.

For a long time, the assumed ethical boundaries of embryo research coincided with the technical possibilities. Now that the possibilities to cultivate and sustain embryos in vitro have increased, the committee believes it is pertinent to critically examine different proposed limits for embryo research and the associated moral criteria. The committee wondered whether it is possible to pinpoint a moment in time beyond which the embryo's moral worthiness is such that it is hard to imagine any research interest that might outweigh it. The committee has assumed that in a pluralistic society there will be a range of reasonable views on the embryo's worthiness of protection.[44] This is not just a fact, it is also a good. To do justice to the ideal of a pluralistic society it is important to establish the extent to which citizens agree on such matters.[45] Such a common basis is also referred to as 'overlapping consensus'.[44] In order to identify the overlapping consensus for this specific topic, the committee assessed the various arguments in varying perspectives to establish, for instance, whether those arguments are consistent and compatible with current scientific insights. And also, whether they are compatible with fundamental ethical values, such as equality. In addition, the committee has attempted to do justice to widespread moral convictions among citizens, and to the principles on which current legislation is based. In this way, the committee has tried to formulate criteria that can reasonably be considered the most compelling in identifying a timepoint when an embryo's moral worth is such that it enforces a universal limit for research. In its search for the most compelling arguments, the committee also examined less compelling criteria. In addition, the committee discusses criteria that, in principle, enjoy a broad level of support in a secular society. The fact that certain groups in society may also have ideological or religious objections is all the more reason not to treat this issue lightly.

3.1.1 Undisputed criteria for moral status

According to the committee, several criteria can be identified that can serve to substantiate moral status. These criteria are difficult to dispute and are widely acknowledged. One of those criteria is self-awareness: an understanding of the self as a subject that exists in time, i.e. a subject that has a past and a future. Self-awareness enables an entity to form memories and intentions, which in turn generate an interest in realising plans for the future and shaping its existence in accordance with its own insights (self-determination), and in forging meaningful relationships with others. This is sometimes also referred to as 'personhood'. Persons owe respect to each other as equal members of the moral community.
This gives rise to the norm that persons should never be treated merely as a means.

In the case of embryos, it is evident that they cannot be considered to have moral status on the grounds of self-awareness or personhood, as they have not yet developed the required cognitive functions. However, not only persons have interests that can potentially be harmed. Entities that possess basic cognitive functions such as awareness and/or the capacity to experience pain and pleasure (sentience) also have such interests.[46] Awareness and sentience are indicative of moral status. Persons have a moral obligation to carefully protect the well-being of entities with such capacities. The brain structures and functions required for perception and awareness are not formed until a gestational age of approximately 24 weeks.[47]

According to the committee, while basic cognitive functions constitute a legitimate and necessary criterion for a certain - albeit limited - moral status, an additional aspect (personhood) is required for an entity to obtain higher moral status. This is consistent with the notion that moral status comes in various degrees.[43] However, it is important not to confuse personhood solely with being human. After all, being human is not a tenable criterion if it is used to argue that solely belonging to the human species is indicative of moral status. This would imply that humans are more valuable because they are more valuable. That would amount to speciesism: discrimination on the grounds of biological species to which an entity belongs.[48] However, if the value of belonging to the human species is explained in terms of having morally relevant capacities that not only human beings possess (such as self-awareness), this does not amount to speciesism. The only problem is that human embryos do not yet have such capacities.

3.1.2 Potential persons

The notion that an embryo in vitro has no interests until the capacity for awareness and sentience arises, seems at odds with the moral intuition that human embryos also merit protection without such capacities. One argument to assign moral status to human embryos without sentience or awareness refers to their potential to *become a person*. This argument, which is also referred to as the 'potentiality argument', explains why an embryo could have a certain moral status even if it lacks awareness, let alone self-awareness.[49] According to the potentiality argument, human embryos must be considered to be potential persons, as they are by nature predisposed to realise their intrinsic destination as persons.[50]

In discussions about the moral status of the human embryo, it is important to specify exactly what is meant by the concept of potentiality. In this context, potentiality does not denote a mere possibility. If it did, the potentiality argument would be vulnerable to the counterargument which states that any entity is potentially a great many other entities.[51] In the case of embryos, moral status would also have to be assigned to egg cells and sperm cells, or even to the nutrients from which they arise, because

those could also potentially be a person.[52,53] This rather absurd conclusion can be avoided by defining potentiality as the capacity of an entity to develop a relevant property X based on factors found within the entity itself. The term that is often used to denote this specific meaning of the concept is 'active potentiality'.[50,51] Active potentiality is at play if an entity develops property X because it is in the nature of that entity to do so.[54] There is no active potentiality when the development process is driven primarily by external factors.

This means that the concept of 'active potentiality' must be recognised if the potentiality argument is to be used in a meaningful way. As a second condition, the potential person must be the same individual as the future person.[55] This condition is referred to as numerical identity: there must be a unique potential person whose essence is maintained over time.

The potentiality argument can be invoked in a variety of ways, depending on the moment in time the potential person is deemed to come into existence. Note that possessing the potential required for moral status does not say much about how high or low that status may be.

Potential person from conception
Some people argue that the human embryo can be considered to be a potential person from the moment of conception (fusion of a sperm cell and an egg cell).[54] The future person is not identical to the sperm cell or egg cell from which it was formed, but it is identical to the embryo that arose from those cells. The problem with this perspective is that it does not satisfy the condition of numerical identity. Until the moment the primitive streak is formed, around day 14 of embryonic development, the embryo has the capacity to split and fuse. Up until that time, a single embryo can still give rise to multiple identical persons. This makes it less plausible for there to be a potential person before this ontological individuation.

Potential person from the moment the embryo can no longer split into identical twins
Some identify the beginning of a potential person as the moment the human embryo can no longer split into identical twins.[56] This perspective satisfies the condition of numerical identity: from the moment the primitive streak appears, there is a potential person whose essence is maintained over time.

Potential person from the time the cardiovascular system or brain functions are formed
Another point in time some identify as the beginning of a potential person is when an organism can be deemed to exist that has the physiological properties of the future human being. According to this perspective, no active potentiality can exist without a functional central nervous system that is able to maintain physiological homoeostasis (self-regulation) and

coordinate the embryo's development.[50] If 'a self-regulating organism' is the criterion to identify a potential person, a parallel can be observed with the concept of death. A human being is dead when blood circulation and respiration have ceased. In medical terms, this is known as death following circulatory failure. Conversely, it could be argued that a potential person comes into being as soon as there is functional heart activity propelling blood circulation and breathing.[50] The formation of the cardio-vascular system is a complex process that covers multiple weeks. Around day 22 after fertilisation, the heart tube begins to beat and that is when circulation starts. However, it takes several more weeks for the heart to gain its definitive shape. This is because the embryonic heart begins as a tube.[57] The size of that tube increases as the embryo develops, forcing the tube to curve and create a loop before the heart acquires its definitive shape.[58] By the time circulation starts and the heart tube begins to beat, the lungs have not yet been formed. It is only around a gestational age of 12 weeks that the cardiovascular system is fully formed. However, it is not until the final stage of pregnancy that the foetus develops the capacity to breathe spontaneously. Premature newborn infants often need support to sustain spontaneous breathing. So, if functional circulation and respiration is the criterion for an embryo to qualify as a potential person, it is not evident at which timepoint this criterion is met.

Alternatively, the criterion of a self-regulating organism can be applied by drawing a parallel with brain death. Brain death means that all brain functions have stopped irrevocably.[59] Conversely, a potential person might be deemed to begin as soon as there is electrical activity in the brain and in the brainstem. Yet even though the initial development of the nervous system takes place in an early stage of embryonic development, when the neural tube is formed, the earliest possible point at which brain activity can occur in human embryos is around week 7 after fertilisation, when the basic brain structures are beginning to take shape. At that stage, this is still a very primitive form of brain activity. The brain structures and functions required for perception and awareness are formed much later, from around week 24 of pregnancy.[47] So again this criterion cannot simply be linked to a single moment in time.

Potential person from the moment the embryo is viable

Some people assume that a developing embryo is a co-production of itself and the pregnant person.[60] According to this perspective, the pregnant person's body offers a great deal more than a nurturing and supporting environment. In this line of reasoning, embryonic development is fuelled by a complex interplay of maternal and embryonic factors. This view accords a much more decisive role to the maternal factors than the view according to which the embryo directs its own development in an autonomous process. Hence, this perspective fails to satisfy the condition of active potentiality. In this view, no active potentiality - and no potential person - could exist until the embryo primarily depends on itself for its development into a person. Potentiality could in that case be identified in

terms of viability outside the uterus. In the case of embryos in vitro there is no maternal body and the question becomes hypothetical: from what point in time does the embryo in vitro become largely dependent on itself for its development into a person? It is impossible to answer that question at the present time, simply because we know too little about the development of embryos in vitro after day 14.

A different account of potentiality: a future like ours

Sometimes reference is made to a variant of the potentiality argument using the concept of “a future like ours”. In this case it is argued that an embryo has a predisposition to become a person and we should not deprive it of the opportunity to attain the type of valuable future that comes with personhood.[61,62] The a priori assumption here is that life is something special and valuable that should not be withheld from embryos.

This presupposes a moral obligation to create the conditions that will enable the embryo to become a person and, at any rate, to ensure it will not perish. As such, this argument introduces a complex problem, as it is possible to identify conditions for all living entities (including plants and ecosystems) in which they either flourish or in which their continued existence is threatened. Some authors have pointed out that having an interest in a favourable continued existence is not sufficient for arguing that we owe it to entities to actually realise their continued existence.

For that to be the case, such a continued existence should be of personal value to an entity that is aware of that interest.[63,64] Given that embryos and foetuses have no self-awareness, the argument of a valuable future cannot apply to them. Others argue that all living entities have an interest in their continued existence. However, that interest may always be weighed against other interests.

No longer a potential person beyond window of implantation?

In a more or less reverse line of reasoning, it could be argued that the embryo in vitro would, at a certain point in time, lose its capacity to become a person. The period when the uterus is receptive for implantation of an embryo, known as the window of implantation, ends approximately 14 days after fertilisation. One provisional conclusion might be that to the extent embryos in vitro have active potentiality, they lose it beyond the window of implantation. However, that does not seem to settle the issue definitively. While successful implantation in the uterus is essential for the embryo’s further development in vivo, there is no evidence that the corresponding 14-day period is equally essential for the further development of an embryo in vitro. For the time being, it will remain difficult to mimic the complex in vivo environment for embryos in vitro.

In the longer term, perhaps, scientists may be able to create an environment to compensate for this problem. Whatever the case, there are no scientific grounds at present to rule out that embryos in vitro have the capacity to go through the various stages of normal embryonic development even after 14 days.

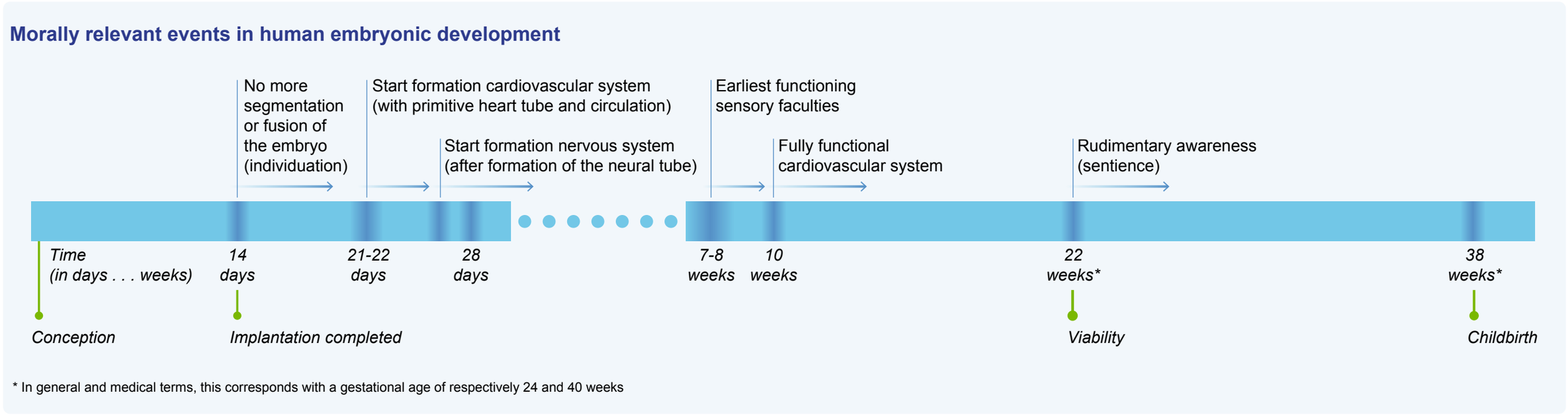

Figure 2 Timeline of embryonic development with regard to morally relevant events in human embryonic development

The potentiality argument as a criterion for moral status

Considering the various ways in which the potentiality argument might be interpreted, the committee is of the opinion that the value of this argument in the context of this advice is limited. The potentiality argument does support the intuitive notion that an embryo is worthy of protection even before awareness and sentience arise, by showing that there are multiple morally significant stages in the development of the human embryo. However, the moral implication of this is not that the embryo, in all of those stages, should enjoy the same level of protection as the future person, but that there is a limited, progressive entitlement to protection that can be weighed against other interests.[65] For this reason, the potentiality argument as such is not sufficient as a tool to set a new limit.[44]

3.1.3 Relational and symbolic value

It is not merely moral status based on intrinsic properties of an entity that prescribes how we should treat entities. Other grounds for moral consideration may be found in the relational value and symbolic value of the entity. In that line of reasoning, an entity's worthiness of being protected does not follow from the intrinsic properties of the entity itself, but from its social or biological relationship with other entities.

Relational value

In conjunction with the potentiality argument, the relational value of the human embryo might explain why an embryo merits special protection before it has any cognitive functions. For example, let us consider the bond experienced by a pregnant person with the embryo in her womb. During pregnancy, moments when a social bond may exist occur when the pregnant person is aware that she is pregnant, or when she experiences the presence of the foetus, which is usually after a number of weeks. This social bond may intensify as the pregnancy progresses.

Embryos formed from the gametes of specific individuals are undoubtedly of significance to those individuals, irrespective of the prospect of a future child. For that reason, their permission in required for any procedure performed on the embryo, even if not aimed at the birth of a child.

Relational value may also exist if there are no specific individuals who have a valuable relationship with the entity. The social or biological relationship that we as a community feel towards newborn infants, foetuses and possibly even embryos in vitro could also be a reason for us to adopt a respectful attitude. For example, the fact that we universally consider newborns to be worthy of protection is not because they already have self-awareness and are making plans for the future. Rather, we believe they are worthy of protection because each newborn is ‘one of us’. The relational value of an embryo in vitro cannot reasonably be deemed to be as high as that of a foetus or a newborn child. At any rate, that value will not be such that it would deem research with embryos to be categorically unacceptable.

Symbolic value

Worthiness of being protected can also be assigned on the grounds of the entity’s symbolic value within a community. Human remains, for instance, based on their symbolic value, are worthy of protection against unacceptable treatment and commercial exploitation.[51] This respect is engendered by our view of the type of society we wish to be. For instance, a flag has more significance than a mere piece of cloth. A flag has a symbolic value associated with the history, values and ideals of a particular country or community. Likewise, an embryo in vitro has a certain symbolic value. From this perspective, human embryos are regarded as much more than just cellular material; they represent the beginning of human life and all the associated social norms and rituals. Due to their symbolic value, embryos deserve moral consideration - which means, in any case, that they should not be used for trivial purposes.

The symbolic value of an embryo probably increases as pregnancy progresses. This value could be associated with a variety of phenomena: being aware of the pregnancy, the visibility of a pregnancy and/or external resemblances between the embryo and a human being. Despite the fact that technically there is no pregnancy in the case of an embryo in vitro,

several moments may have a symbolic significance owing to the parallel with pregnancy. For example, implantation of the embryo in the uterus (14 days after fertilisation) appears to be of symbolic significance as this is the earliest moment pregnancy can be detected. Interestingly, this symbolic value is transferred to embryos in vitro - even though in the latter case implantation never occurs. In addition, the majority of fertilised egg cells never successfully complete implantation, and perish as a result.
The question is what weight we should assign to an embryo's symbolic value. Entities with symbolic value will always be less worthy of protection than the entities they symbolize. If we assign value to a 14-day-old embryo because of its symbolic reference to a newborn baby, we will assign greater moral weight to the newborn than to the embryo.

According to the committee, embryos in vitro have a certain relational and symbolic value. The more the embryo resembles a human being, the greater the significance of both its symbolic value and relational value. This is consistent with the notion of the embryo's gradual and progressive moral worth which, especially at the beginning, need not exclude the possibility of being weighed against substantial research interests.
The relational and symbolic value of human embryos may also provide a non-speciesistic argument to favour animal research over research with human embryos. The a priori assumption is that non-sentient human embryos are more worthy of protection than sentient animals. This is because subject to conditions, medical scientific research on most sentient animals is – albeit not uncontroversial - permitted. As such, in embryo research the requirement of subsidiarity is often interpreted in such a way that the use of human embryos is deemed unacceptable if the same research can be carried out using animals. It could be argued, from this perspective, that human embryos are more worthy of protection 'because human embryos have a greater relational and symbolic value', rather than because they belong to the human species per se.

3.2 The interest of scientific research

Important processes take place throughout the development of the human embryo. All tissues and organs emerge from the fertilised egg, eventually forming a new individual. The period from fertilisation up to the birth of a full term baby takes approximately 38 weeks. This corresponds to a gestational age of 40 weeks. This is because pregnancy is counted from the first day of the last menstruation, which is around two weeks before fertilisation. In vitro, however, the moment of fertilisation can be precisely determined, which is why in this case the development is deemed to start from that moment. A whole range of developments take place during this period (Figure 1). Most of those developments are complete by the time the embryo is 24 weeks old. At present, a premature baby can be sustained outside the womb from 22 to 24 weeks of pregnancy (foetal age 20-22 weeks).

Problems can occur in the development of the embryo. Developmental disorders in the first few weeks of pregnancy can be at the root of infertility or early miscarriages. Examples include implantation disorders or a development failure in the period before implantation. Disorders in subsequent phases of embryonic development can result in late miscarriages or congenital anomalies in the child. Scientific research with human embryos can yield important insights into a period of embryonic development which has remained virtually invisible to science (particularly the period between days 14 and 28). Such research is expected to generate fundamental knowledge, a better understanding of diseases and developmental disorders, clinical applications (prevention of disease and treatment of infertility) and scientific validation of research methods.[30]

A brief description of the main study areas is given below. A more comprehensive overview can be found in the background document.

3.2.1 Fundamental knowledge

Research with embryos in vitro beyond day 14 is expected to generate fundamental knowledge about human embryonic development.
For instance through insights into the gene expression and molecular processes behind the physiological changes in the embryo.[27] The third week of embryonic development is when the body axes are formed, among others. Organ formation (organogenesis) begins in the fourth week of embryonic development. By acquiring more knowledge of normal embryonic development, such as organogenesis, scientists can find out how and why developmental disorders can occur. For this type of fundamental research, it is necessary to study the embryo in its entirety. Research cannot be limited to the use of organoids (embryo-like structures, which constitute only a few organ systems).

Congenital heart defects

The precursor of the heart, the primitive heart tube, is formed in the third week of embryonic development. It is one of the first structures to be formed in the embryo.[66] The embryonic heart develops as an almost symmetrical tube, in the centre of the embryo.[57] The heart tube eventually increases in size and bends to form a loop. The process leading to the transformation of a straight cardiac tube into a loop is known as cardiac looping. Looping is the first process that breaks the symmetry of the embryo and is therefore also related to the formation of the body axes in the embryo. Looping plays an important role in the formation of the heart, and any disruptions of this process can cause a multitude of congenital abnormalities.[58]

Approximately 1 in every 100 newborns is born with a congenital heart defect. Congenital heart defects are the most common type of congenital abnormalities and they account for 40% of all prenatal deaths. In many cases, the causes of congenital heart defects are unknown.[67] What is clear, however, is that 15% of heart defects have a genetic cause, another 30% are associated with environmental factors.[57]

The genetic regulation of cardiac looping is the subject of a great deal of research, mostly animal studies involving chicken and fish. This research has been of considerable value for our understanding of the human heart. However, scientists need more information about the human embryonic heart to be able to compare data with those of animal models.[68] To improve their understanding of the formation of the heart, scientists need to be able to study the embryo as a whole, given the connection with the body axes and a functional circulatory system. Research beyond the 14-day limit could provide new knowledge about the formation of the heart and, as such, about the causes of congenital heart defects.

3.2.2 Understanding of developmental disorders and disease prevention

By studying embryos in vitro beyond day 14, researchers obtain more information about the etiology of congenital abnormalities (See Background Document, Table 2). In the Netherlands, 3% of all children have a congenital defect.[69] The nature and severity of those defects vary. Congenital abnormalities can arise as a result of a genetic predisposition (chromosomal abnormalities or specific gene mutations). This is the case, for example, in children with Patau's syndrome, which have three instead of two copies of chromosome 13. This causes heart defects and defects in other organs, as well as serious mental disability. Congenital defects can also be caused by, what have thus far appeared to be, spontaneous defects in the development of the embryo. This is the case, for example, with neural tube defects (see box). Exposure to toxic substances during pregnancy is another potential cause of congenital defects, for example in the case of foetal alcohol syndrome (FAS).[70] The causes of other defects are still unknown, such as situs inversus, where some or all organs are located on the other side of the body. Once scientists understand the causes of congenital abnormalities, they may be able to prevent them through active or preventive intervention. In vitro research with embryos beyond day 14 may provide new insights in this area. Therefore, it is to be expected that this type of research will prove to have added value for future generations.

Neural tube defects

Neural tube defects are among the most common congenital abnormalities. These defects originate in the third and fourth weeks of embryonic development. The development of the neural tube (neurulation) begins at the end of week 3 and ends around day 26 of embryonic development.[27] Abnormalities occur because of incomplete closure of the neural tube or neural folds.[71]

Parts of the nervous system remain exposed to the environment if the neural tube fails to close properly, potentially resulting in nerve damage. The type and severity of a neural tube defect depends on where exactly the neural tube did not close properly.[72] In the case of spina bifida, there is an opening along the spine. The vertebrae and/or the skin covering the spinal cord are incompletely formed and the corresponding area of the spinal cord is exposed. As a result, the spinal cord or nerves can be damaged in that area. The closer the opening is to the head, the more serious the consequences may be.[73] Anencephaly is a condition in which the skull fails to develop, or to develop properly, as a result of which the brain cannot grow. Newborns with this defect are either stillborn or die shortly after birth.[74]

Neural tube defects are suspected to be attributable to multifactoral causes, involving both environmental and genetic factors. Much remains unclear about the genetic component. The knowledge available today about neural tube closure comes from animal studies and embryo-like structures (ELS).[72] Since models can only visualise a part of the development process, they are not an adequate alternative to embryo research. For thorough research into the formation of the neural tube, scientists need to be able to study the entire embryo. Research beyond the 14-day limit can improve our understanding of neural tube defects, offering scope for the development of treatments or preventive intervention strategies.

3.2.3 Effectiveness and safety of fertility treatments

Embryo research is essential for determining the effectiveness and safety of existing and new fertility treatments. It is important to conduct in vitro studies before new fertility treatments are made available for clinical applications. As this necessarily involves procedures on human embryos, there are no alternatives to this type of research. Likewise, insights into the causes of infertility and repeated pregnancy loss due to implantation problems can only be obtained from research with embryos after day 14. Fifteen per cent of all couples of reproductive age have infertility issues.[75] In vitro fertilisation (IVF) can help them. Since the first IVF treatments, their effectiveness has increased. However, the success rate of IVF has remained stable at only around 30%. In other words, the majority of the embryos that are implanted in the uterus do not result in pregnancy. This is generally assumed to be due to stagnation in the development of the embryo or its failure to implant in the uterus. Specific chromosomal defects in the embryo may play a role in this, but not much is known about this yet.[76] A better understanding of the causes of unsuccessful embryo transfer or of the stagnation in their development could help to significantly increase the success rate of IVF treatments.

Embryos and IVF

A haploid egg and a haploid sperm cell (each with a set of 23 chromosomes) form a euploid embryo in the process of fertilisation (with 23 pairs of chromosomes, so 46 chromosomes in total). It is known that many embryos are aneuploid, which means they have either too many or too few chromosomes. This can be due to the egg or sperm cell not having the right number of chromosomes, or to improper cell division during the embryo's development. The latter almost always involves 'mosaic' embryos, which have both euploid and aneuploid cells.

The embryo's in vitro environment during IVF treatment may affect the risk of mosaicism.[77,78] By extension, the in vitro environment might also influence the effectiveness of IVF treatment. It is not sufficiently clear whether and, if so, to what extent mosaic embryos are able to develop into a healthy baby. However, it is becoming increasingly clear that embryos have self-correcting ability. They can reject abnormal cells or move them to the outside of the embryo, where the placental tissue forms.[79] So it seems that some mosaic embryos do have healthy cells on the inside and could therefore grow into a healthy baby.[80]

Mosaic embryos pose a problem when applying preimplantation genetic testing (PGT). If couples have a significantly increased risk of having a child with a serious hereditary condition or, have an increased risk of a miscarriage due to a chromosomal defect, it is possible to test the embryos for genetic abnormalities in the IVF process. In a specific type of PGT (testing for aneuploidy (PGT-A)), one or more cells are taken from the embryos and the number of chromosomes in those cells is examined. Embryos found to contain abnormal cells will not be transfered. In this way, mosaic embryos - which may be viable - may inadvertently be identified as clinically unsuitable. Exclusion of mosaic embryos may reduce the chance of pregnancy in patients undergoing PGT-A.[81]

(continued)

Once it is possible to allow embryos to develop beyond the 14-day limit, further insights may be obtained into the development of genetically mosaic embryos: can they still grow into a healthy embryo? And how does the in vitro environment affect the formation of mosaic embryos? Over time, this knowledge may help to improve the chance of successful pregnancy in IVF treatments.[55,82] Again, animal models and ELS cannot serve as an adequate alternative to research with embryos here. This is because the outcomes of animal studies cannot be extrapolated to humans. Non-integrated ELS (which only partially represent an embryo) are not an alternative, because they do not contain the cells required for the formation of the extraembryonic tissues.

3.2.4 Validation of research models

Most knowledge about human embryonic development is currently obtained from scientific research using models based on human stem cells and models based on animals (especially mice). It is expected that it will eventually be possible to model the entire integrated development of the embryo, using human embryo models. Those models are essential to improve our understanding of normal and pathological embryonic development. In order to validate the extent to which such models match in vivo processes, however, human embryos will have to be used as a benchmark. Due to the knowledge gap between day 14 and day 28, it is not currently possible to research the extent to which ELS actually correspond to a classic embryo in the same developmental stage.[83]

3.3 Societal perspective

Along with the embryo's moral worth and the interest of scientific research, the societal perspective is a third relevant aspect in political decisions surrounding the 14-day rule for embryo research.[84]

Medical scientific research with embryos is a sensitive issue that is approached from a variety of perspectives in society at large.[85] As pointed out in section 3.1 above, doing justice to those perspectives - as long as they concern reasonable views on how to deal with embryos - is in itself an important ethical requirement. Support among the wider public enhances the moral legitimacy of laws and regulations, or any amendments thereto. Needless to add, it is important that society is properly informed about the relevant facts.[86] As an added advantage, recognition of the societal perspective will also help to maintain (a high level of) trust among the general public in science and government.[87] More specifically, as regards the 14-day rule there is a risk that public support for embryo research in general will be eroded if the limit for embryo research is extended beyond the term deemed acceptable in society. In short, any decision to amend the 14-day rule should take the range of views into account that exist about this issue in society. In the past, for example in the case of the well-known Warnock report, societal acceptance was explicitly mentioned as a reason to introduce a specific limit for embryo research.[15]

So far, little is known about views in Dutch society about a possible extension of the 14-day rule. In 2020, the Rathenau Institute conducted a survey on views of Dutch citizens on embryo research in general. In one sub-question in that survey, respondents were asked whether they would support an extension of the 14-day rule to 28 days. Thirty-four per cent of the respondents said they felt that extending the limit to a maximum of 28 days was acceptable. However, 46% said the limit should not be changed, and 20% said they did not know.[85] The survey also showed that 39% of the respondents would appreciate receiving more information about the benefit and necessity of the studies that would enabled if the 14-day rule were extended.[85] It was found that the specific objective of research

involving the use of embryos (such as gaining knowledge about serious disorders or fertility treatments) influenced respondents' views on whether such research was acceptable. It appears, therefore, that sufficient information about the research, and hence about the reasons for conducting it, is essential to ensure societal acceptance of a possible extension of the 14-day rule.

According to the committee, the importance of the societal perspective gives rise to a number of considerations. First, the committee is of the opinion that a uniform legal limit for embryo research is necessary even if moral and scientific considerations do not directly result in an absolute limit and if the interests involved could be balanced against each other per research protocol. According to the committee, specific laws and regulations should be able to count on a sufficient level of support in society. The absence of an unambiguous legal limit for research could result in diminished public trust. In addition, one condition for extending the existing limit is that the scientific importance of doing so is sufficiently plausible and can be sufficiently articulated. To that end, it is crucial that citizens are properly informed about the objectives and possibilities of scientific research involving embryos. This is about more than just explaining the reasons for the research. If researchers are transparent about their objectives, citizens can see for themselves that those objectives are consistent with objectives valued by society at large.
In addition, it is important to emphasise that if the 14-day rule is extended, this does not automatically imply permission for all embryo research up to the new limit. The scientific relevance of every study involving embryos in vitro will continue to be subject to review by the CCMO. One of the CCMO's review criteria is that it should be sufficiently made plausible that the research will generate knowledge which is important for medical science and that the interest served by the research outweighs the interest of respect for (early) human life. In addition, it should be impossible to obtain the expected scientific insights in any other way (without using embryos). According to the committee, these considerations are essential to maintain public trust in medical-scientific research with embryos, and indeed in science in general.

3.4 Assessment and conclusion

Setting a legal limit for medical-scientific research with classic embryos calls for a balanced consideration of the embryo's worthiness of protection, the interests served by scientific research and, tied to this, the societal perspective. To balance these various interests, the committee has attempted to answer the following question: until what specific timepoint may the balance between the opposing interests still be considered reasonable?

The ethical-scientific literature shows that a variety of views exists on the moral status of the human embryo and its worthiness of being protected. The committee set out to identify a common ground where these varying

perspectives converge, to the extent they meet the standards of reasonableness. According to the committee, there are no reasonable arguments to refute the notion that an entity has moral status as soon as it has interests. Interests arise, at any rate, in the case of self-awareness (personhood), awareness and sentience. However, the idea that a human embryo is only worthy of protection if it has awareness or self-awareness is at odds with the moral intuitions shared by many people.

To substantiate those intuitions, reference is often made to the capacity to become a person, with different kinds of criteria and arguments being proposed for 'potential persons', such as the embryo being past the stage of becoming identical twins, or the onset of the cardiovascular system and brain functions. Other grounds for a human embryo's worthiness of being protected are the relational and symbolic value assigned to embryos in vitro. Because of this type of value, the human embryo may be assumed to have moral worth well before it can be considered to have awareness. In the committee's assessment, however, this relational and symbolic value is less compelling - compared with moral status on the basis of intrinsic properties - and, as a result, can always be weighed against other interests.

There is broad agreement in society that upon fertilisation the human embryo has a limited moral worth that progressively increases, and that this worth can be weighed against other interests. To propose an unambiguous limit for embryo research, the committee attempted to identify a timepoint in human embryonic development when the embryo's worthiness of protection is such that it is hard to imagine any research interest that might outweigh it. According to the committee, the earliest moment is when an embryo starts having a rudimentary level of awareness and sentience. The most recent scientific insights suggest that this capacity does not arise until late in the third trimester (approximately week 24) of pregnancy. It is impossible at the present time to identify a timepoint from which an embryo developing in vitro could be deemed to be sentient. It is as yet impossible to complete human embryonic development outside the uterus (ectogenesis). At the moment, only the first part of embryonic development (embryos before implantation) and the last part (premature babies) have been successfully completed outside the uterus. Consistency demands that from the moment the embryo in vitro possesses sentience, it must be deemed to have interests and, hence, moral status; indeed, its moral status may be such - also in view of the human embryo's relational and symbolic value – that it is hard to imagine that it could be outweighed by any research interest. While considerations concerning potential persons and the relational and symbolic value of embryos are morally relevant to the notion of increasing worthiness of protection, they are not sufficiently distinctive to attribute more than a limited moral status.

With respect to the interest of scientific research, the committee observes that from day 14 after fertilisation, processes are activated that are

essential to normal embryonic development. It is also evident that most abnormalities first arise in embryos from day 14. Given the fact that research involving human embryos beyond day 14 after fertilisation is currently impossible and that alternatives only provide an incomplete picture of embryonic development in vivo, it can be said that there is a knowledge gap from day 14 after fertilisation. The committee expects that research with embryos in vitro will remain important as a source of knowledge about the causes of diseases and disorders during embryonic development and for testing the effectiveness and safety of fertility treatments. The benefits, however, are impossible to specify at the moment, as the research has not yet been done. On scientific grounds, no clear distinction can be made between moments in embryonic development when the scientific interest is first high and then low. As all stages are equally important for an embryo's normal development, every moment in that development is a relevant point for research into abnormalities. It is possible however to distinguish between research questions than can only be answered using embryos in vitro and research questions for which reasonable alternatives exist, such as foetal tissue from abortions. Foetal tissue from abortions that is suitable for research into embryonic development is available from day 28 after fertilisation. While this tissue is not a full alternative to all research with embryos in vitro (as it rarely consists of an entire embryo), it could help to argue that, in view of the current scientific interest, a 28-day limit could be defensible. This applies all the more in view of the fact that so far there have been no indications to suggest that it will become technically possible, in the foreseeable future, to cultivate embryos beyond that term in a way that is representative of normal in vivo embryonic development.

On the grounds of neither the mere worthiness of being protected nor the scientific interest is it possible to identify a specific point in time when research with embryos in vitro that was acceptable becomes unacceptable. Nevertheless, the committee does believe there is a need to set a limit – which, moreover, is not an arbitrary limit. According to the committee, a new limit can be based on the period of time during which the relevant considerations for and against embryo research are reasonably balanced. As an embryo develops, its worthiness of being protected increases; in addition, the committee notes that in the course of time, it will become increasingly less likely that embryo research is the only way to obtain necessary knowledge in this field. There is a point in time where these two opposing lines – worthiness of being protected versus scientific interest - intersect. For a long time, that point was day 14. As long as it was not possible to keep embryos alive in vitro for more than 14 days, the benefits of embryo research from day 14 were zero. In that situation, views on the moral status of the embryo beyond day 14 were irrelevant, because there were no counterbalancing interests. Once it becomes possible to cultivate embryos for more than 14 days, the balance between the worthiness of being protected and the scientific interest may begin to shift. In that situation, it is conceivable that the two opposing lines

intersect at some different point. A limit based on such arguments is not merely pragmatic; indeed, from a societal perspective it is morally meaningful. Aspects that citizens consider to be decisive do not concern categorical answers but rather concern the way in which opposing interests have been weighed against each other, and the preconditions applied (such as proportionality and subsidiarity). Political decisions based on such a weighing of interests generally enjoy greater public support. Such support is an important basis for the legitimacy of political decisions. Now that the boundaries of what is technically possible appear to shift, the societal perspective once again helps to set a concrete limit.

The committee argues that while embryo research from day 28 could, in rare cases, conceivably be desirable and acceptable, the benefits according to current insights would be extremely limited. It is unlikely that it will become possible within the foreseeable future to cultivate embryos in vitro for longer than 28 days, and from that point in time reasonable alternatives to embryo research will be available. From a societal point of view, however, a lot is at stake should the limit be set beyond day 28: without a clear prospect of the benefits this could bring, many people would find such a limit difficult to accept. The committee believes that a limit of 28 days would meet the requirements of proportionality and subsidiarity, in view of the embryo's worthiness of being protected, the current legal ban on research between day 14 and day 28, the valuable information to be obtained from embryo research and the societal perspective.

On what grounds does the Health Council recommend a limit for research with human embryos of 28 days after fertilisation?

The embryo's worthiness of being protected

Based on:

Moral status

Symbolic and relational value

Other than in a late stage of embryonic development, it is not possible to identify a specific moment when research with embryos becomes unacceptable

Scientific importance

Knowledge gap between 14 and 28 days
This involves important knowledge of, among others, organ development, congenital abnormalities and fertility issues. From 28 days after fertilisation, foetal tissue obtained from abortions is suitable and available for research.

Societal perspective

Scientific research after 14 days should serve a clear, evident and justifiable interest, in order to maintain public trust and acceptance of embryo research.

04 research limit for embryo-like structures

Scientists can use stem cells to create embryo-like structures (ELS) for research purposes. Such ELS can have different forms. One relevant distinction is the one between ELS that represent the integrated development of an entire embryo and ELS that do not. According to the committee, ELS that represent an entire embryo are comparable to a classic embryo in terms of moral status and worthiness of being protected. Hence, such 'non-conventional embryos' should be subject to the same 28-day development limit.

4.1 Embryo-like structures (ELS)

Stem cells can be manipulated to represent the integrated development of the entire embryo in vitro, or recapitulate some, but not all aspects of the embryo. These entities are known by a variety of names, including embryoids, synthetic or artificial embryos, embryoid bodies or SHEEFs (synthetic human entities with embryo-like features).[55] The term used in this document to cover all these concepts is ELS (embryo-like structures).

ELS can be generated from embryonic stem cells or from somatic cells, such as skin cells. Somatic cells will first need to be programmed or induced before they will behave like stem cells.[88] After that, they are known as induced pluripotent stem cells (iPSC).[89] Pluripotency means that the stem cells concerned can differentiate into all adult and embryonic cell types, except the cell types of extraembryonic tissues (which form part of the placenta, the umbilical cord and the amnion).[55] However, recent studies have shown that human pluripotent stem cells may also be able to differentiate into cells of extraembryonic tissues.[90] This would also introduce the possibility to create integrated ELS that recapitulate all aspects of the integrated development of an entire embryo. Each ELS is a genetic clone of the stem cells from which it was generated, in contrast to classic embryos, which are formed by fertilisation (and have 23 chromosomes of a sperm cell and another 23 from an egg cell).[55]

In addition to the difference in how they are created, ELS can also be distinguished in terms of structures that represent the integrated development of an entire embryo and structures that only recapitulate some aspects of the embryo. The latter group includes ELS that do not represent an entire embryo. While non-integrated ELS can contain all types of embryonic cells, they do not in any case contain all extra embryonic tissues that should be present in the developmental stage represented by the ELS concerned, but only one organ or organ system. For example, there are ELS that only develop lung tissue, and ELS that are used to create a number of blood vessels without organs.[91]

It is not clear at present what level of legal protection ELS enjoy. To qualify as an embryo, a cell or a connected set of cells must have the capacity to become a human being (see Section 1 of the Dutch Embryo Act). As it is not possible, in practice, to examine whether ELS meet that criterion,

there is uncertainty about the legal status of (certain types of) ELS and their level of protection may be insufficient.[6]

4.2 Developmental limit for non-conventional embryos

The committee has tried to answer the question of whether ELS (and if yes, which ELS) qualify for protection under the Dutch Embryo Act. In this context, the general principle is that the Dutch Embryo Act protects (early) human life. According to the committee, in order to qualify for protection under the Act the entities concerned must have the capacity to develop into a human being. What is at play in this case is not the potentiality argument for moral status, but a property generally regarded in society as morally relevant. There are reasonable grounds to assume that ELS which partially recapitulate embryos and do not contain all types of embryonic and extraembryonic cells do not have the capacity to develop into a human being. On that ground, the committee believes such entities do not qualify for legal protection under the Dutch Embryo Act.

However, in the case of ELS that recapitulate all aspects of an entire embryo, their capacity to develop into a human being cannot be ruled out. After all, these ELS are biological entities with a largely human genome. They may have been formed other than by the process of fertilisation, but they do contain all the cell types required to complete all stages of the integrated embryonic development in its entirety. Under the microscope, such integrated ELS resemble classic embryos and they also behave like classic embryos, at least until day 14. Integrated ELS of mice do not at present appear to have the capacity to develop into a mouse; when transferred to the uterus of a mouse, these ELS do not produce young mice. However, in vitro these mouse ELS can develop up to a stage equivalent to one third of a full pregnancy, and they contain all embryonic and extraembryonic cells present in the developmental stage they represent, including a beating heart and blood circulation.[92] It is not known whether this also applies to integrated ELS of human origin.

The committee has taken note of recent statements to the effect that it is unlikely for human ELS to develop into a human being.[93] At the same time, some research suggests that ELS may in fact have this capacity.[94-97]

As long as it is scientifically impossible to rule out that ELS which represent entire embryos can develop into a human being, the committee believes it is necessary to ensure that such ELS have the same level of protection as classic embryos. How the entity came into being is irrelevant for its entitlement to legal protection. To highlight their moral equivalence, the committee refers to such entities as non-conventional embryos. As in the case of classic embryos, the interests of scientific research involving non-conventional embryos may conflict with the interest of respect for (early) human life.

Given the fact that classic embryos and non-conventional embryos should enjoy the same level of protection under the Dutch Embryo Act, the committee carried out the same exercise with non-conventional embryos

as it did with classic embryos to establish the limit for research with non-conventional embryos. In doing so, the committee also asked the same questions:

- During which period is the need for research with non-conventional embryos the greatest (where are the knowledge gaps)?
- When could non-conventional embryos first be deemed to possess sentience and awareness, as undisputed criteria for moral status?
- What relational value and what symbolic value does society assign to non-conventional embryos?
- What research benefits can be obtained using non-conventional embryos?
- What are people's expectations regarding a societally acceptable limit for research involving non-conventional embryos?

The committee considers that classic embryos and non-conventional embryos serve the same important research objectives. The greatest knowledge gap is observed in the period between day 14 and day 28. From a fundamental-ethical perspective, it is impossible to identify a strict limit for research involving non-conventional embryos. That is to say, not a strict limit that precedes the timepoint when a non-conventional embryo would develop awareness. It is not known to what extent non-conventional embryos could ever be made to develop normally up to the point where awareness arises. In the committee's assessment, the relational and symbolic value of non-conventional embryos is approximately the same as that accorded to classic embryos. The committee points out though that to date, little research has been carried out into citizens' views of research with non-conventional embryos. The sparse research available shows that people identify both differences and similarities between non-conventional embryos and classic embryos. One the one hand, people seem to regard classic embryos as more 'natural' than their more 'artificial' non-conventional counterparts. On the other hand, this does not reflect a clear view that non-conventional embryos are less worthy of protection.
The capacity to develop into a human being is felt to be morally relevant, just as the fact that a non-conventional embryo is a genetic clone of the cells from which it was created.[98] It is impossible to precisely determine the extent to which the relational value and symbolic value of non-conventional embryos differ from those of classic embryos. Non-conventional embryos will no doubt have a certain symbolic value and possibly also some relational value, but it will be acceptable to weigh this value against research interests. By analogy with the approach to classic embryos, the legal limit will then be determined mainly by societal and pragmatic considerations. Weighing the moral worth of non-conventional embryos against the interest of scientific research, the committee concludes that it is defensible to set the limit at day 28.

When defining the development limit, it is important to note that the prohibition in the Dutch Embryo Act (unlike the corresponding formulation by the Warnock Committee) does not refer to developmental features

such as the moment when the primitive streak first appears. The Act states that the embryo should not develop outside the body beyond day 14. When created, an integrated ELS corresponds to an embryo of a certain number of days, as a result of which it is in a later stage of development after 14 days than a classic embryo that is 14 days old.[5] The committee argues that it would not be consistent if non-conventional embryos were allowed to develop for longer than classic embryos. According to the committee, therefore, non-conventional embryos should be allowed to develop up to the stage corresponding to 28 days of development in classic embryos. As it is currently unknown what this stage will look like, in creating non-conventional embryos scientists should, in practice, identify the corresponding developmental age of the structure concerned upon its creation. This developmental age should then be subtracted from the 28 days. For example, if the non-conventional embryo, when created, has the features of a classic embryo 5 days after fertilisation, the remaining development period is 23 days.

4.3 No alternative to classic embryos

It is frequently mentioned that integrated ELS are preferable for research to classic embryos.[5] Various arguments are put forward in support of that view, the most important of which is that the use of integrated ELS allegedly raises fewer ethical and legal objections. According to the committee, this argument is not valid, since the committee has argued that integrated ELS are in fact proper embryos (‘non-conventional’ ones) and, as such, are morally equivalent to classic embryos. Integrated ELS would only be a morally more desirable alternative if they were *not* morally equivalent. The committee is of the opinion, therefore, that the two types of embryos qualify for the same legal treatment and that any legal rule regarding their creation for research purposes, whether it be a ban or permission, should equally apply to both. On an earlier occasion, the Health Council of the Netherlands stated that creating human embryos for research purposes is permissible, subject to conditions.[39,99] The committee sees no reason to deviate from that standpoint.

An argument frequently put forward to prefer the use of non-conventional embryos instead of classic embryos, despite their moral equivalence, is that no egg cell donor is required to produce a non-conventional embryo. This is an advantage, because egg cell donation is a burdensome procedure. However, this advantage becomes less material if leftover egg cells are used to create classic embryos. Due to the fact that fewer and fewer egg cells are fertilised in IVF practice, nowadays more egg cells will remain available that might be used for this purpose.

Finally, it is argued that non-conventional embryos have the advantage of being able to be produced on a large scale, making them the most efficient means for embryo research. Unlike classic embryos, the properties of unconventional embryos can be adapted in advance to make them more suitable for studying specific clinical problems. Again, these

advantages are limited, as non-conventional embryos will not be a scientifically equal alternative to classic embryos for all research questions. For example, non-conventional embryos are not suitable for research into the fertilisation process.

According to the committee, given their moral equivalence, non-conventional embryos are not a morally more desirable alternative to the use of classic embryos. Having said that, the committee points out that the use of non-conventional embryos does have practical advantages, as it does not require egg cell donors and non-conventional embryos can be produced on a large scale. However, according to the committee these advantages do not mean that non-conventional embryos are only worthy of a lower level of legal protection.

4.4 ELS that do not represent entire embryos

In addition to non-conventional embryos there is another type of ELS, namely those that do not represent entire embryos. Given the fact that these ELS do not recapitulate all aspects of an entire embryo and do not contain all the required cell types of the embryonal and extraembryonic tissues, it is ruled out that they will ever develop into a human being. For that reason, this category of ELS is not accorded the same moral and legal status as embryos. Even so, ethical issues arise when such non-integrated ELS develop morally significant properties.[100] For example, ELS can be used to create models of specific areas of brain tissue. It is not inconceivable, hypothetically, that these ELS could have or develop awareness in the future. According to the committee, entities that possess awareness have a certain moral status and, for that reason, are worthy of a high degree of protection.

At the present moment, non-integrated ELS do not enjoy any degree of legal protection. The committee is of the opinion that they should. The Dutch Embryo Act is not the appropriate vehicle for that purpose, but the Control of Body Materials Act (*Wet zeggenschap lichaamsmateriaal*), yet to be introduced, could be worded to include one or more provisions about non-integrated ELS.

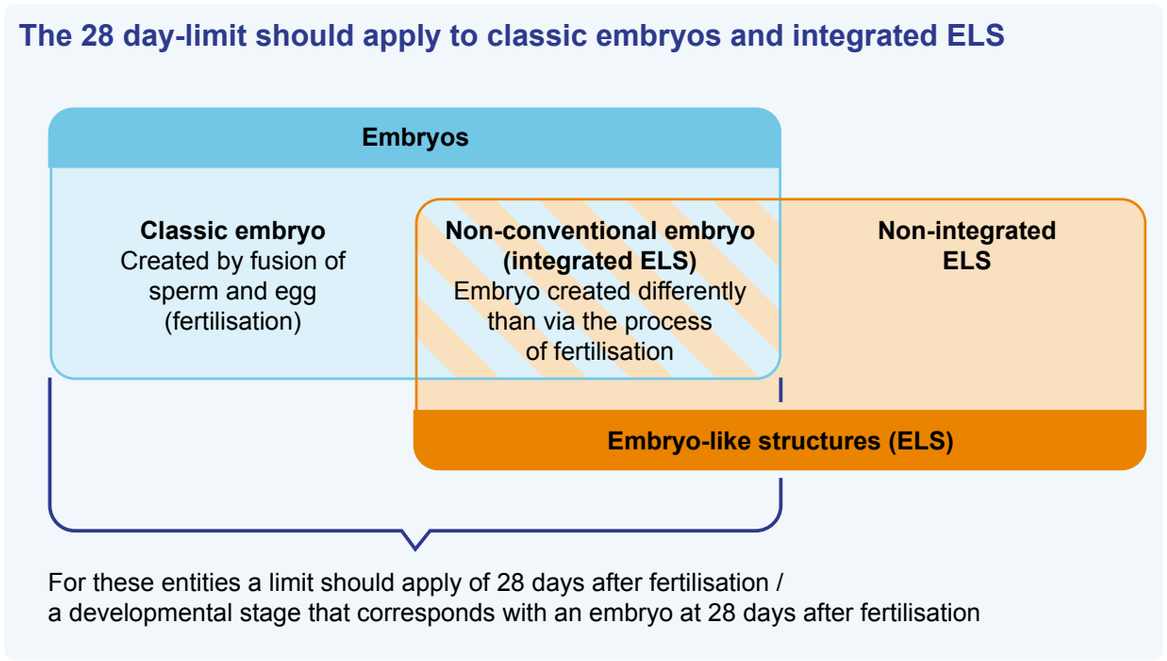

Figure 3 Schematic representation of the relation between embryos and embryo-like structures

05 recommendations

The Dutch Embryo Act prohibits medical-scientific research with human embryos in vitro beyond day 14 after fertilisation. The embryos used for this research remain after IVF procedures and have been donated to science. The committee recommends to extend this limit to day 28 after fertilisation and to apply this limit to classic embryos and non-conventional embryos alike. In this context, it remains essential to subject proposed research to thorough review by the CCMO.

A new limit for research with embryos

In reviewing the limit, the committee considered the human embryo's worthiness of being protected, the scientific importance of research beyond day 14 and the societal perspective.

The committee considered whether there are any arguments pertaining to the human embryo's worthiness of being protected that would make research beyond day 14 unacceptable. The committee maintains that undisputed criteria for moral status are awareness (including sentience) and self-awareness. Combined with the relational and symbolic value of the human embryo, consciousness and sentience impose a level of protection that makes it hard to imagine any prevailing research interest that might justify the use of embryos with those properties. Awareness and sentience are acquired relatively late in embryonic development. Moral intuition suggests that the embryo is worthy of protection even without those properties, due to its potential to become a person (the criterion that also underlies the existing Dutch Embryo Act). In that sense, the embryo would be worthy of protection on the strength of the fact that it is a potential person. According to the Committee, this criterion, while being useful as an indicator of morally significant stages of development, does not lead to a compelling and unambiguous limit for research.

Apart from moral status, the relational or symbolic value of a human embryo in society may also entitle it to protection. This might explain why the embryo is worthy of special protection even before it can be said to possess sentience or awareness. The more embryos resemble a human being, the more their symbolic value and relational value grow in significance. This is consistent with the notion of gradual and progressive moral worth.

However, an embryo's relative, progressive worth does not exclude the possibility of it being weighed against substantial research interests, especially in early stages of embryonic development. According to the committee, therefore, the ethical arguments provide no grounds for an unambiguous moment in time when research with embryos in vitro changes from being acceptable to being unacceptable.

Nevertheless, the committee believes that a uniform legal limit for embryo research is necessary, in view of the risk of diminished public confidence,

uncertainty and erosion of public trust in science. The 14-day rule cannot be extended without support for such a decision in society at large. One condition for this support is that such a new limit serves a clear, evident and justifiable scientific interest. The committee considers that there is a gap in scientists' knowledge on embryonic development between day 14 and day 28 in particular, and that this knowledge can only be obtained through research involving human embryos. This specific period is important for our understanding of developmental disorders, congenital abnormalities and fertility problems. This had led the committee to set the limit for scientific research involving embryos at day 28.

One alternative to research with classic embryos is the use of ELS. To the extent that ELS could undergo normal embryonic development and recapitulate all aspects of an entire human embryo in the developmental stage concerned (which is what non-conventional embryos do), the committee equates such ELS to classic embryos. According to the committee it cannot be ruled out that non-conventional embryos have the potential to develop into a human being. For that reason, the committee argues, they deserve the same level of protection as classic embryos. This is why the committee recommends also applying the 28-day limit to research involving non-conventional embryos. It is important to bear in mind that non-conventional embryos, when they come into being, correspond to a classic embryo of several days old. The committee recommends allowing non-conventional embryos to develop only to the stage that corresponds to the development of a classic embryo at day 28. In practice, this means that when a non-conventional embryo is created, its corresponding developmental age should be subtracted from those 28 days.

Thorough review by the CCMO

While the committee believes that a 28-day limit is acceptable, this is not to say that the embryo is not worthy of any protection until that time. As described in chapter 2, the legal limit for research is not the only instrument available to protect embryos in vitro. It is up to the CCMO to weigh the research interest against the embryo's worthiness of being protected. The CCMO already does so in the context of embryo research, reviewing proposed studies for proportionality and subsidiarity. Important considerations in this context are whether the study can reasonably be expected to result in new insights in medical science, and whether any practical alternatives to research with human embryos are available. In any event, the embryos should not be allowed to develop for longer than strictly necessary to answer the research question. In addition, embryo research is only appropriate if it can be assumed that the use of alternatives will not suffice to answer the research question. Generally speaking, the later the developmental stage, the more alternatives are available for embryo research.

Final remark

A legal limit for the scientific use of embryos is the outcome of a balanced consideration of various factors and cannot be based, according to the committee, on a single biological, scientific or moral argument. Moreover, those factors are highly context-dependent. This was the case when the 14-day rule was introduced, during the present deliberations of the committee, and it will also be the case in the future. This means that in the future, new insights may lead to new judgements. The committee believes it is conceivable that, as medical science progresses and views in society evolve, the legal limit will be reconsidered once again at some point in the future. While the underlying ethical principles remain valid, it is possible that the committee's current ethical considerations will then be weighed differently. The societal context and scientific possibilities may also change in the future. In that situation, too, the embryo's worthiness of protection will not only be safeguarded by a legal limit, as the emphasis will remain on review by the CCMO.

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[a] Consulted experts are consulted by the committee for their expertise. Structurally consulted experts and observers have the right to speak at committee meetings. They however have no voting rights and bear no responsibility for the content of this advice report. The incidentally consulted experts were invited for presentations during a committee meeting and did not participate in any of the deliberation. They bear no responsibility for the content of this advice report.

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