THE SWEDISH NATIONAL COUNCIL ON MEDICAL ETHICS
Smer, Socialdepartementet, SE-103 33 Stockholm
Tel +46 8 405 10 00 • smer@gov.se • www.smer.se

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# Embryos and embryo models – the need for an updated regulatory framework for research on early human development

**Summary**

Research on early embryo development in humans can provide important knowledge that can increase opportunities to treat infertility and prevent congenital diseases, for example. While research on human embryos has a clear scientific and clinical benefit, it is also ethically sensitive. A number of countries, including Sweden, apply the '14-day rule', which permits research on embryos to continue for a maximum of two weeks after fertilisation.

Unlike in the past, it is now technically possible to culture human embryos outside the body for longer than 14 days. Research carried out in this period can provide valuable insights into a relatively unexplored period of human development. A new technology has also been developed that uses stem cells to create models that mimic embryonic development. In some instances, these embryo models may be an alternative to using human embryos in this research, but their use also raises ethical questions.

In this Letter, the Swedish National Council on Medical Ethics (hereinafter SMER or 'the Council'), analyses the ethical issues raised by the technological developments in embryo and stem cell research in recent years. Based on this analysis, SMER recommends that the Swedish Government inquires into:

- an extension of the time permitted for research on human embryos under Chapter 5, Section 3 of the Genetic Integrity Act (2006:351) that would enable research in an important period of embryo development where much remains unknown;
- ethical review requirements based on specific criteria for research conducted on human embryos;
- ethical review requirements based on specific criteria for research on human stem cell-derived embryo models representing embryonic development as a whole;

- a limit on how long human stem cell-derived embryo models representing embryonic development as a whole are permitted to develop;
- ethical review requirements for research on human embryo models that do not represent embryonic development as a whole but raise specific ethical questions;
- an expansion of the current prohibition on implantation to include stem cell-derived embryo models; and
- an explicit prohibition on reproductive cloning.

## 1. Introduction

Research on early embryo development in humans can provide important knowledge that can lead to greater opportunities to treat infertility and prevent congenital diseases, for example. However, research on human embryos is ethically sensitive. There is a widespread view that the human embryo is worthy of protection in its capacity as the origin of a human life. The scientific benefit of research on human embryos therefore needs to be balanced against their worthiness of protection and the community's acceptance of this research. Sweden and many other countries apply the *14-day rule*, according to which research on human embryos may be carried out for no more than 14 days after fertilisation.

When the 14-day rule was formulated in the 1970s and 1980s, it was not technically possible to culture embryos for as long as two weeks. More recently, techniques have been developed that would likely make it possible to culture human embryos for longer than 14 days. Research methods have also been refined, and we now have quite different options available for obtaining genetic and other knowledge from biological material than when this rule was first formulated.

In parallel, a new technology has emerged that uses stem cells to create structures that mimic various stages in embryonic development. These *embryo models* can offer an alternative or complement to embryos for acquiring knowledge about the different stages of embryo development. Already, some embryo models are strikingly similar to embryos and are able to undergo several of the developmental stages that an embryo undergoes. It is anticipated that in the near future, models that exhibit even greater similarity to embryos will be created. Despite their similarity to embryos, in most countries, including Sweden, human embryo models fall outside the regulatory framework governing embryo research and are not regulated any differently than research on other human cells and tissues.

Technological developments in embryo and stem cell research raise the question of whether the current regulatory framework for research on early human development is fit for purpose and constitutes a reasonable balance between the benefits derived from the research and other important considerations. In this Letter, the Swedish National Council on Medical Ethics (SMER) analyses the ethical issues raised by developments in biotechnology and makes a

number of recommendations to the Swedish Government regarding the need to review the current regulatory framework for research on early human development.

## 2. Terminology

In the scientific literature and the mass media, a number of different terms are used to denote the stem cell-derived embryo structures discussed in this Letter. In addition to embryo models, names such as embryoids, synthetic embryos, artificial embryos, non-conventional embryos, synthetic embryo systems (SES), embryo-like structures (ELS) and synthetic human entities with embryo-like features (SHEEF) are used.

Different terms can lead one's train of thought in different directions, so the choice of term is not a trivial issue. Calling the entities[1] concerned synthetic or artificial embryos suggests that they constitute a form of embryo, which in turn may lead to the conclusion that they should be ethically equated with 'natural' embryos and treated in the same way as these. On the other hand, names such as embryo models or embryo-like structures indicate that they are different from embryos, which could justify their being treated differently.

In this Letter, SMER has chosen the term used by the International Society for Stem Cell Research (ISSCR), which is embryo models. This is justified on purely pragmatic grounds and should not be understood as the Council prejudicing the issue of their moral status. An entity that exhibits ethically relevant properties should be treated appropriately, no matter what it is called.

Another terminology issue concerns the term 'embryo'. In the debate around embryo models, it has been argued that an entity that has the same capability to develop into an individual as a fertilised egg is an embryo, and should be called an embryo, no matter how it came into being. This kind of definition means that it may sometimes be necessary to specify whether one is talking about 'natural' or other embryos. Since this Letter largely deals specifically with research on embryos that have developed from fertilised eggs, for the sake of simplicity the term 'embryo' is reserved for such entities.

## 3. From fertilisation to foetus

Embryonic development begins with the union of a sperm and an *oocyte* (unfertilised egg cell) to form a fertilised egg, a *zygote*. After some days, the zygote begins to undergo repeated cell division, and after three to four days has formed a compact cell mass called the *morula*.

After a further few days, a cavity forms in the cell mass and the morula transforms into a *blastocyst*. The blastocyst consists of a surrounding outer cell mass, which gives rise to *extra-*

[1] 'Entity' is used in the following as a general term to denote something that exists, whether it be a dead object, a clump of cells, or a human being.

*embryonic* structures[2] such as the placenta and foetal membranes, and an inner cell mass clustered to one side of the cavity, giving rise to the foetus and other extra-embryonic structures. The blastocyst is the last stage before *implantation*, the process by which the embryo attaches and embeds itself into the uterus. Implantation is only possible during a limited time window, which in humans begins about six days after fertilisation.

After implantation, the blastocyst continues to differentiate[3]. The cells in the inner cell mass form a round disc. When the embryo is about 14 days old, the so-called *primitive streak* forms on the surface of the disc, defining the body axes. The primitive streak is the first step in *gastrulation*, the process that forms the three primary cell layers (the germ layers). All the organs of the body develop from the germ layers in a process called *organogenesis*. After about 8 weeks, all the organs have been formed, the embryo is fully developed and the foetal period continues until birth.

## 4. Research on human embryos

The potential benefits of knowing more about early human development are many. Humans have an unusually high rate of early miscarriage compared with other mammals.[4] Knowledge of the early development of the embryo can provide insights into the causes of miscarriage and fertility problems, and ultimately contribute to the development of new or improved methods for treating infertility. Many congenital diseases, and even some diseases that occur later in life, are due to disturbances in the early development.[5] More knowledge about genetic and environmental causes of disturbances in early embryonic development can contribute to the development of new treatments – preventive as well as therapeutic. Another area of application for knowledge of early embryonic development is the development of methods for assisted reproduction and new methods of contraception. Knowledge of how cells differentiate and organs arise could also be used in regenerative medicine to replace or restore damaged tissue and ultimately enable the manufacture of organs for transplantation.

Valuable knowledge can be obtained through studies of embryos from other mammals. However, studies have shown that human embryo development differs in many respects from that of other species, including non-human primates.[6] This means that animal studies cannot entirely replace studies of human embryos. Therefore, studies of human embryos are necessary in order to fully realise the potential scientific and clinical benefits mentioned above.

[2] Although these structures are called extra-embryonic, they are in reality part of the embryo. They have developed from the fertilised egg and have the same genetic setup as the nascent foetus.

[3] Cell differentiation is the process by which a cell changes from one cell type to another cell type. Differentiation involves a progressive limitation of the cells' ability to develop and an increasing specialization of functions.

[4] Jarvis 2017.

[5] Pera 2017.

[6] Pereira Daoud et al. 2020; Clark et al. 2021; Gerri et al. 2020.

At the same time, research on human embryos raises ethical questions, particularly related to the question of their moral status.[7] There are diverging opinions about whether the early human embryo has moral status, how this status might change as the embryo develops, and on what property/properties of the embryo this moral status is based.[8] Although views on the moral status of the human embryo vary, there is a widespread view that, in its capacity as the origin of a human life, the human embryo is worthy of special protection, and that this must be weighed up against the value of acquiring knowledge about early human development.[9] Many countries that permit research on human embryos apply the *14-day rule*.[10] This rule, first formulated in 1979, permits research on human embryos to continue for a maximum of 14 days after fertilisation. One argument for this limit was that it coincides with the appearance of the primitive streak, which is the first step towards the genesis of the various organs, including the nervous system. By prohibiting research after this point, the risk of causing pain to the embryo could be ruled out. Another argument was that after the appearance of the primitive streak, the embryo can no longer divide and form identical twins. Therefore, it is only at this point that the embryo can be deemed to have begun its development towards becoming a distinct individual.

Although ethical arguments of this kind have been put forward for the 14-day limit, most people do not regard the rule as an expression of the view that the embryo acquires moral status at precisely 14 days of age. Instead, the rule should be seen as a pragmatic compromise, with the aim of enabling important research while showing respect for the existence of different moral views concerning the origin of life.[11]

For a long time, the 14-day rule has had limited practical significance for what research has been carried out, as the technical possibilities of culturing human embryos for as long as two weeks did not exist. However, more recently, methods have been developed that allow culturing until at least day 13/14 (the studies were aborted when the embryos reached this age so as not to breach the regulations).[12] Recently, two research groups in China have reported successfully culturing embryos from monkeys, which are not covered by the 14-day rule, outside the uterus for 25 days.[13] This progress means that there is reason to assume that it is now possible in practice to culture human embryos for longer than the 14 days that are permitted.

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[7] The fact that someone or something possesses a moral status means that we are obliged to take its interests into account – not because it benefits someone else, but because these interests carry a moral weight of their own. Some consider moral status to be an all-or-nothing issue, something that is possessed or not, while others suggest that different entities may possess a moral status of a greater or lesser degree.

[8] Even those who believe that human embryos possess a moral status may have different views on what the embryo's interests are, and thus how it may be treated, at different stages of the embryo's development.

[9] Cf. SOU 2002:119, p. 62

[10] Matthews & Moralí 2020.

[11] Cavaliere 2017.

[12] Deglincerti et al. 2016; Shahbazi et al. 2016.

[13] Gong et al. 2023; Zhai et al. 2023. The embryos underwent gastrulation, the formation of the three primary germ layers and continued cell differentiation, including the formation of the primordial gametes.

## 5. Stem cell-derived embryo models

Embryo models is a new technology that is undergoing rapid development. An embryo model is a 2- or 3-dimensional structure made up of stem cells that model a certain stage or phase of embryonic development. The basis for the development of embryo models is progress in reprogramming, combining, and arranging stem cells *in vitro*[14]. The stem cells that form an embryo model can come from an embryo (embryonic stem cells) or from a developed individual (induced pluripotent stem cells). Currently, the most advanced embryo models are based on cells from mice, but increasingly complex embryo models are also being developed from human cells.

### 5.1 Types of embryo models

Different embryo models differ from each other in terms of, for example, which cell types have been used, which aspects of the embryo's development they are intended to mimic, and whether they are capable of further development. According to the International Society for Stem Cell Research (ISSCR), there is a fundamental distinction between non-integrated and integrated embryo models.

#### 5.1.1 Non-integrated embryo models

Non-integrated embryo models mimic some, but not all, aspects of the early embryo. As a rule, they lack extra-embryonic cells which do not give rise to a foetus but are necessary for the embryo's continued development. Non-integrated embryo models are therefore not capable of further development. Examples of non-integrated embryo models created from human cells are gastruloids, which aim to mimic various aspects of gastrulation. Human gastruloids have been produced that mimic the development of the embryo up to early organogenesis, including the first steps in the formation of the nervous system.[15] Other types of non-integrated embryo models are neuruloids, which specifically mimic the first steps in the formation of the brain and nervous system, models that mimic events linked to the development of the amniotic sac, and models that mimic the early blood formation.[16] It is anticipated that in the near future many more types of non-integrated human embryo models will be developed, representing a variety of processes in the first months of human embryo development.[17]

#### 5.1.2 Integrated embryo models

Integrated embryo models aim to represent embryo development as a whole. They include extra-embryonic cells and can achieve a level of complexity where they are capable of undergoing further development. One type of integrated embryo model is called a blastoid, which mimics the blastocyst, the last stage before implantation. Thus far, blastoids have been

[14] The term *in vitro* refers to cells, microorganisms or biomolecules existing outside their normal biological context, usually in a laboratory environment.

[15] Liu et al. 2023.

[16] Haremaki et al. 2019; Shao et al. 2017; Hislop et al. 2024.

[17] Clark et al. 2021.

developed for mice, monkeys and humans. Recently, several research groups have reported that they have managed to get human blastoids cultured *in vitro* to mimic development up to gastrulation.[18] In mice and monkeys, researchers have managed to get blastoids to attach inside the uterus (however, they lacked the capability to develop further).[19] Human blastoids have been shown to be able to attach to cells from the endometrium *in vitro*.[20]

Other integrated models skip the blastocyst stage and mimic the embryo after implantation right from the start. For mice, 'post-implantation' integrated embryo models have been developed that recapitulate a series of developmental stages after implantation, including gastrulation and the genesis of various organ systems such as the heart, brain and nervous system, and gastrointestinal tract.[21] In 2023, a number of laboratories reported that they had produced integrated human embryo models that had developed up to or just past the first stages of gastrulation.[22]

A key question is whether in the future integrated embryo models could be created that would have the potential to give rise to viable embryos capable of further development into an individual. What is clear is that in order to achieve this, a number of technical and biological impediments must be overcome. In the long term, however, it is predicted that it may become possible to produce integrated embryo models with the potential to progress to later stages of development.[23]

### 5.2 Human embryo models in research, development and treatment

Embryo models that mimic different phases of embryonic development can contribute knowledge about the mechanisms behind embryo development, the differentiation of cell types, and the development of different tissues and organs. They can provide knowledge of the causes of diseases and infertility, and contribute to the development of new or improved methods for treating infertility and congenital diseases, and new contraceptives. They can be used to study how drugs affect embryo development. There are hopes that human embryo models will be able to replace human embryos to some extent in research into early human development and become an alternative that avoids the ethical and legal issues arising from research conducted on human embryos.

An alternative to research on human embryos could be research on animal embryos, in particular embryos from non-human primates. However, such research raises its own ethical questions related to the welfare of the laboratory animals from which the embryos originate. The

[18] Karvas et al. 2023; Imamura et al. 2023; De Santis et al. 2024.

[19] Li et al. 2019; Li et al. 2023.

[20] Kagawa et al. 2022.

[21] Amadei et al. 2022; Tarazi et al. 2022; Dupont et al. 2023.

[22] Weatherbee et al. 2023; Oldak et al. 2023; Pedroza et al. 2023; Liu et al. 2023.

[23] Rivron et al. 2018; Nicolas, Etoc, & Brivanlou (2021);Sawai et al. 2020.

possibility of conducting research using human embryo models could instead reduce the need for animal experiments.

Embryo models also have methodological advantages. Unlike embryos, they can be produced on a large scale. If they are produced with cells from the same stem cell line, they will be genetically identical, while each embryo has its own unique DNA. Embryo models can also be genetically and physically modified in ways that can be difficult to achieve in human embryos. Genetically identical embryo models that are modified in different ways could be used to investigate how genetic or environmental factors affect embryo development and the risk of miscarriage, and to discover and test new drug candidates.[24]

It is also thought that advanced embryo models could ultimately be used to produce cells and tissue for transplantation. If the embryo model is produced from the stem cells of the individual to be treated, transplants could be produced that do not risk being rejected by the recipient's immune system.[25]

# 6. Current regulatory framework

## 6.1 National regulatory framework

### 6.1.1 14-day rule

In 1991, the 14-day rule was incorporated into Swedish legislation by the Act concerning Measures for Purposes or Research or Treatment involving Fertilised Human Ova (1991:115), which included a provision that experiments on fertilised eggs may be carried out no later than the fourteenth day after fertilisation. In the legislative history, the responsible minister made the assessment that the provision meant that important knowledge could be gained without this activity coming into conflict with a humanistic view of humanity.[26]

In 2005, the Act concerning Measures for Purposes or Research or Treatment involving Fertilised Human Ova was revised. By that time, the first cloned mammals had seen the light of day. The technique used for cloning is called cell nuclear transfer, where the nucleus of an unfertilised egg cell is replaced by the nucleus and thus the genetic material from another cell. In addition to creating cloned individuals (called reproductive cloning), the technique can also potentially be used to produce cells for cell therapies (called therapeutic cloning or somatic cell nuclear transfer).[27] An embryo that develops from an egg that has been subject to cell nuclear transfer does not originate from a fertilised egg. Research on such embryos was therefore not covered by the 14-day rule as the legislation was then formulated. When the Act concerning Measures for Purposes or Research or Treatment involving Fertilised Human Ova was revised,

[24] Clark et al. 2021; Moris et al. 2021).

[25] Rivron et al. 2018; Relagado 2022; Agence France-Presse 2022.

[26] Govt Bill 1990/91:52, p. 33

[27] Cell therapies based on somatic cell nuclear transfer could avoid the problem of rejection.

the 14-day rule was expanded to include eggs used in somatic cell nuclear transfer. The aim was to guarantee that research on human ova was only conducted for important purposes and in ethically satisfactory forms.[28]

The Act concerning Measures for Purposes or Research or Treatment involving Fertilised Human Ova was repealed in 2006 and the 14-day rule was transferred to the Genetic Integrity Act (2006:351). This Act states that experiments for the purpose of research or treatment on fertilised eggs and eggs used for somatic cell nuclear transfer may be carried out no longer than up to and including the fourteenth day after fertilisation or cell nuclear transfer, respectively. If a fertilised egg or an egg used for somatic cell nuclear transfer has been used for such an experiment, it shall be destroyed without delay when the measure has been accomplished (Chapter 5, Section 3). The period during which the egg has been frozen is not included in the period during which experiments may be carried out (Chapter 5, Section 4).

### 6.1.2 Prohibition on implantation of eggs that have been used in experiments, etc.

In addition to the prohibition on carrying out experiments on fertilised eggs for more than 14 days, the Act concerning Measures for Purposes or Research or Treatment involving Fertilised Human Ova also prohibited introducing a fertilised egg that has been used for an experiment into a woman's body. The same applied if the egg before fertilisation, or the sperm used for fertilisation, had been used for such an experiment. The purpose was to avoid the risk of passing on genetic changes that could occur during the research and lead to unforeseen consequences for the prospective child.[29]

In connection with the revision of the Act in 2005, the implantation prohibition was expanded to include eggs that had been the subject of somatic cell nuclear transfer. The purpose was to prohibit reproductive cloning.[30] Here too, the legislator indicated the medical risks, but also argued that a procedure whereby a human being was artificially produced as a genetic copy of another individual would raise moral concerns.[31] The prohibition on implanting eggs that had been the subject of somatic cell nuclear transfer applies regardless of whether the eggs have been used in experiments or not.

This provision was also introduced in 2006 into the Genetic Integrity Act, which states that if a fertilised egg has been used for an experiment for purposes of research or treatment, the egg may not be introduced into a woman's body. The same applies if the egg before fertilisation, or the sperm used for fertilisation, have been used in such an experiment, or if the egg has been subject to somatic cell nuclear transfer (Chapter 5, Section 5).

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[28] Govt Bill 2003/04:148, p. 46.

[29] Govt Bill 1990/91:52, p. 34.

[30] Govt Bill 2003/04:148, p. 46.

[31] Govt Bill 2003/04:148 pp. 47–48.

### 6.1.3 The Ethical Review Act

The Act concerning the Ethical Review of Research Involving Humans (2003:460) (the Ethical Review Act) aims to protect the individual and respect for human dignity in research. The Act applies to research that subjects a research subject to a physical intervention (Section 4, point 1) and research that relates to studies of biological material that has been taken from a living person, and can be traced to that person (Section 4, point 3).[32]

Research that is coved by the Ethical Review Act may only be conducted if it has been approved subsequent to an ethical review by the Swedish Ethical Review Authority (Section 6). The Act sets out a number of general starting points for the assessment. The research may only be approved if it can be conducted with respect for human dignity (Section 7). Human rights and fundamental liberties must always be taken into account as part of ethical review, while the fact that new knowledge can be developed as a result of research must also be considered. The welfare of people should always be given precedence over the needs of society and science (Section 8). Research may only be approved if the risks it may pose to the health, safety and privacy of the research subjects are counterbalanced by its scientific value (Section 9). Research cannot be approved if the anticipated result can be achieved by some other means that entails fewer risks for the health, safety and privacy of the subject of the research (Section 10). Finally, the research may only be approved if it is to be conducted by or under the supervision of a researcher who has the necessary scientific competence (Section 11).

#### Application of the Ethical Review Act to research on embryos and embryo models

Research on donated embryos and on cells derived from them (embryonic stem cells) is subject to the ethical review requirement in Section 4, point 3 of the Act. This applies even if fertilisation took place outside the woman's body, as the gametes that gave rise to the embryo were taken from a man and a woman.[33] The requirement for ethical review under Section 4, point 3 also applies to research on embryo models that use induced pluripotent stem cells, provided that the cells can be traced to the person(s) who donated them. Research on cells where no individual connection remains is not covered by the requirement for ethical review.[34] In certain situations, Section 4, point 1 may also be applicable, for example, if a woman is undergoing treatment to produce egg cells from which to produce embryos for research, or when cells are taken from a human to produce induced pluripotent stem cells.

## 6.2 International law

### 6.2.1 The Oviedo Convention

The Council of Europe Convention on Human Rights and Biomedicine, called the Oviedo Convention, is the only legally binding source of law that specifically deals with research on

[32] Section 4 of the Ethical Review Act.

[33] Govt Bill 2002/03: 50 p. 108.

[34] Govt Bill 2002/03: 50 p. 108.

embryos *in vitro*. Under Article 18(1) of the Convention, in countries where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo. Article 18(2) explicitly prohibits the creation of human embryos for research purposes.

Sweden has signed but not ratified the Oviedo Convention.[35] One of the reasons for this is that Sweden has chosen not to prohibit the production of embryos for research.[36]

### 6.2.2 European Court of Human Rights

The Oviedo Convention is used as one of the sources when questions concerning biology and medicine are decided by the European Court of Human Rights within the framework of the European Convention for the Protection of Human Rights and Fundamental Freedoms. Consequently, the Oviedo Convention can have a bearing for Sweden, even though Sweden has not ratified it.

The general line taken by the European Court of Human Rights is that on questions where there is significant disagreement between Member States, there is more scope for national legal systems to decide how to balance competing interests. The Court has ruled that the question of the protection to which embryos are entitled is such a question.[37] Similarly, the Court has concluded that research on embryos is an area where there is a lack of consensus on sensitive ethical questions, and therefore an area where Member States must be afforded a large margin of discretion.[38]

## 7. Challenges for the current regulatory framework

Technological developments in embryo and stem cell research have raised the question of whether the current regulatory framework for research on early human development is fit for purpose or needs to be adapted to the new opportunities opened up by technological developments. Two questions are the focus of the discussion. The first concerns whether the 14-day limit for research on human embryos should be extended to permit research that could lead to new discoveries with clear potential patient benefit. The second concerns the need to regulate research on human embryo models. This section presents the main arguments put forward in the ongoing debate, and some of the positions taken by other actors.

### 7.1 Extension of the 14-day rule for research on human embryos

For a long time, the 14-day rule has had limited practical significance for what research has been carried out, as the technical possibilities of culturing human embryos for as long as two weeks did not exist. Advances in technology mean that it is probably already possible today to

[35] The fact that Sweden has not ratified the Convention means that Sweden is not legally bound by it. However, by signing the Convention, Sweden has undertaken not to act in ways that run counter to the purpose of the Convention (see Zillén, Mattsson & Sloken-berga 2020).

[36] Govt Bill 2003/04:148; SOU 2004:20, pp. 350–351.

[37] Vo v. France (53924/00) 8/7/2004, p. 84.

[38] Parrillo v. Italy (46470/11) 27/8/2015, pp. 175–180.

culture human embryos for longer than the 14 days permitted. This has sparked a debate as to whether there is reason to review the rule and permit research on human embryos older than 14 days.

### 7.1.1 Arguments for an extension

The arguments put forward for extending the period permitted for research on human embryos focus on the prospect of acquiring new knowledge and the benefits that this knowledge could generate. One argument concerns the possibility of acquiring knowledge about the embryo's development after day 14, a critical period during embryonic development that includes gastrulation and the beginning of organ formation. It is a period when the embryo is particularly vulnerable to genetic and environmental factors that can interfere with its development and lead to diseases, developmental disorders or miscarriage. In terms of knowledge, this important period is often described as a 'black box'. *In vitro* studies are prohibited in this period and it is only possible to follow the embryo's development in the uterus, where it is difficult to study due to its small size, and where experimental research cannot be carried out for ethical reasons. Unlike in later stages, there is no access to aborted material for study from this period. Much of the current knowledge about this period is based on animal studies or on the Carnegie collection, a series of human embryos at various stages of development that were collected many years ago. This material can provide information about how different kinds of tissue and organs develop, but does not provide any opportunity to study the mechanisms underlying their development.[39]

Being able to culture and study human embryos *in vitro* for longer than 14 days would provide new opportunities for acquiring knowledge about the embryo's development at this important stage, and how cells differentiate into different kinds of tissue and organs.[40] Studies of the embryo in its 14–28 day development period and how it is affected by, for example, genetic factors, chemicals and drugs could also increase our understanding of the causes of miscarriage and developmental disorders, and how processes in this early stage of development affect long-term health.[41] For example, individual genes could be knocked out using CRISPR technology and their significance for embryo development could be investigated.[42] Ultimately, this knowledge could lead to new strategies for preventing or treating disease and infertility, new methods for assisted reproduction and new methods of contraception. More knowledge about which substances affect embryo development and which do not could make more drug treatments available to pregnant women. In addition to these related applications, as with other basic research the knowledge gained can also pave the way for other applications that we cannot foresee today.

[39] Hurlbut et al. 2017.

[40] Chan 2018; Appleby & Bredenoord 2018.

[41] Williams & Johnson 2020; Pera 2017.

[42] Hurlbut et al. 2017.

Being able to test new methods for assisted reproduction is another argument for an extension of the 14-day rule. It has been pointed out that a number of new technologies for assisted reproduction are under development, such as mitochondrial replacement techniques, gametes developed from stem cells (artificial gametes) and techniques based on gene editing. These techniques could help more infertile people become parents. They could also provide prospective parents with an opportunity for parenthood in accordance with their wishes and values. For example, same-sex couples could have children genetically related to both parents, and more couples who carry genes predisposing them to serious hereditary diseases could have genetically related children without the disease genotype.[43] Being able to follow the embryo *in vitro* beyond day 14 would increase the chances of ensuring that new methods of assisted reproduction are safe and effective.[44] Existing methods could also be improved, for example by better predicting which eggs/embryos are most likely to lead to a pregnancy and live birth in connection with IVF.[45]

A third argument concerns being able to assure the quality of research conducted with human embryo models (see Section 5). There are hopes that human embryo models will be able to replace human embryos in research into early human development and become an alternative that avoids the ethical and legal constraints that apply to research conducted on human embryos. However, embryo models need to be compared to actual embryos to verify that they produce accurate results. Research results from studies conducted on embryo models may also need to be verified through experiments on a small number of human embryos. This also applies to models that mimic stages of development that occur later than day 14. The need to be able to validate these kinds of embryo models has been put forward as an argument for extending the time limit for research on human embryos.[46] Ultimately, this could lead to fewer embryos and laboratory animals being used in research, while creating more opportunities to research a critical and relatively unexplored period in early human development.

While research on embryos beyond 14 days can provide valuable knowledge, some contend that the arguments once presented for this limit have been weakened. One reason for letting the development of the primitive streak – a process that precedes the formation of the various organ systems – constitute a limit was to rule out the possibility that the embryo would feel pain. However, research has shown that important steps in the development of the nervous system that are essential for experiencing pain occur much later.[47]

### 7.1.2 Arguments against an extension

A criticism of the 14-day rule argued by those who do not want to see any research at all on human embryos as well as those who want to permit this research for a longer period is that

[43] McCully 2021; Appleby & Bredenoord 2018.

[44] Appleby & Bredenoord 2018; Hurlbut et al. 2017.

[45] Hurlbut et al. 2017.

[46] McCully 2021; Appleby & Bredenoord 2018; Lovell-Badge et al. 2021.

[47] Castelyn 2020; Hurlbut et al. 2017.

the rule is arbitrary. Nothing happens with the embryo after precisely 14 days that would justify changing its moral status. An objection to this criticism is that the rule does not aim to draw an ethical line, but to enable research to be conducted on embryos while safeguarding public trust. From the outset, the rule was intended as a compromise that expressed respect for the existence of a range of moral views concerning the early stages of human life. Given that there are still significant differences in views on the embryo's moral status, some individuals may feel alienated from society if the 14-day rule were to be extended.[48]

Others point out that there may be risks in changing a rule that has been applied for many years and has broad international support, both politically and within the research community. Changing the time limit now that it is possible to culture embryos for a longer period, and the rule has practical significance for the first time, would risk undermining public trust in embryo research and in society's ability to maintain limits when it comes to ethically sensitive research.[49] Some also warn that extending the 14-day rule will give those who claim that the rule runs the risk of becoming a slippery slope grist for their mill.[50]

Advocates for a change agree that the 14-day rule has been a successful example of international consensus, but argue that the rule must not become a dogma. In fact, not revising the rule risks undermining respect for it, because it will be seen as not serving a useful purpose. That will send a dangerous message to those involved in medical research and development, and to those people, especially prospective parents, who could benefit from the research.[51] Others emphasise that a society must be able to reconsider its positions in the light of new facts and changing values. What is important for maintaining trust in research and preventing a slippery slope is that there is a robust regulatory framework with effective supervision.

While many who oppose an extension of the 14-day rule do so on ethical and societal grounds, there are also critics who question its supposed benefit. They point out that new technologies often lead to inflated expectations that are not always met. Those who argue for an extension ought to make a reasonable case that the potential benefit is so great that it justifies changing a well-established rule.[52] Others point out that methods for culturing embryos up to 14 days *in vitro* have only been around for a few years and that much remains to be learned about the period from day 7 to day 14. It is therefore too early to raise the question of extending the period for research further.[53] It has also been argued that the laboratory environment differs considerably from the environment in a uterus, and that the information that the research

[48] Cavaliere 2017.

[49] Matthews et al. 2021..

[50] Warnock 2017; Cavaliere 2017.

[51] Appleby & Bredenoord 2018.

[52] Norwegian Biotechnology Advisory Board 2022.

[53] Blackshaw & Rodger 2021; Warnock 2017; Matthews et al. 2021.

would generate may be of too little practical value to justify the ethical cost of an extension of the rule.[54]

### 7.1.3 Positions of other actors

#### International Society for Stem Cell Research

Since 2006, the International Society for Stem Cell Research (ISSCR) has published ethical and scientific guidelines for research on embryos and stem cells. The guidelines are not binding, but set an internationally recognised standard for responsible research in the area. Many research funding bodies, research organisations and scientific journals require that the research they fund or publish follows these guidelines.

In connection with the most recent revision of these guidelines in 2021, the previous absolute limit of 14 days for research on embryos was removed. Provided that there is public support and the legislation permits it, the ISSCR proposes that it should be possible to culture embryos for longer than 14 days subject to a specialised scientific and ethics oversight process. The process should aim to establish whether scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives. The reasons given for the change are that studies in the period after 14 days can provide better knowledge about and interventions for infertility, pregnancy loss and developmental disorders, as well as the need to be able to validate stem cell-derived embryo models, which could be a more practical alternative in the future in research on early human development.[55]

#### Health Council of the Netherlands

The Netherlands' health minister commissioned the Health Council of the Netherlands to consider the question of an extension of the 14-day rule. The Health Council's assessment is that research up to day 28 can yield valuable knowledge that may be used to prevent developmental disorders and treat fertility problem. Research between day 14 and day 28 is ethically acceptable provided that the research interest justifies the use of human embryos (proportionality) and that there is no other means for obtaining the knowledge (subsidiarity). On that basis, the Health Council recommends extending the limit to 28 days.[56]

#### The Norwegian Biotechnology Advisory Board

The Biotechnology Advisory Board has expressed its opinion on embryo research and embryo models in a letter to the Norwegian Government. Six of the 15 members are of the opinion that, following a special application process, it should be possible to conduct research on human embryos until day 21 or 28, if the research aims to acquire new knowledge about foetal

[54] Hurlbut et al. 2017.

[55] ISSCR 2021.

[56] Health Council of the Netherlands 2023.

development in the sensitive period when formation of organs and tissues begins. Six members were of the opinion that the current regulations are well balanced from an ethical and scientific perspective, while three members wanted to prohibit all research on human embryos.[57]

#### French *Conseil D'orientation*

The *Conseil D'orientation*, an advisory body to the French government agency *Agence de la biomédicine*, expressed the view in a statement that an extension of the 14-day rule is not necessary, as embryo models are available as an alternative.[58]

### 7.2 Regulation of research on human embryo models

There is an expectation that human embryo models will enable the study of early human development without the need to consider the ethical and legal constraints that apply to research on human embryos. Here however, there is a built-in contradiction. On the one hand, embryo models are assumed to be sufficiently different from human embryos that the constraints that apply to the latter are not relevant to them. On the other hand, the models need to be sufficiently similar to human embryos to be able to generate results that are valid even for these. Rapid development is currently occurring with new models being developed that represent embryo development better and better and more and more completely. Many have pointed out that as the biological differences decrease, certain human embryo models may pass a point where the ethical issues raised by research on human embryos cannot be avoided.[59]

While in most countries research on human embryos is subject to special rules,[60] research on human embryo models in many countries, including Sweden, is not regulated any differently than research on other human cells and tissue. Technological developments in embryo and stem cell research have led to demands for a review of the regulation surrounding embryo research.[61] Many warn that unregulated research on increasingly sophisticated human embryo models does not meet the expectations of the public. If researchers start to exploit 'loopholes' in the legislation in such a sensitive area as the origin of human life, there is a risk that the reputation of the research will be harmed.[62] The lack of a regulatory framework also risks hampering this research. Most researchers are anxious that their research is seen as ethically acceptable, and the lack of regulation may make them more cautious than necessary.[63] Just like with research on human embryos, a regulatory framework is needed that reasonably balances

[57] Norwegian Biotechnology Advisory Board 2022.

[58] Bruno et al. 2023.

[59] Rivron et al. 2023; Germani & Biller-Andorno 2022; Aach et al. 2017; Pereira Daoud et al. 2020; Hyun et al. 2020.

[60] In addition to the prohibition on culturing embryos for longer than 14 days, a number of countries require authorisation of research on human embryos based on specific criteria.

[61] See, for example, Rivron et al. 2023; Germani & Biller-Andorno 2022; Blasimme & Sugarman 2023; Foreman et al. 2023; Science Media Centre 2023.

[62] Blasimme & Sugarman 2023.

[63] Foreman et al. 2023.

various partly conflicting interests such as worthiness of protection and scientific benefit, while being applicable in practice and understandable to researchers and the public.[64]

### 7.2.1 Which embryo models should be regulated?

The question of whether research on human embryo models should be regulated, what types of models should be covered, and what appropriate regulation should look like is closely tied up with the question of what property/properties of a human embryo make it worthy of protection. Whether human embryo models should be regulated depends on the extent to which they share these ethically significant properties.

#### Origin

One view is that its origin in a fertilised egg gives the embryo a special status. Embryo models do not share this origin and therefore cannot be ethically equated with embryos, even if they have the same properties.[65] However, the notion that its origin should be decisive for the embryo's worthiness of protection is rejected by others.[66] In addition, in many countries, eggs that have been subject to cell nuclear transfer are covered by the 14-day rule, which could be interpreted as its origin in a fertilised egg not being seen as decisive for whether or not it is worthy of protection.[67]

#### Developmental potential

Another view is that it is the human embryo's potential to develop into a human being that gives it a special status compared to other human cells and tissue. For many, it is precisely the possibility that certain embryo models may have the capacity to undergo development similar to an embryo that prompts the need for regulation.[68]

The development of stem cell-derived embryo models has led some commentators to call for an adjustment in the legal definition of a human embryo.[69] By defining the embryo on the basis of its developmental potential, and not, as in the Swedish legislation, on the basis of its origin, certain embryo models could be subject to the constraints that apply to research on human embryos.[70] The advantage of this kind of solution is that it is technology-neutral and would be applicable even if other technologies for producing entities with developmental potential were to be developed in the future. A problem with this is that it is difficult to definitively determine the developmental potential of a human embryo model without implanting it into a uterus, which most consider to be unacceptable for ethical reasons. This raises the question of how knowledge uncertainty should be addressed. Should a precautionary principle be applied, where

[64] Blasimme & Sugarman 2023; Hyun et al. 2020; Foreman et al. 2023.

[65] Bruno et al. 2023.

[66] Blasimme & Sugarman 2023; Rivron et al. 2023; Health Council of the Netherlands 2023.

[67] In cell nuclear transfer, unfertilised eggs are used, and no fertilisation occurs.

[68] See, for example, Health Council of the Netherlands 2023; Germani & Biller-Andorno 2022; ISSCR 2021; Rivron et al. 2023.

[69] Rivron et al. 2023; Blasimme & Sugarman 2023.

[70] Already today, the legislation in a number of countries defines the human embryo on the basis of its developmental capacity. Thus, in principle these countries' regulatory frameworks could be applicable to embryo models (see Matthews & Moralí 2020).

all human embryo models in which developmental potential cannot be ruled out should be covered by the regulatory framework? Or, as suggested by some researchers, only models that pass some sort of test that assesses their developmental capacity?[71] Another objection to defining the embryo on the basis of its developmental capacity is that some entities worthy of protection could fall outside the regulatory framework, such as non-viable human embryos.[72]

An alternative is a regulatory framework that recognises concrete properties that are a prerequisite for developmental capacity, for example the presence of all the cell types that are present in an embryo at the corresponding developmental level and which are necessary for further development into a new individual. It would probably be easier to determine whether an entity satisfies a criterion of this kind. However, this criterion is already satisfied by existing integrated human embryo models, which are assessed as being far from a point where it would be possible for them to develop into a new individual. Therefore, there may be a risk that regulation of this kind would apply too broadly and thus hamper research.

#### Sentience

Alongside developmental potential, consciousness and sentience (including the capacity to experience pain) is usually considered to be an important basis for an entity's moral status. It has been argued that it may soon be possible to produce human embryo models that develop nervous systems. Embryo models of this kind could potentially develop a primitive consciousness and the capacity to experience pain, even if they lack the potential for further development. Research on embryo models of this kind also raises ethical questions that prompt the need for regulation.[73]

### 7.2.2 Types of regulation

Alongside the question of which embryo models should be regulated, another question is what appropriate regulation of research on human embryo models would look like. One possibility could be to impose strict limits like the 14-day limit for embryos. Alternatively, authorisation could be required for research on (some) embryo models. A combination of both is also possible.

Some commentators argue that requiring authorisation is preferable, as a prohibition could have negative consequences on the unique research opportunities that the technology promises.[74] Instead, they propose that permission to conduct research on integrated human embryo models should only be granted by an ethics committee (the same requirements are proposed for integrated models that combine human and non-human cells), while other research on human or synthetic embryo models should be reported to the ethics committee. Others argue that in light of the rapid development that is occurring, defining thresholds that research must

[71] Rivron et al. 2023.

[72] Health Council of the Netherlands 2023.

[73] Aach et al. 2017; Germani & Biller-Andorno 2022.

[74] Hyun et al. 2020.

not pass is a matter of urgency, mainly in relation to models that can develop into a new individual and/or develop structures that could allow for sentience or pain perception.[75]

If the aim is to prevent embryo models with developmental capacity from being permitted to develop beyond a certain stage, one idea might be to include such models in the rule applicable to embryos (currently 14 days). A problem with this is that embryo models do not develop in a regular way, reaching different developmental stages at certain times, but are created to directly mimic a certain developmental stage. A model younger than 14 days may mimic a stage that in an embryo occurs later than 14 days after fertilisation. Such a rule for embryo models therefore needs a different design in order to more directly address developmental stages that must not be passed.[76]

### 7.2.3 Positions of other actors

#### International Society for Stem Cell Research (ISSCR)

Regarding the regulation of human embryo models, the ISSCR bases its guidelines from 2021 on the degree of integration in the models. Research on non-integrated embryo models that only represent certain aspects of embryo development, does not require any special ethical review beyond what is customary. On the other hand, research on integrated embryo models that represent the embryo as a whole, should undergo a separate scientific and ethical review process that assesses, among other things, the scientific rationale of the research, and whether there are alternative ways of acquiring the same information. According to the ISSCR, integrated embryo models should only be cultured for the minimum time necessary to achieve the scientific objective.

The ISSCR guidelines prohibit the implantation of human embryo models into an animal or human uterus since, according to ISSCR, such experiments lack a compelling scientific rationale and are widely considered to be unethical.

#### Health Council of the Netherlands

The Health Council of the Netherlands argues that as long as it is impossible to rule out that an embryo model can develop into a human being, it must have the same level of protection as a 'classic' embryo. Human embryo models that represent the embryo as a whole should therefore be permitted to develop up to a stage equivalent to that of a 28-day-old human embryo. Human embryo models that do not represent the embryo as a whole should also be given legal protection, according to the Health Council.[77]

[75] Germani & Biller-Andorno 2022.

[76] Aach et al. 2017.

[77] Health Council of the Netherlands 2023.

#### The Norwegian Biotechnology Advisory Board

All members of the Norwegian Biotechnology Advisory Board urge the Norwegian Government to update the regulatory framework for embryo research and recommend that a regulatory framework for stem cell-derived embryo models should distinguish between non-complete/non-integrated embryo models and complete/integrated embryo models with developed nervous systems or with the theoretical potential to develop further into a foetus.[78]

#### French *Conseil D'orientation*

The *Conseil D'orientation* proposes that research on integrated embryo models, especially those that are the most complete, should be permitted up to a stage equivalent to the 28th day of a natural embryo.[79]

# 8. The Council's positions and recommendations

## 8.1 14-day rule

### 8.1.1 Ethical analysis

Research on human embryos involves a conflict of objectives between, on the one hand, the possibility of acquiring new knowledge with significant potential patient benefit and on the other, the human embryo's worthiness of protection. In order to maintain trust in research, it is important to have transparent regulation that specifies the conditions under which research can take place. In this regard, the 14-day rule has played an important role. However, the limit was set at a time when it had no practical significance, and society therefore had no reason to reflect at a fundamental level on where the limit should be. It is only after it has become technically possible to culture embryos for longer than 14 days, at the same time as we have acquired knowledge that allows us to evaluate the potential benefit of an extension, that we can assess the advantages and disadvantages of different limits. In SMER's view, a new ethical analysis is needed in light of the new facts that have arisen. In the following, the Council analyses the issue on the basis of three aspects: knowledge gains, the human embryo's worthiness of protection, and societal factors.

#### Knowledge gains

The first weeks after implantation in the uterus are a key period in early embryo development when the embryo transforms from a blastocyst with only a few cell types into a fully developed embryo with all organ systems in place. There are currently few real alternatives to studies of human embryos *in vitro* for acquiring knowledge of the mechanisms underlying this process. The embryo is difficult to study in the uterus due to its small size, and experimental research cannot be performed in the uterus for ethical reasons. Studies of animal embryos may provide

[78] Norwegian Biotechnology Advisory Board 2022.

[79] Bruno et al. 2023.

some knowledge but cannot fully replace research on human embryos due to the differences in embryonic development between different species.

Extending the period during which *in vitro* research on human embryos is permitted would increase opportunities to acquire knowledge about an important period of development where much remains unknown. According to SMER, getting answers to the almost existential question of how a human comes into being would have a value in itself. Knowledge of the causes of disruptions in this period of development could eventually lead to new strategies for preventing or treating disease and infertility. Another potential benefit of the research is new or improved methods for assisted reproduction and new methods of contraception. More knowledge about which substances affect embryo development and which do not could make more drug treatments available to pregnant women. In addition to these related applications, as with other basic research the knowledge gained about early human development can also pave the way for other applications that we cannot foresee today.

Stem cell-derived embryo models may reduce the need for human embryos in research and enable new research designs that are not possible with embryos. In particular, there are hopes that these models will contribute new knowledge about the relatively unexplored period after day 14. However, in order to ensure that embryo models produce reliable results, they need to be validated against embryos at the same level of development. According to SMER, being able to take advantage of the research opportunities that human embryo models provide is another reason in favour of being able to conduct research on human embryos for more than 14 days.

Since the 14-day rule was formulated in the 1970s, knowledge of development in the period immediately following fertilisation has increased. There have also been major methodological advances in, for example, being able to modify genes and measure cell gene expression. This means that, on a purely scientific basis, there is more justification today for progressing to research on older embryos, as the prospects of generating new, high-quality results from this research are greater.

#### The human embryo's worthiness of protection

SMER's view, which it can be assumed most people in Sweden would share, is that from the moment of conception (fertilisation) the human embryo is worthy of protection, but that this protection is not unconditional. In some instances, other interests may outweigh it. As it develops, the embryo's worthiness of protection increases, and stronger reasons are needed if the embryo's protection is to yield to other interests.

The human embryo's potential to develop into one (or more) future person(s) is one basis for protecting it. However, embryos intended for research will be destroyed after the experiment has been completed or the permitted time limit has been reached. Inducing an embryo to develop into a new individual is not possible today once the window of time for implantation in a uterus has been passed. Furthermore, given the medical risks it would entail for the

prospective individual, implanting an embryo that has been used in experiments is out of the question for ethical and legal reasons. The question of the embryo's survival and the possibility of it developing into a new individual is thus not relevant to research on embryos *in vitro*.

Regardless of the prospects of further development into a new individual, an entity that has developed a basic consciousness and the capacity to experience pain is worthy of protection and this must be seen as weighing heavily in relation to any potential benefits from the research. However, the biological structures that are a prerequisite for consciousness and sentience mature much later during foetal development, and there is no risk that an embryo would suffer in the period 14–28 days.

An entity may deserve respectful treatment not only by virtue of its inherent interests, but also by virtue of the fundamental values it represents. A widely held view, and one shared by SMER, is that the human embryo has a special status compared to other human cells and tissue in its capacity as the origin of human life. Treating human embryos with respect is an expression of solicitude for their humanness, which is fundamental to respect for human dignity. This requires that human embryos are treated with respect, even if they will never develop into new individuals. Human embryos should not be used for trivial purposes or be exploited commercially. Experiments on embryos should only be carried out where there are no adequate alternatives and where the research can be anticipated to generate valuable new knowledge.

According to SMER, a reasonable view is that also in this respect the human embryo's worthiness of protection increases as it develops and acquires more human traits. Being able to culture embryos for a long time outside the uterus would risk leading to a reification of the human that is not compatible with respect for human dignity. However, in the Council's view, the embryo's worthiness of protection remains limited in the period 14–28 days. Provided that the research is carried out for important purposes, according to SMER the extension by a couple of weeks of the period during which research on embryos is permitted would be compatible with respect for the human embryo's worthiness of protection.

#### Societal aspects

The fact that the human embryo is generally considered to be worthy of protection in ways that differ from other human cells and tissue makes research on human embryos sensitive. In order not to undermine support for this research, regulation is necessary to ensure that research that many would see as unethical is not carried out.

Given that the embryo's worthiness of protection increases gradually with its age and development, and can be balanced against other important interests, it is difficult to set an exact limit beyond which research on human embryos is no longer ethically acceptable[80]. A fixed legal limit might therefore be perceived as arbitrary. In order not to jeopardise support for this

[80] At least before the embryo has developed a primitive consciousness and the capacity to experience pain.

research, there still needs to be a transparent legal limit beyond which research on embryos may not be carried out. A transparent limit also reduces the risk of an uncontrolled shift in customary practice when assessing which research on human embryos is ethically acceptable.

From a democratic perspective, it is important that the regulation represents a balance between different societal values that is seen as legitimate by the citizens. If the limit for embryo research is extended beyond what the population would find legitimate, support for and trust in research would also be at risk of being undermined. An essential question that must be asked when taking a position on a possible extension of the 14-day limit is to what extent the population would accept an alternative limit. The Council notes that our society rests on a fundamental belief in the value of knowledge, both in itself and as the foundation for development and prosperity. The view that it is important to be able to prevent congenital diseases, assist with infertility and promote reproductive autonomy is considered to have broad support in the community. At the same time, most people share the view that the human embryo's worthiness of protection increases gradually and can be balanced against other values. Provided that the research is perceived as important and valuable, SMER assesses that the population would likely accept extending the time permitted for research on embryos until day 28, and that such an extension does not jeopardise trust in the research.

### 8.1.2 SMER's positions

According to SMER, looking at the potential knowledge gains, at questions related to the embryo's worthiness of protection, and at societal aspects, on balance this suggests that the time permitted for research on human embryos should be extended to 28 days. At the same time, the ethical review of research on human embryos needs to be more appropriate. Research on human embryos should also be registered in an international register. The reasons for this are as follows:

SMER assesses that it is in the period up to 28 days that research on embryos has the greatest potential to generate valuable knowledge, while at the same time it is the period for which we have the least access to alternatives. The limit of 28 days provides a reassuring margin in relation to the point in time when a functioning nervous system develops. There is thus no risk that the research would be done on embryos/foetuses that have developed a primitive consciousness and the capacity to feel pain.

A human embryo is worthy of protection in a way that distinguishes it from other human cells and tissue. A number of other countries impose special conditions for granting permission to conduct research on human embryos.[81] In Sweden, research on human embryos is only ethically reviewed in light of the criteria in the Ethical Review Act. These aim primarily to ensure that research subjects are not subject to unjustified risks. In addition, there is a general provision

[81] Denmark, Norway, the UK, France and the Netherlands are some of these countries. Examples of requirements in these countries' regulatory frameworks are that the research is conducted for certain specified purposes, that the research should be able to generate significant knowledge gains, that the method has the potential to provide answers to the research questions, and that there are no alternative methods to achieve the intended knowledge goal.

that research may only be approved if it can be carried out with respect for human dignity. In SMER's view, this regulatory framework is not geared to the specific ethical issues raised by research on human embryos. In order to ensure that research on human embryos is justified on the basis of its scientific value, that it is carried out for important purposes, and that it is carried out in ethically sound forms, according to SMER research on human embryos should be subject to ethical review according to specific criteria. Examples of criteria that could be included in the review are the absence of adequate alternative methods, the study in question having a sound scientific rationale, the use of no more embryos than necessary, and that they are not cultured for any longer than necessary.

As part of safeguarding trust in research and ensuring compliance with the regulatory framework, SMER believes that there should be greater transparency concerning this research. In order for researchers, healthcare professionals and the general public to be able to follow developments in this area, SMER is of the opinion that all research on human embryos should be registered in an open international register in the same way as clinical trials. The register should be easy to search and contain information on the purpose and results of studies.

### 8.2 Research on human embryo models

Embryo models developed from human stem cells can reduce the need for both human embryos and laboratory animals in research on early human development. They can also enable new types of research that cannot be performed with embryos. This research field is relatively new and it remains to be seen what contribution stem cell-derived embryo models will make to the development of new knowledge and new treatment methods. Nevertheless, SMER's assessment is that the technology may become an important tool in biomedical research in the future.

Since the scientific value of embryo models lies in their capacity to replicate the processes that occur in actual embryos, there is a strong motivation to make them as similar to actual embryos as possible. Despite a sometimes striking similarity in appearance, there are still significant differences at the molecular level between the integrated embryo models developed so far and actual embryos. None of the existing models, whether human or for any other species, are capable of developing into a new individual. However, there is very rapid development in this area, and experts do not rule out the possibility that integrated human embryo models capable of further development into later stages *in vitro* or in a uterus will be developed in the future. That it could become possible to produce human embryo models that develop nervous systems and thus could potentially develop a primitive consciousness and be able to experience pain is also predicted.

Current Swedish legislation governing research on embryos covers fertilised eggs and eggs that have been subject to cell nuclear transfer. Human embryo models are not developed from fertilised eggs but are created from reprogrammed stem cells and are therefore not covered by the regulatory framework. Research on human embryo models is therefore not regulated any

differently than research on other human biological material. If the cells from which the models are made can be traced to a living or deceased individual, the research must be ethically reviewed under the criteria specified in the Ethical Review Act. If the cells come from anonymised cell lines, there are no requirements for ethical review.

### 8.2.1 SMER's positions

In SMER's view, how an entity was created is not relevant to the question of whether it is worthy of protection. According to the Council, there are no grounds for treating a human embryo model – or another embryo-like entity based on human cells – that can develop a primitive consciousness and sentience, or can be presumed to have the potential to develop into a new individual, any differently from an embryo with equivalent capacities. In order to avoid ethically problematic research on human embryo models and to maintain trust in research into the early human development, SMER assesses that there is a need to regulate research on human embryo models.

#### Human embryo models that represent embryonic development as a whole

For an embryo model to have developmental capacity, it must represent the embryo as a whole, including the extra-embryonic structures necessary for the further development of the embryo (or, alternatively, it can be cultured in an environment that serves the functions of the extra-embryonic structures). However, the fact that an embryo model has all the cell types that an embryo at the equivalent level of development has does not mean that it has developmental capacity. The definitive test to determine the developmental potential of a human embryo model would be to allow it to develop as far as possible in a uterus or *in vitro* to see if it gives rise to a new individual. In SMER's opinion, such an experiment would be unacceptable in view of the risks to both the prospective individual and (if there is implantation in a human uterus) for the woman concerned.

In a situation where developmental capacity cannot be determined with certainty, SMER's opinion is that the starting point must be caution. In SMER's view, research on human embryo models representing embryonic development as a whole, and whose developmental capacity cannot be ruled out should be subject to an ethical review similar to that proposed by the Council for research on human embryos. One starting point for the review should be that the scientific benefit should be greater the longer a human embryo model representing embryonic development as a whole is allowed to develop. The possibility of using less complete models to achieve the scientific goal should be considered.

Furthermore, according to SMER a limit on how long human embryo models representing embryonic development as a whole should be permitted to develop should be considered. One possibility could be to expand the proposed 28-day limit for embryos to cover these kinds of embryo models.[82] When it comes to the precise design of such a regulatory framework, one

[82] Because age and level of development are not necessarily related in embryo models in the same way as in embryos, in practice this would mean that they would be permitted develop at the most to a stage corresponding to 28 days in a human embryo.

option is to define a human embryo in the legislation in such a way that it includes other embryo-like entities which can be presumed to have developmental capacity. Certain embryo models would therefore be subject to the constraints currently applicable to fertilised eggs. The advantage of such a solution is that it could also include other types of entities with developmental capacity if they were to be created. Depending on its design, one problem could be that certain entities seen as worthy of protection would fall outside the regulatory framework, such as non-viable human embryos. There may also be difficulties in determining which entities are covered by the provision in cases where there is uncertainty about the entity's developmental capacity.

Another alternative is to introduce a provision that recognises concrete properties as a prerequisite for developmental capacity, for example the presence of all the cell types that are necessary for further development into a new individual. It would probably be easier to determine whether an entity is covered by such a provision, while it could also risk applying too broadly, thereby constraining research more than is desirable.

#### Human embryo models that do not mimic the embryo as a whole

In the case of embryo models that mimic only certain aspects of the embryo and do not contain all the cell types necessary for further development into a new individual, their worthiness of protection depends mainly on the structures that the model mimics. In particular, models representing different aspects of the emerging brain and nervous system could in some cases be deemed worthy of protection, which must be balanced against the scientific benefit. To ensure that research on human embryo models that do not represent embryo development as a whole is conducted in an ethically acceptable manner, ethical review requirements for research on such models should also be considered. In order not to create more administration than necessary, the requirement could be limited to, for example, research on models representing more advanced stages of development.

In order to monitor developments and ensure that the regulatory framework functions as intended, SMER's opinion is that research on human embryo models should be registered in an open, international register, as the Council has also proposed for human embryos.

### 8.3 Prohibition on implantation

Swedish legislation prohibits the introduction into a woman's body of a fertilised egg that has been used in research or treatment. The same applies if the egg before fertilisation or the sperm used for fertilisation have been used in such an experiment, or if the egg has been subject to somatic cell nuclear transfer. The prohibition was introduced to avoid exposing the prospective individual to medical risks due to changes resulting from the research or culturing *in vitro*. In the case of eggs which have been the subject of somatic cell nuclear transfer, there are also ethical concerns associated with reproductive cloning.

The prohibition on implantation does not cover implanting an embryo model in the uterus of a woman for experimental or treatment purposes, since by definition the embryo model was not developed from a fertilised egg but created from reprogrammed stem cells. Nor is it illegal to introduce a human embryo model (or a human embryo) into the uterus of an animal.

The fact that these measures are not regulated is hardly likely to be due to a conscious intention that these measures should be permitted, but to the fact that embryo models are a new technology that could not be foreseen when the Act was written. Implanting an embryo model in a woman would entail taking a great risk with the woman's health. Should the model prove viable, the prospective individual would also be exposed to considerable medical risks. In theory, embryo models could also be used to circumvent the prohibition on reproductive cloning. An individual developed from an embryo model produced from induced pluripotent stem cells from a donor would be a genetic clone of the donor, but the technique used would not be cell nuclear transfer.

It can be noted that the prohibition on implantation does not either cover the implantation of chimeric embryos[83] or other entities with embryo-like properties. Although most estimate that the use of artificial wombs (ectogenesis) lies quite a long way into the future, it can also be noted that current legislation does not rule out that a fertilised egg used in research or for cell nuclear transfer could be developed into a new individual if it were possible in the future to let this happen outside the uterus.

### 8.3.1 SMER's positions

Strong ethical reasons related to the protection of both the woman and the prospective individual suggest that the current prohibition on implantation should also cover embryo models and other entities with embryo-like properties. In order to further strengthen the protection of prospective individuals against being exposed to unacceptable risks, one option that should be considered is legislation that also covers implantation in, for example, a non-human primate or in an artificial womb.

Embryo models have also demonstrated shortcomings in the regulation of reproductive cloning of humans. The regulatory framework aims to prevent the production of genetic copies of humans. However, the fact that the prohibition targets a specific technology – cell nuclear transfer – makes it possible to circumvent the prohibition if other reproductive cloning techniques were to become available. Embryo models are an example of a technology that does not involve cell nuclear transfer but could theoretically be used for reproductive cloning. Other alternative technologies could also become available.[84] To obviate the need to adjust the legislation for each new technology developed, an explicit prohibition on reproductive cloning should be introduced, according to SMER.

[83] An embryo consisting of cells from more than one species.

[84] One such technique is Tetraploid complementation. See Deutscher Ethikrat 2014.

### 8.4 Recommendations

SMER recommends that the Swedish Government should inquire into:

- an extension of the time permitted for research on human embryos under Chapter 5, Section 3 of the Genetic Integrity Act (2006:351) that would enable research in an important period of embryo development where much remains unknown;
- ethical review requirements based on specific criteria for research conducted on human embryos;
- ethical review requirements based on specific criteria for research on human stem cell-derived embryo models representing embryonic development as a whole;
- a limit on how long human stem cell-derived embryo models representing embryonic development in its entirety may be permitted to develop, and in this context consider
  - defining an embryo in Chapter 5, Section 3 of the Genetic Integrity Act so that (certain) human embryo models are also subject to the constraints that apply to research on embryos; or alternatively
  - introduce a specific provision for embryo-like entities made up of human cells that represent embryonic development as a whole;
- ethical review requirements for research on human embryo models that do not represent embryonic development as a whole but raise specific ethical questions;
- an expansion of the current prohibition on implantation to include stem cell-derived embryo models; and in this context consider
  - legislation that also covers other entities with embryo-like properties;
  - legislation that also covers implantation in, for example, a non-human primate or in an artificial womb; and
- the possibility of introducing an explicit prohibition on reproductive cloning.

Since research is by nature is cross-border and often takes the form of international collaborations, the value of harmonising the regulatory framework between different countries should be taken into account when considering different regulatory alternatives.

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The decision on this Letter was made at an extraordinary meeting on 21 March 2024.

Sven-Eric Söder, chair; and Yasmine Bladelius, Åsa Gyberg-Karlsson, Sofia Nilsson, Anton Nordquist, Thomas Ragnarsson, Per Ramhorn and Anna Starbrink – all members of SMER – participated in this decision. Lilas Ali, Erika Borgny, Anders Castor, Göran Collste, Titti Mattsson, Kerstin Nilsson, Olle Olsson, Nils-Eric Sahlin, Mikael Sandlund, Marie Sten and Kristina Wikner – all expert members of SMER – also contributed to the preparation of this Letter.

Per Landgren, member of SMER, has expressed his reservation regarding the recommendation to the government to investigate an extension of the time that research on human embryos is permitted.

A working group consisting of Anders Castor, Göran Collste, Åsa Gyberg-Karlsson, Per Landgren, Titti Mattsson and Kerstin Nilsson assisted the Secretariat in the preparation of this matter. Michael Lövtrup, Research Officer, has been the rapporteur.

For the Council,

Sven-Eric Söder
Chair
The Swedish National Council on Medical Ethics

## Reservation by Per Landgren, Christian Democrats (KD)

I do not support the first recommendation to the Swedish Government to investigate an extension of the time permitted for research on human embryos under Chapter 5, Section 3 of the Genetic Integrity Act (2006:351).

The grounds for my reservation are as follows:

1 Medical ethics (including bioethics) is not its own form of ethics. The ethical perspectives and theories are the same as those applied in the context of other phases of human life.

2 When research on human embryos was first conducted in the 1980s in Sweden, the focus was on researching methods for *in vitro fertilisation* (IVF). The specific aim was to help couples who were involuntarily childless, not to conduct basic research. See Govt Bill 1987/88:160 *Om befruktning utanför kroppen* (On Fertilisation Outside the Body).

3 When treating a woman with hormone therapy, more eggs were deliberately harvested and fertilised than were transferred into the uterus. The leftover fertilised eggs, which were not needed for the treatment of involuntary childlessness, were then frozen and made available for research.

4 In Section 3 of the Letter*, From fertilisation to foetus*, a range of technical terms from embryology are used, such as *zygote*, *morula* and *blastocyst*. These technical terms describe real life, denoting different phases of human life in a similar way as more familiar terms such as baby, child, teenager, and adult are used to identify other life stages. According to the Swedish Government Inquiry *Genetic Integrity* (SOU 1984:88), the above-mentioned technical terms were summarised in Swedish legislation by the term "embryo". The word *embryo* in classical Greek corresponds to the word *foetus* in Latin. In the past, the term "pre-embryo" has also been used to refer to the entire phase from conception to implantation. However, when the woman's egg cell has united with the man's sperm, normally a genetically unique human individual is formed. We call this stage of an individual's life 'zygote' – a Greek word meaning 'joined' or 'yoked'. Once an early human life (zygote) has divided into 16 cells, it is called a 'morula' – a Latin word meaning 'mulberry'. After five to six days, the human life develops into a little ball of cells, called a 'blastocyst' – a synthetic word composed of the Greek word 'blastos' meaning 'sprout' or 'bud' plus the word 'kystis' meaning 'bladder' or 'capsule'. These technical terms can easily result in a kind of *Entfremdungseffekt*, that is, an alienation and distancing effect from its humanity, which may affect how we treat the entities in question.

5 These technical terms can conceal the fact that human life is a continuum: all the way from the fertilised egg cell (*zygote*) to, for example, the elderly man (*senex)*. Because of this continuum of life stages of the same entity, fertilised eggs develop *as* human entities, not *into* human entities. (See the section of the Letter on *The Human Embryo's Worthiness of Protection*, second paragraph). They develop *as* human individuals, not *into* individuals. In usual parlance, they also develop *as* persons, not *into* persons. If an early separation into identical

twins or more occurs, it is logical that their value is multiplied by the number of individuals, not that it is relativised.

6 We have all once been embryos – little clumps of cells. And we are still actually clumps of cells – big clumps of cells. However, to say "clump of cells" does not capture what is *human* – whether the little or the big. If we apply the principle of equal value and equal treatment retrospectively, we should not subject any human entity/individual/person to research during its embryonic stage – or at any other later stage of its life – unless it is in the interests of that entity/individual/person.

7 Section 4 of the Letter stresses that the extended time frame for embryo research "can provide important knowledge" for the treatment of infertility and congenital diseases, etc. But it advocates for the gain of knowledge at the expense of human life. The fact is that the research in question is lethal for the individual, which paradoxically also becomes a requirement for the research. The value of knowledge is prioritised over the fundamental value of life. Without life there are no other intrinsic values, i.e. the values that motivate action for their own sake. The Letter's reasoning is consequentialist and utilitarian, and could eventually be applied to research into all phases of human life. The result is that a potential benefit would be prioritised over the life on which the research is to be conducted. Human life would be relegated to the level of an instrument merely utilised for a research project.

8 Before SMER proceeds to outline more potential benefits and knowledge, shouldn't the 14-day rule be evaluated according to the same consequentialist reasoning? What benefits and outcomes has it brought? The scientific method should surely require that SMER first draw up such an inventory of the benefits already observed.

9 There are reasons to turn against such a utilitarian line of reasoning where ethical boundaries are crossed, and where human life is sacrificed for outcomes, we cannot anticipate or really know much about. Not infrequently, researchers must forgo the acquisition of knowledge that could have been gained through research that would rely upon sources that are ethically and/or morally toxic. In this specific case, the consequences could include a massive and inhumane culturing of human embryos, and then the subsequent destruction of human embryos. This tragedy would be avoided through the prudent use of non-integrated embryo models.

10 The concept of the "continuum of life" provides a rationale for all research. Diagnostics (and research) are done in the interests of the patient, regardless of age. Regular foetal diagnostics/screenings (and research) are done in the interests of the foetus. So, I believe it is logical and consistent on the basis of the principle of human dignity to pursue diagnostics (and research) in the interests of the human embryo.

11 The principle of human dignity is predicated on the fact of *existence* – not on *different functions*. (See the Healthcare and Medical Services Act, Chapter 3, Section 1 as well as Government Bill *Genetic Privacy Etc.* 2005/06:64 page 34.) Section 4 of the Letter refers to the question of the moral status of the human life stage now called the *embryo*. But nothing

stated there captures the essence of what distinguishes humans from other species of living beings, i.e. the species-specific. Tracing back to the philosopher Aristotle, this deals with the underlying and fundamental thing: "*hypokeimenon*", which is the substance, that which is not accidental. The key point is not what we have in common with other living beings, but what makes us specifically human. This follows us through all of the phases of human life, whether related to the potentiality or actuality of our existence. The Roman statesman and philosopher Boethius (480-524) established in Western discourse the fact that "being a person" is a consequence of one's existence, not of any function. A comparison, *mutatis mutandis*, could be drawn with the Clouded Apollo butterfly. It seems that they are threatened with extinction. If only a single caterpillar were to remain, and a person kills it, what is then made extinct? The caterpillar or the butterfly? Similarly, one cannot artificially separate the phases of a human life. A life is normally one and the same entity, individual and person.

12 It is important to examine SMER's Letter based on the concepts of *human dignity* and *worthiness of protection.* One perspective might be that "worth" obviously increases as different functions, characteristics and properties are added during the development of a human life. This view would be predicated on the effort expended to employ one's abilities, until the clump of cells/the entity/the individual/the person has been able to attain human worth and human dignity. But SMER concludes on its own website: "Human dignity is thus not tied to properties, but is attached to every individual regardless of attainments."[85]

Syllogism 1.

1. Premise from SMER: Human dignity is not tied to properties.

2. Premise from SMER's Letter: "An entity that has developed a basic consciousness and the capacity to experience pain is worthy of protection, and this must be seen as weighing heavily in relation to any potential benefits from the research." (See the section in the Letter on *The Human Embryo's Worthiness of Protection*, 3rd paragraph).

3. Premise from SMER's Letter: Human embryos do not have the properties of consciousness and the capacity to experience pain. (See the section in the Letter on *The Human Embryo's Worthiness of Protection.)*

4. My conclusion based on SMER's Letter: Human dignity IS tied to properties.

Syllogism 2.

1. Premise from SMER's Letter: It is not wrong to conduct research and kill human embryos/human life, if by law they must be destroyed anyway.

2. Premise from SMER's Letter: Much knowledge and benefit can come from research on embryos and on human life up to 28 days.

[85] See *Några medicinsk-etiska begrepp: människovärde och människosyn* (Some medical ethics concepts: human dignity and view of humanity). https://smer.se/etik/nagra-medicinsk-etiska-begrepp/

3. My conclusion based on SMER's Letter: It is justifiable that human embryos/human life are cultured, consumed and destroyed – provided that they are used for beneficial research.

This ethical argumentation is based on an outlook similar to paternity testing, whereby one is seeking to recognise or deny fatherhood. In this case, the human embryo is denied its human dignity – not because the embryo is not deemed human, but because it does not yet have a number of properties that it will, by virtue of being human, develop if allowed to grow and mature. By the same analogy, it could be argued that the Letter is based on a type of patriarchal position of power, which autocratically denies the human embryo its humanity and its human dignity. This seems to me, however, to be unfair to the human embryo and is, in fact, hazardous. SMER does not ascribe the human embryo its humanity, which disrupts or removes the ontological security of the embryo. As illustrated by the syllogisms above, SMER's argumentation is functionalistic and contradictory. SMER's way of distinguishing a human life's worthiness of protection, and a human life's human dignity, is based on *function*. If this concept were to become normalised, it could have terrible consequences if it is eventually applied to other phases of human life, such as when the elderly experience declining capabilities and their functions begin to fail.

13 The section of the Letter on *Research on Human Embryos* identifies the background and rationale for the proposed amendment from 14 to 28 days is:

a) There are better technical possibilities today for culturing and maintaining non-implanted embryos for a longer period of time.

b) The benefits arising from conducting research using embryos and embryonic cells at a later stage (i.e. after 14 days) have become clearer with advanced methodologies.

If further progress is made in both areas, and more potential therapeutic opportunities can be discerned or discovered, then an important question must be asked: Based on SMER's text, are there any real arguments for *not* someday pushing the proposed 28-day limit even further? What would prevent the expanded culturing and development and research on later phases of human life?

14 This leads us to the dangerous "slippery slope" argument. Once you have crossed the Rubicon, you cannot turn back. There would no longer be any consistency of logic that would require a research "stopping point" at 28 days. Positional arguments on ethical grounds against further time-frame extensions will likely slide right down the slippery slope. In spite of the lack of factual and observable results, the argument focused on potential knowledge gains is convincing to many. And this willingness to pursue knowledge will only grow stronger if there are *no* fixed and logical time limits. Researchers will always want to go further. Jacob Hanna, a prominent researcher in the field, has reportedly already applied for a 48-day limit in Israel. Swedish researchers will then feel that they have somehow been left behind. Those who carry out this kind of research, and who advocate for the extension of a potential 28-day limit, will not want to be "forced" to travel to countries where it would be permitted.

15 This leads to the necessity of understanding how vital it is that we highlight the importance of international consensus. It appears that there is still a consensus, based upon the legislation in different countries. But it will not remain intact much longer if we look at some of the ethics committees named in the Letter. My sincere hope was that the draft of the Letter would be voted down, and that SMER would stand firm against any push for a change in the legislation. Reaching an international consensus can be a long and arduous political process. It could be claimed that the existing 14-day rule has actually served research well. It has been possible to avoid *hausse* and hype, and to maintain respect for the principle of human dignity. At the same time, the existence of unified and equal terms for this research around the world has enabled advancements in infertility research. But unfortunately, SMER is now recommending a break with this international consensus.

16 Under Article 18(1) of the Oviedo Convention, the Council of Europe Convention on Human Rights and Biomedicine states: "Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo." A signature affixed to this document means that there is a commitment to ratify and not to legislate in contradiction of the Convention before ratification. In Note 35 of SMER's Letter, the following is a glaring contradiction: "The fact that Sweden has not ratified the Convention means that Sweden is not legally bound by it. However, by signing the Convention, Sweden has undertaken not to act in ways that run counter to the purpose of the Convention (see Zillén, K., Mattsson, T., Slokenberga, S. (2020) Introduction. In: K. Zillén, T. Mattsson, S. Slokenberga (eds.) *Medicinsk rätt*. Norstedts Juridik.)"

The Oviedo Convention was an attempt to apply the principle of human dignity in time and in line with the declarations on human rights mentioned in the Preamble. However, a complete consensus was not achieved – as some countries (including Sweden) changed their mind after signing the Convention. The significant question now is whether SMER is calling on the Swedish Government and the Parliament to "act in ways that run counter to the purpose of the Convention".

17 Consistency and coherence are logical requirements when setting forth arguments and proposals. Within SMER, long-established principles are being challenged by a consequentialism whereby actions are no longer assessed on the basis of their conformity with the hierarchy of fundamental human values. The value of life must always take priority. But according to SMER, human life should now be cultured and, in the words of German philosopher Robert Spaemann, "consumed for research". That would open the way for a most dangerous logical consistency, based on consequentialism, which would allow similar arguments to negatively impact other phases and stages of human life.

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