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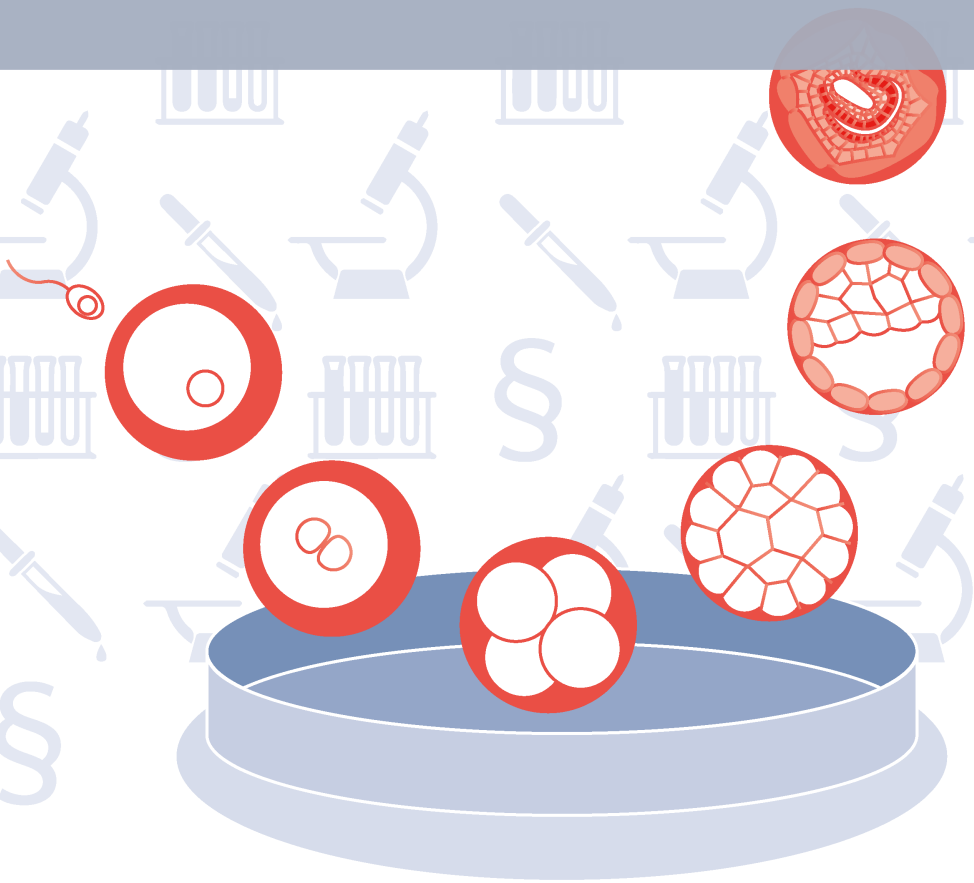
Statement

Re-evaluating the protection of *in vitro* embryos in Germany



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Re-evaluating the protection of *in vitro* embryos in Germany

In memory of Henning M. Beier

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1. Summary and recommendations

How exactly does human life develop after fertilisation? How can reproductive medicine achieve better results with fewer side effects? How can stem cell lines be used to treat common conditions like diabetes, osteoarthritis, heart attack and stroke? These are just some of the questions which scientists in the fields of biology and medicine worldwide are trying to answer through their research on early human embryos. Matters like these are of general relevance to society, including in Germany. However, to date, scientists working in Germany have only been able to contribute very little to help answer such questions. This is because research of this kind on early human embryos is prohibited in Germany under the Embryo Protection Act *(Embryonenschutzgesetz, ESchG)*, which was passed in 1990.

From the outset, the ESchG has constituted a compromise in the attempt to find an appropriate way to treat human embryos outside of the body. This is an issue which attracted and continues to attract highly divergent views. Those with the strictest views on the protection of life, from both an ethical and legal perspective, give a full moral status to human embryos from the moment of egg cell fertilisation. According to this viewpoint, early human embryos are entitled to the same protection of life and dignity as human beings are after birth. A key argument of those advocating strict embryo protection laws is that of potentiality, where the biological developmental potential justifies the right to comprehensive protection. However, many people are not convinced by this argument because they believe it is incompatible with other ethical grounds. They claim that the actual realisation of this potential – in other words, the complete development of the embryo into a human being – is dependent on numerous conditions and can be affected by various factors. The granting of intrinsic rights of protection to human embryos can arguably only be justified by characteristics which have actually been formed and therefore actually exist. According to supporters of this viewpoint, biological sub-criteria, such as characteristics determined by the genome of a fertilised oocyte (egg cell) but not yet actually formed, are no justification for the granting of such rights.

For these reasons, many people seem to find a graduated approach towards embryo protection more convincing, meaning that the embryo is gradually granted more protection as it develops. In recent decades, this topic has been widely debated without any signs of a consensus being reached. Given the diverse range of opinions, it is worth asking whether it would be better to adopt a different approach to finding an ethical solution to this question. Liberal societies are characterised by their tolerance of different ethical opinions and their desire to find political compromises. This means that instead of being as restrictive as possible, legal regulations should give the parties concerned leeway and a certain degree of freedom to make their own decisions. In every-day life and real-life legal practice, a graduated approach towards embryo protection is already applied in many cases.

The international scientific community believes that many important research questions can only be answered with the help of embryo research. With this in mind, it is high time to re-examine the permissibility of research on embryos for research objectives of outstanding interest in Germany. In addition to resolving fundamental matters concerning embryonic development and the early stages of diseases, embryo research can also help to give important insights into reproductive medicine. It can be used to find better fertility treatments, to improve the survivability and healthy development of embryos and foetuses during pregnancy, and to help prevent premature births.

In Germany, a large number of embryos created during reproductive treatment are never used because the intended parents do not wish to have any (more) children, for example. To date, the only options are to discard such "surplus embryos" or – despite the present lack of precise legal regulations – to donate them to another couple. Currently, there is no third option of using such embryos for research objectives of outstanding interest in Germany.

Against this background, the Leopoldina and the Union of the German Academies of Sciences and Humanities recommend the following:

1.1 Permission to conduct research on early embryos *in vitro*

In vitro research (i. e. research conducted outside of the human body) on embryos in the early stages of development which are no longer needed for reproductive purposes (referred to as "surplus embryos" in the following) should be allowed in accordance with international standards. Research should only be permitted for objectives of outstanding interest, where fundamental research is used to gain scientific knowledge and to expand medical knowledge for the purpose of developing diagnostic, preventative or therapeutic procedures. Scientists should also be permitted to obtain human embryonic stem cells from surplus embryos to use for research objectives of outstanding interest. The outstanding nature of each research project should be verified by a specially created committee.

The science academies believe that the following research objectives could be considered to be of outstanding interest:

- investigations into early molecular processes in human developmental biology;
- the scientific evaluation and improvement of methods used in reproductive medicine;
- the identification and treatment of genetic, epigenetic and environmental causes of infertility, miscarriage, birth defects and hereditary diseases;
- the research and use of embryonic stem cells for regenerative and personalised medicine, and
- the critical analysis of possible effects or side effects of germline interventions *in vitro* to enable scientists to better assess the opportunities and risks of the long-term objective of correcting hereditary diseases.

1.2 Expansion of the freedom of choice for couples receiving IVF treatment

The decision of whether to make their surplus embryos available for research purposes should always lie with the couple who created the embryos. To help them make an informed decision, couples should have the opportunity to receive independent counselling.

1.3 Development of a new set of regulations

A legal framework should be established to regulate the use of surplus embryos in research projects. As part of this, a federal authority could work together with an ethics committee to decide on a case-by-case basis whether projects should be permitted. This would be comparable to how the Robert Koch Institute and the Central Ethics Committee for Stem Cell Research (ZES) provide permission for outstanding research on human stem cells as provided in the German Stem Cell Act *(Stammzellgesetz, StZG)*. The aim must be to ensure that the research projects are actually of outstanding interest and that the embryo research is monitored as per the process followed, for example, by the Human Fertilisation and Embryology Authority (HFEA) in the United Kingdom. This would have the additional benefit of creating transparency and facilitate informed public discourse. This kind of legal amendment would give scientists working in Germany the opportunity to participate in international research projects in this field.

1.4 Consideration of unfolding scientific developments

The new regulatory framework should also consider current and unfolding scientific developments, such as the creation of embryo-like structures ("embryoids") or artificially created embryos, for example embryos created *in vitro* from gametes.

The international discussion on the culture of and research into more advanced stages of embryonic development beyond the usual period of 14 days studied to date should also be taken into account.

Statutory review and reporting periods should be put in place to enable a response to new developments.

2. Introduction

How does human life develop? How does a fertilised oocyte survive the journey from the fallopian tube to the uterus? How does a microscopic sphere of barely more than 100 cells, each of which is in possession of a set of chromosomes from the mother and a set from the father, manage to outwit the mother's immune system? Why do so many embryos die *in vitro* or in the early stages of pregnancy? Why do some couples need medical support to conceive? How can scientists improve fertility treatment whilst also taking into account the increasing age at which people want to have children? How can doctors prevent serious genetic diseases from being passed on from one generation to the next? And can stem cell lines be used to treat common conditions like diabetes, osteoarthritis, heart attack or stroke? These are just some of the fundamental research questions which scientists worldwide in the fields of biology and medicine are trying to answer through their research on early human embryos. Although these are issues of huge importance to society, so far scientists working in Germany have only been able to contribute very little to help answer such questions. This is because research of this kind on early human embryos is prohibited in Germany under the Embryo Protection Act *(Embryonenschutzgesetz, ESchG)*, which was passed in 1990.

Following the development of *in vitro* fertilisation (IVF) outside of Germany, it became possible for early human embryos to be created outside of the human body for the first time. Thirty years ago, the German legislature sought to find a way to enable IVF to be used to treat infertility in Germany, whilst simultaneously protecting early human embryos. Opinions on what should be permitted or prohibited from an ethical standpoint when treating human embryos varied widely. Exponents of the various viewpoints agreed that early human embryos were not simply "biological material" and that their use had to be regulated. But what they failed to agree on was the extent to which such regulations should apply.[1] As a result, the legislature had to find a compromise. The ESchG allows human embryos to be created *in vitro* for reproductive purposes, but prohibits any manner of research on the microscopic spheres of cells (see Figure 1) which are cultured in the lab during the initial few days of their development.

1 Cf. Eberbach (2020).

In contrast, in countries such as the United Kingdom – where IVF was developed in the 1970s – Denmark, Sweden, the USA and Japan, research may be conducted on surplus early embryos, i.e. embryos which are no longer needed for reproductive purposes. In some of these countries, embryos can also be developed from donated gametes and used during their early stage of development specifically for research purposes (see Chapters 3.5 and 5.2). Over the past few decades, research of this kind conducted outside of Germany has provided important scientific findings which have improved reproductive treatments and made them safer.[2] It has also provided important insights into early human embryonic development and the mechanisms behind (epi)genetic diseases (see Chapter 3.2). As demonstrated by recent studies on the treatment of age-related macular degeneration, which causes severe vision loss, human stem cells from early embryos are highly promising for use in regenerative and personalised medicine (see Chapter 3.3). In Germany, research results like this are often willingly – albeit with some delay – implemented into medical practice.

It has been thirty years since the ESchG entered into force. The academies believe that it is time to reevaluate the legally permissible and ethically justifiable ways of treating early human embryos. This would require both justifiable research interests and ethical and constitutional aspects relating to the possible use of early embryos to be taken into account. The research developments presented below form a basis for discussion.

2 One example of such developments being used in reproductive medicine in various countries is elective single embryo transfer (eSET). During this procedure, a larger number of oocytes are fertilised, but only one embryo – the one whose morphological criteria indicate the greatest chance of development– is selected and transferred into the uterus. This prevents risky multiple pregnancies while keeping the chances of success roughly the same. In the United Kingdom, these research findings have systematically been used to improve the quality of IVF treatment. As a result, the number of multiple pregnancies and the associated serious risks for both mother and child of premature labour have been significantly reduced over a span of ten years.

Figure 1. Early embryonic development *in vitro* and inside the woman's body

Before implantation in the uterus, early human embryos are microscopic spheres of cells (simplified diagram based on Gerri et al. 2020). During this stage, it becomes clear whether the combination of the mother's and father's genetic material is viable and able to develop into a human being. The first few days following fertilisation could be described as a "multi-stage quality control process", during which around one in two embryos dies as a result of the maldistribution of chromosomes or mutations causing them to be unviable.

In vitro

In vitro research on early human embryos is permitted under strict conditions in countries like Israel, Sweden, the United Kingdom, France and Japan. Here, research may be conducted on "surplus embryos" for 14 days following fertilisation. After this, the embryos must be discarded. The possibility of extending this, for example to 28 days, is being discussed internationally.

Uterus

The microscopic embryo can only develop into a foetus once it is implanted in the uterus. It is estimated that 30 percent of all "naturally" fertilised oocytes result in a live birth (Macklon et al. 2002).

Development *in vitro*

Fertilisation
Under natural conditions, the haploid sperm cell penetrates the haploid oocyte in the woman's fallopian tube. During *in vitro* fertilisation, sperm cells can either penetrate the oocyte independently or be injected directly into it via ICSI.

Pre-nucleus stage
The parental genomes initially remain in their respective pre-nuclei, which are formed from the nucleus of the sperm cell or oocyte.

Zygote
When the oocyte and sperm cell fuse, a diploid cell with a full set of chromosomes is formed.

2-cell stage
After the membranes of the pre-nuclei have dissolved, the resulting nuclei contain both the maternal and paternal sets of chromosomes. As suggested by observations of mouse embryos (Reichmann et al. 2019), this is presumably the stage at which the parental chromosomes first mix.

4-cell stage
The embryonic genome is activated. This is essential for protein synthesis and cell division.

8-cell stage
After this stage, cellular differentiation begins, causing the cells to lose their totipotency and to become pluripotent.*

16- and 32-cell stage
From this point, the embryo is referred to as a **morula**. It divides further and reaches the uterus around 4 days after fertilisation. Some of the cells move towards the centre, while the rest remain on the outside.

Blastocyst
The embryo now comprises around 60 to 100 cells. The cells become flatter and more compact, eventually forming a hollow sphere with two cell layers. During IVF, this is usually the stage at which the embryo is transferred into the uterus.

Days 11–14 *in vitro*
Under special culture conditions, it is possible to obtain an early stage of **gastrulation** (Shahbazi et al. 2016). During natural embryonic development, this corresponds to the stage at around day 11.

Day 2 · Day 3 · Day 4 · Day 5 · Days 6–10 · Days 14–16

Implantation of the blastocyst
In order to continue growing and thrive, the blastocyst, which comprises some 100 cells, must implant itself into the uterine wall between days 6 and 10.

Gastrula
The germ layers form during gastrulation. The actual embryo continues to develop from these germ layers and the surrounding cells form the extra-embryonic membranes and placenta.

Day 70
The embryo becomes known as a **foetus** from the 10th week of pregnancy, as all the organs and limbs have formed by this stage.

Development in the fallopian tube

Development in the uterus

Size comparison

Day 70
Foetus
25 mm

Day 14
Gastrula
0.4 mm

Day 1
Zygote
0.1–0.2 mm

*Under the appropriate conditions, every totipotent cell is capable of developing into a complete organism and also has the ability to form the embryonic part of the placenta. Pluripotent cells only have the potential to differentiate into any of the tissue types found in the body.

3. The importance of research on early human embryos

3.1 Unanswered questions on early human development

Research on early human embryonic development paves the way towards a better understanding of human developmental biology.[3] The objective is to gain more detailed insights into the molecular and morphological processes which take place in the first two weeks following the fertilisation of the oocyte until shortly after the implantation of the blastocyst in the uterus (see Figure 1). This could potentially open up new and improved ways of avoiding or treating infertility, miscarriages, premature labour, genetic diseases or birth defects.

Box 1: Technological change in the life sciences

In recent years, technology has opened up new ways of conducting biological and medical research, which can also be used for *in vitro* research on early embryos. One example is the development of high-throughput technologies, collectively known as the "omics" *(genomics, epigenomics, proteomics, transcriptomics, metabolomics)*[4]. These technologies are used to holistically research cellular processes and an organism's genetic makeup at a molecular level all the way down to analysing single cells *(single cell multiomics*[5]*)*. New microscopic processes enable detailed observations of embryonic development in real time.[6] Genome editing techniques enable the modification of genetic information much more accurately and efficiently than conventional genetic engineering methods. One notable example is the CRISPR-Cas9 system, which won its developers the Nobel Prize in October 2020. Also known as "genome surgery", these methods can be used on human cells.[7]

All these methods are opening up new avenues for research scientists in the fields of human biology and medicine. This will advance research into the development of human life, the epigenetic, genetic and environmental causes[8] of diseases, and targeted treatment methods. However, investigations in these areas cannot be conducted on animals alone because many processes are specific to humans – such as the fertilisation of oocytes, cell division, the point in time at which the embryonic genome is activated and the way in which it is regulated.

Under normal circumstances, every cell in an early human embryo has two sets of 23 chromosomes (euploid embryos) – one set from the mother and one from the father, whose genomes are both passed on to all the daughter cells after the oocyte has been fertilised. For the embryo to develop normally, the chromosomes must be divided evenly during cell division. After decades of research on cell cultures, scientists now understand some of the many molecular safeguards involved in enabling cells in the body

3 Suwińska & Ajduk (2019).
4 See also Leopoldina (2014).
5 Li et al. (2018); Perez-Palacios & Bourc'his (2018).
6 Strnad et al. (2016); McDole et al. (2018).
7 See Reich et al. (2015); Leopoldina et al. (2015).
8 Monk et al. (2019).

(somatic cells) to detect and correct cell division errors. A surprisingly high proportion of early embryos have an abnormal number of chromosomes in some or even all of their cells (aneuploid embryos).[9] Aneuploidy, i.e. the presence of an abnormal number of chromosomes (chromosome imbalance) in a cell, has been found in around a third of all clinically investigated foetuses following a miscarriage, making it the most common cause of spontaneous pregnancy loss. Scientists require a better understanding of the causes behind this high rate of chromosome imbalance in human embryos in order to provide effective advice and treatment to couples who have suffered repeated miscarriages as a result of this abnormality. Risk groups include women over the age of 38 or women who have already had miscarriages, couples who have experienced failed IVF attempts and men with fertility problems. Couples who have had a previous pregnancy during which the unborn child was found to have a chromosomal abnormality are also at greater risk.

Miscarriages are, however, far from the only consequence of abnormal embryonic development. Scientists still have an insufficient understanding of serious developmental defects, such as commonly occurring congenital heart defects and disorders of the central nervous system,[10] which do not lead to pregnancy loss, but nevertheless cause serious health impairments. Although scientists have identified some risk factors – such as the expectant mother being underweight or overweight, nicotine and alcohol consumption, or other harmful environmental influences or genetic factors – the causes are still unknown in the majority of cases. This is another area where embryo research can play an important role.

Another objective of embryo research is the desire to gain a better understanding of the regulation of gene expression in early embryos. This is crucial for healthy development, from the formation of the first tissue types and organ rudiments to implantation in the uterus. To date, scientists do not understand the molecular mechanisms behind these processes. There is also a lack of knowledge on how abnormal development may be the cause of disorders and diseases which emerge in later life.

Research on early human embryos is also used to investigate the extent to which the differentiation of embryonic and induced pluripotent stem cells[11] *in vitro* corresponds to embryonic development in normal conditions (see Chapter 3.3).

9 Harper et al. (2014); Capalbo et al. (2017); Popovic et al. (2020).

10 Hyun et al. (2021).

11 Induced pluripotent stem cells are produced by reprogramming fully differentiated adult somatic cells. Pluripotent means that the cell can theoretically differentiate into any of the cell types found in an organism.

3.2 The importance of embryo research for reproductive treatments

IVF is used around the world as a standard treatment for certain types of infertility.[12] To date, around 8 million children have been born worldwide as a result of IVF. In Germany, 319,119 children were born through IVF between 1997 and 2018, which is roughly equivalent to the population of cities like Bonn or Münster. The treatment method now achieves a birth rate of 23.6 percent per embryo transfer.[13] The increased proportion of multiple pregnancies, which is particularly high in Germany, still poses a challenge, due to the greater risk of premature birth and the associated health risks for mother and child.[14]

One of the key features of IVF is that the human embryo initially spends up to 6 days outside of the body in a culture medium, where it is exposed to artificial conditions. During natural conception, the oocyte is fertilised in the fallopian tube by a sperm cell around 12 hours after ovulation takes place. The resulting embryo then travels along the fallopian tube until it reaches the endometrium (uterine lining), where it implants itself between the sixth and tenth day following fertilisation (see Figure 1). IVF is a different process altogether: Following the administration of hormones, around 10 oocytes are collected from the woman and brought into contact with the man's sperm in a culture medium. During an ICSI treatment (intracytoplasmic sperm injection), the sperm cell is injected directly into the egg cell. The culture conditions aim to mirror conditions in the fallopian tube to the extent possible (in terms of temperature, ions, amino acids, proteins, pH value, concentration of osmotically active particles, concentration of oxygen, nitrogen and carbon dioxide, etc.).[15]

It is essential that scientists are able to continue researching and systematically standardising these conditions and processes because there are still numerous questions to be answered. Examples include:

- What are the reasons for the high mortality rate (41 to 56 percent) between the pre-nucleus stage[16] and the blastocyst stage?[17] Due to this mortality rate, the German Middleway *(Deutscher Mittelweg)* generally involves more than 3 oocytes being fertilised and cultured in preparation for a transfer (see Chapter 3.5).

12 IVF is commonly used as a treatment for women with severely damaged fallopian tubes or endometriosis. IVF-ICSI treatment (ICSI = intracytoplasmic sperm injection) is prescribed in cases of very low sperm count or low sperm motility, and involves a sperm cell being injected directly into the oocyte.

13 German IVF-Registry (Deutsches IVF-Register) (2020); de Geyter et al. (2020).

14 A detailed analysis of the medical, ethical and legal questions surrounding reproductive medicine and the legal situation in Germany can be found in a statement published by the German National Academy of Sciences Leopoldina and the Union of the German Academies of Sciences and Humanities: Leopoldina & Union of German Academies (2019).

15 Hanevik et al. (2016); Berntsen et al. (2019); Storey et al. (2021).

16 The pre-nuclei are formed before the maternal and paternal sets of chromosomes fuse to form a new diploid genome. The male pre-nucleus is formed from the nucleus of the sperm cell which has penetrated the oocyte. The female pre-nucleus is formed from the nucleus of the oocyte. This stage of the fertilisation process is called the pre-nucleus stage. Once it is complete, the nuclear membranes of the two pre-nuclei dissolve.

17 Guerif et al. (2007).

- During singleton pregnancies following IVF without cryopreservation, are the embryo culture conditions the cause for these children to be born a week earlier on average than children who are conceived naturally?[18] Also, children conceived through IVF are born slightly underweight for their gestational age.[19]
- In cases where pre-nucleus stages and embryos have been cryopreserved,[20] the children are also born slightly too early on average, but have a slightly higher average birth weight.[21] Do these differences have long-term effects as the children continue to develop?
- Why is the rate of birth defects and certain diseases higher following IVF and, in particular, ICSI treatment than it is among newborns conceived naturally? The rate of morphological abnormalities among newborns conceived naturally is around 5 percent, compared with around 7 to 9 percent among children born following IVF and ICSI treatment.[22] Certain rare epigenetic diseases such as Beckwith-Wiedemann syndrome also occur slightly more frequently following IVF treatment.[23] There are also indications that there may be a higher incidence of arterial hypertension (high blood pressure), diabetes, cancer and neurological disorders (e.g. autism, epilepsy or attention deficit hyperactivity disorder – ADHD) as well as low sperm quality among offspring conceived using ICSI.[24]

The above-mentioned abnormalities could be caused by factors relating to the child's parents or could just as well be a result of the processes used during assisted fertilisation. Embryo research could play a decisive role in answering these questions, hopefully helping to reduce the health risks for mother and child as well as to improve fertility treatments. For example, research is presently being conducted into an *in vitro* maternal spindle transfer method to treat a specific form of female infertility caused by a serious defect during early embryonic development.[25]

18 See German IVF-Registry (Deutsches IVF-Register) (2020).

19 Ludwig & Ludwig (2018); Berntsen et al. (2019).

20 During cryopreservation, water is firstly withdrawn from the pre-nucleus stages/embryos. This water is replaced by cryo-protectant (antifreeze) so that the pre-nucleus stages/embryos can be cryopreserved (frozen) at -196 degrees Celsius. During thawing, these steps are "reversed" and the embryos are then observed to check that they continue to develop normally.

21 Ludwig & Ludwig (2018).

22 Wen et al. (2012); Hansen et al. (2013).

23 Elbracht et al. (2020); Henningsen et al. (2020).

24 Scherrer et al. (2012); Svahn et al. (2015); Belva et al. (2016); Rumbold et al. (2017); Meister et al. (2018); Chen et al. (2014); Källén et al. (2010).

25 According to the authors, the method, which was initially developed in animal experiments, is currently being tested using human embryos, see Costa-Borges et al. (2020).

3.3 The importance of human embryonic stem cells in regenerative medicine

The first stem cell lines were generated from human embryonic stem cells (hES cells) in the late 1990s. Due to their pluripotency, these hES cells can develop into different cell types. There is great hope for research using these cell lines, particularly in the area of cell replacement therapy, which is used to repair damaged tissue in regenerative and personalised medicine. However, this technique is ethically controversial because the embryos do not survive the generation of these hES cells. In Germany, the generation of hES cells is prohibited under the ESchG. The German Stem Cell Act *(Stammzellgesetz, StZG)*, on the other hand, uses a legal construct which permits prohibited activities under certain conditions to allow hES cells to be imported to a limited extent for research objectives of outstanding interest.

Approximately 15 years ago, researchers succeeded in using reprogramming to turn fully differentiated adult somatic cells into induced pluripotent stem cells (iPS).[26] Like hES cells, iPS cells are able to differentiate into various organ-specific cells depending on the culture conditions. However, unlike hES cells, the manner in which they are generated is less ethically problematic: iPS cells can be produced by reprogramming adult skin or blood cells from donors or patients. However, there is some evidence to suggest that iPS cells exhibit certain genetic and epigenetic differences to hES cells. One of the possible reasons for this is that iPS cells can retain epigenetic patterns from the adult cells from which they are generated. Another reason is that mutations which accumulate in the original adult cells in the course of a lifetime are passed on to the iPS cells.[27] A better understanding of cellular differentiation processes necessitates a scientific comparison of these cells with the corresponding stem cells in the embryo's cell cluster and with hES cells. Such studies should also provide insights into the potential of iPS and hES cells for the development of cell therapies and research into the causes of diseases and disease progression.[28] Clinical studies involving both cell types are already exploring how they can be used in cell replacement therapy to treat conditions like age-related macular degeneration.[29]

Since the hES cell lines which have been established for years and, in some cases, may have been generated and further cultured under very diverse conditions, have accumulated genetic and epigenetic alterations and may be contaminated with pathogens (e.g. prions and mycoplasma),[30] it is also necessary to generate and characterise new hES cell lines under clearly defined conditions, and to ensure that they are suitable for clinical applications.

26 Okita et al. (2007).

27 Attwood & Edel (2019); Halliwell et al. (2020).

28 Barker et al. (2017); Parmar et al. (2020).

29 Da Cruz et al. (2018); Deinsberger et al. (2020).

30 Hay et al. (1989); Krejciova et al. (2011); Cobo et al. (2006).

3.4 The importance of embryo research for gene therapy

Another pioneering field of medical research is the use of genome editing to genetically "correct" hereditary diseases. There are two different approaches, depending on the disease. The first involves genetically correcting body cells (somatic cells) and the second involves editing the embryonic genome *in vitro*.[31] The first method, which is known as somatic gene therapy, is already being tested. It can only be used to treat an individual patient, who in most cases is already unwell. The second method, which modifies the germline, is much more problematic from an ethical point of view because the possible long-term effects on the individual and, in particular, the potential impact on future generations, is as yet unclear.[32] Germany law prohibits such interventions in the human germline. To date, a few laboratories around the world have conducted experiments on this type of genetic modification. As far as is known, this has been done without the intention of creating a pregnancy and no pregnancies have resulted from such experiments. An exception to this occurred in China in late 2018, but was met with outrage from the scientific community.[33]

The overwhelming majority of the international scientific community agrees that it is currently not justifiable to use germline interventions to pursue the objective of bringing a person into the world. The main points of criticism are the risks involved and the argument that it is insufficiently justified given the availability of pre-implantation genetic diagnostics (PGD)[34], which in many cases can be used alternatively to prevent serious genetic diseases from being passed on. Critics also fear that application of the technology could go beyond disease treatment and actually be used to improve biological characteristics (enhancement). Fundamental research on germ and somatic cells and on early human embryos could nevertheless prove useful, at the very least for the purpose of critically examining and evaluating the opportunities and risks of this type of gene therapy. Such research could also reduce the off-target effects still associated with this method (e.g. extensive sequence loss in the genome and even chromosome loss).[35] The majority of members of the German Ethics Council and, more recently, the Bioethics Committee of the State of Rhineland-Palatinate *(Bioethik-Kommission des Landes Rheinland-Pfalz)* are therefore in favour, from an ethical perspective, of generally allowing such research to be conducted on early human embryos *in vitro*.[36]

31 See Leopoldina et al. (2015).

32 See, for example, Nuffield Council on Bioethics (2018); Deuring (2019); Taupitz & Deuring (2020).

33 Krimsky (2019); German Society for Gene Therapy (Deutsche Gesellschaft für Gentherapie) (2018).

34 This includes tests in the fields of cell biology and molecular genetics which are used to help determine whether an embryo created using IVF should be implanted into the uterus.

35 For more information on the potential risks of this method, see, for example, Zuccaro et al. (2020); Ledford (2020). Also, German National Academy of Sciences Leopoldina (2017); also Olson (2016). International summit on human gene editing: A global discussion. In International Summit on Human Gene Editing: A Global Discussion. National Academies Press (US); International Commission on the Clinical Use of Human Germline Genome Editing (2020).

36 See p. 240 of the Statement by the German Ethics Council (2019); Bioethics Committee of the State of Rhineland-Palatinate (Bioethik-Kommission des Landes Rheinland-Pfalz) (2020).

The science academies wish to use this statement to express their agreement with this appraisal of the situation.

3.5 Embryo donation for research

Although some countries permit embryos to be created from donated gametes specifically for research purposes (see Chapter 5.2), in the majority of countries most of the embryos used for research were originally created for reproductive purposes, but are no longer needed for this. Germany also has a significant number of cryopreserved embryos which are no longer required for use in fertility treatments.

As is the case with natural fertilisation, the most embryos created *in vitro* are not fully viable.[37] The "German Middleway" *("Deutscher Mittelweg")* allows doctors to decide on the number of oocytes to culture beyond the pre-nucleus stage, meaning that the number of embryos transferred (maximum of three) can be determined in advance for each couple. This decision is made in consultation with the couple, taking their specific situation into account.[38] In some cases, this method creates more embryos than the number actually transferred to the patient. These "surplus embryos" are generally cryopreserved for potential future treatment cycles. If a woman no longer wishes to have these embryos transferred because she does not want any (more) children, for example, German law allows the donation of these embryos to other patients undergoing fertility treatment or for these surplus embryos to be discarded with the couple's consent. In 2012, around 5,000 cryopreserved early embryos and 28,500 cryopreserved pre-nucleus stages were stored at centres managed by the German Embryo Donation Network *(Netzwerk Embryonenspende Deutschland e.V.)*.[39] According to the ESchG, pre-nucleus stages are not defined as embryos, but are still not lawfully permitted to be created for research purposes or to be thawed and further cultured for such purposes (see Chapter 5.1). While the total number of pre-nucleus stages and embryos currently in storage across Germany is unknown, experts estimate that the actual number is over ten times as high as that mentioned above. From the current figures in the German IVF-Registry *(Deutsches IVF-Register)*, it can be concluded that approximately 20,000 embryos were cryo-preserved and almost 10,000 embryos were thawed and transferred for the purpose of initiating a pregnancy in Germany in 2019.[40] As already pointed out, experience has shown that not all surplus embryos are used to initiate a pregnancy. Unused embryos are discarded – in spite of the fact that they could be made available for research of outstanding interest.

37 It is, of course, difficult to gather reliable data on this. Nevertheless, it is estimated that only around 30 percent of all "naturally" fertilised oocytes result in a live birth. Cf. Macklon et al. (2002).

38 Taupitz & Hermes (2015).

39 German Ethics Council (Deutscher Ethikrat) (2016).

40 German IVF-Registry (Deutsches IVF-Register) (2020).

Surveys conducted abroad involving couples who have the opportunity to donate surplus embryos for research purposes show that a high proportion are willing to do so.[41] This is understandable given that these couples have themselves often benefited from the reproductive treatments developed as a result of such research. Furthermore, their own experience may have shown them how desirable it is to improve fertility treatment, which can often be very stressful without any guarantee of success. The high number of cryopreserved surplus embryos and pre-nucleus stages in Germany and the expectation that German couples would also be willing to donate[42] support the reform of the legal framework governing research on early embryos for the purpose of achieving research objectives of outstanding interest.

Certain matters can, however, only be investigated using *in vitro* embryos which have been created from donated gametes specifically for research purposes. This is the case where the experiment is based on the fertilisation process itself. This type of research has been used to investigate the following fundamental scientific questions, among others:

- the role of certain ions in the culture medium during the IVF of oocytes,[43]
- fundamental methods involved in mitochondrial transfer for the prevention of serious hereditary diseases in the parents' offspring,[44]
- fundamental methods involved in maternal spindle transfer for the treatment of female infertility associated with repeated deficiencies during early embryonic development[45] and
- gene correction in embryos for the prevention of a hereditary heart condition.[46]

At least 15 countries[47] permit embryos to be created for research purposes under certain circumstances. As a general rule, the researchers involved are required to justify why the available surplus embryos are insufficient in number or unsuitable for the research project in question.

41 Cf. Wånggren et al. (2013) as well as the other references discussed in detail in this article.

42 For information on the willingness to donate among German couples, see the results of the survey from 2012: Armbrust (1985), pp. 41–44.

43 Storey et al. (2021); Swann (2018).

44 Kang et al. (2016); Hyslop et al. (2016).

45 According to the authors, the results gained during experiments on mouse embryos are currently being reviewed using experiments performed on human embryos, see Costa-Borges et al. (2020).

46 Ma et al. (2017).

47 The list of countries includes Australia, Belgium, Canada, China, Denmark, India, Israel, Japan, Singapore, South Africa, South Korea, Spain, Sweden, the United Kingdom and some states in the USA. See Ishii et al. (2013).

3.6 Embryo-like structures and artificially created embryos

In recent years, scientific progress has resulted in the lines between somatic cells and gametes becoming increasingly blurred. International stem cell research has created various cell formations with embryo-like features.[48]

In mice, researchers have already managed to create sperm from embryonic stem cells[49] and have replicated the entire oocyte formation process (oogenesis) *in vitro* using pluripotent and reprogrammed somatic cells (iPS cells). After the oocytes formed in this way had been fertilised, the resulting mouse embryos were implanted into female mice and developed into mice capable of reproduction.[50] Researchers have also succeeded in producing artificial embryo-like structures (embryoids)[51] from pluripotent stem cells in mice without meiosis.[52] Even though it is still unclear to what extent findings and methods from animal models like this can be applied to research on human embryo-like structures, it has already become important to begin discussing such matters from an ethical perspective.

In humans, researchers have already succeeded in generating egg precursor cells (known as oogonia) with two sets of chromosomes (diploid)[53] and postmeiotic cells with a single set of chromosomes (haploid)[54] from iPS cells completely *in vitro*. Researchers have also managed to produce various embryo-like structures (e.g. blastoids) from human (induced) pluripotent stem cells[55] and to develop gastrula-like structures from human embryonic stem cells.[56] The developmental potential of these structures is yet to be determined. It is, however, more likely than not that scientists will be able to generate viable human embryos from reprogrammed somatic cells or adult human stem cells in the near future.

48 Aach et al. (2017).

49 Zhou et al. (2016).

50 Hikabe et al. (2016).

51 Rivron et al. (2018); see Weatherbee et al. (2020) for an additional overview.

52 Unlike with normal nucleus division (mitosis), the number of chromosomes halves during meiotic cell division (meiosis), resulting in two genetically different haploid nuclei.

53 Yamashiro et al. (2018).

54 Eguizabal et al. (2011).

55 Zheng et al. (2019); Moris et al. (2020); Liu et al. (2021); Yu et al. (2021).

56 Moris et al. (2020).

The International Commission on the Clinical Use of Human Germline Genome Editing[57] recommends conducting more intense fundamental research into the development of functional gametes from human stem cells to make it easier to assess the opportunities and risks of using this method in reproductive medicine.[58] Discussions are currently ongoing as to whether this method could possibly give couples the opportunity to have children who are genetically related to them in the event that, for certain specific reasons, they are unable to use any of their own gametes or are unable to produce viable embryos using their own gametes.

The legal and ethical position of gametes and embryos which could possibly be artificially produced in this way in the future is also controversial, partly because the wording of the ESchG does not seem to allow this to be clearly assigned.[59]

57 Further information on this Commission, which was established to develop science-based clinical standards for modifications of the human germline, can be found at https://www.nationalacademies.org/our-work/international-commission-on-the-clinical-use-of-human-germline-genome-editing.

58 See Recommendation 7 in International Commission on the Clinical Use of Human Germline Genome Editing (2020).

59 Advena-Regnery et al. (2018).

4. Ethical aspects

4.1 Treatment of human embryos – issues and controversies

Legal regulations and social attitudes surrounding reproductive medicine and research on early human embryos largely have their roots in beliefs on moral obligations in the context of treating human life in its prenatal phase. These may include obligations

- towards the (future) parents of an embryo (who, for example, want their child to be as healthy as possible);
- towards the future child (whose health depends on the embryo being treated appropriately);
- towards society (which is reliant on the protection of central ethical standards);
- and not least towards embryos *in vitro* and *in vivo* for their own sake.

It is this last aspect which in ethics is described as the embryo's (intrinsic) "moral status"[60] and is the subject of controversial debate. A full moral status guarantees the right to the protection of life and dignity. A prevailing opinion is that a full moral status is indubitably accorded to all human beings from the moment they are born. If it were also accorded to embryos in the early stages of development *in vitro*, the protection of their development would prevent trade-offs in favour of the freedom of scientific research, knowledge acquisition, and the interests of parents and future patients. The issue of status is thus the crossroads which one must pass before questions of considering and balancing other ethical aspects can be considered.

For a long time, these questions only concerned contraception, abortion, and birth complications (see Box 2). However, since the 1970s, the range of questions in this field has broadened significantly to include modern reproductive medicine, in which new technical methods have been developed to aid those struggling with infertility to have a child or to promote the health of future children. The ethical debate is no longer limited to whether an embryo or foetus growing in a woman's uterus has a right to the same protection as a human being after birth. Rather, it is also concerned with the appropriate way of treating a fertilised oocyte in a Petri dish. Not only is an embryo's right to life at issue, but also questions are being asked about the legitimate means and motives for artificially creating human life. As a result, increasing attention is being paid to issues of ethically responsible parent-child relationships. Furthermore, the range of people involved has grown to include reproductive health professionals and researchers using artificial fertilisation to gain access to embryos outside of women's bodies. This means that a framework for responsible professional conduct needs to be established. Ethicists around the world have contributed to a comprehensive and fiercely debated body of literature on these issues. The following section focuses solely on ethical issues in the context of research on early human embryos.

60 Jaworska & Tannenbaum (2018) "An entity has moral status if and only if it or its interests morally matter to some degree for the entity's own sake." Some authors also differentiate between an intrinsic and extrinsic status. The latter encompasses the rights which arise, in particular, as a result of parents' relationships with their embryos – or also from the intentions of third parties, such as researchers or society.

Box 2: Highlights from history

The existence of early human embryos outside of the female body only became possible with the birth of modern reproductive medicine, raising a host of new questions. Previously, debates focused exclusively on embryos *in vivo* in connection with pregnancy, which meant that they generally revolved around much later stages of development.

Ethical positions on how to treat embryos *in vivo* have varied significantly over time and have been based on prevailing opinions on the nature of the unborn and the role of women in society. Aristotle's theory that human embryos gradually developed a soul meant that during Greek and Roman antiquity foetuses were generally not granted the same protection of life as a born human. These teachings continued to hold sway until well beyond the Middle Ages. In contrast, Christianity has always viewed abortion as immoral, but due to its assumptions about prenatal ensoulment, it regarded early termination as less serious. It was only in the late 19th century that the Catholic Church stopped making this distinction and took a strict stance on an embryo's right to life. Nevertheless, even the Catholic Church permitted a pregnant woman's right to life to be placed above that of the embryo under certain circumstances. Protestant theology tended to have more liberal and less uniform view on this matter.[61]

In the late 19th century, the women's rights movement called for women to have a right to abortion. Most advocates of the right to abortion implicitly understood the embryo's moral status to be subordinate to the mother's right to health and self-determination. Here, self-determination referred to women's decisions about their own bodies and reproduction, their health and that of their children as well as the preconditions for a wholesome family life. As women gradually became more emancipated, the way they viewed their own bodies and their perspectives on pregnancy, birth, and starting a family began to feature more heavily in scientific and political discourse and were taken into greater consideration. At the same time, in many countries, quite a number of philosophers in the emerging field of secular bioethics began to debate the status of the embryo. However, this development came much later in Germany than in the Anglo-American world, for example.[62]

Against this backdrop, the public debate in Germany on the regulation of IVF (in the 1980s and 1990s), and subsequently the German Stem Cell Act (2002), too, was shaped to a greater extent by religious arguments than in some other Western countries. Nevertheless, some of the members of the Benda Commission *(Benda-Kommission)* – a working group established by the German Federal Minister of Research and Technology and the German Federal Minister of Justice in 1984 to evaluate IVF, genome analysis, and gene therapy – voted in favour of allowing research of outstanding interest on early human embryos. They argued that in cases where the research is limited to investigations during the initial cell divisions, it should be possible to balance research interests against the requirement to protect life.[63] Since then, ethical debates surrounding the protection of embryonic life have been more widely accepted in Germany and many new contributions have been made to the discourse.

61 The arguments of various individuals like Norman Ford, Mary Warnock and Jeff McMahan were pivotal to the debate.

62 Cf. Thomson (1971); Tooley (1972); Warren (1973); Noonan (1970); one of the early pioneers in Germany: Hoerster (1991).

63 Joint working group of the German Federal Minister of Research and Technology and the German Federal Minister of Justice *(Gemeinsame Arbeitsgruppe des Bundesministers für Forschung und Technologie und des Bundesministers der Justiz)* (1985), p. 30. The 19 members only included one woman, namely Liselotte Mettler, the Deputy Director of the Department of Obstetrics and Gynaecology at the University Hospitals Schleswig-Holstein.

4.2 Questions of status

The question of the embryo's (intrinsic) moral status is pivotal in the debate about research on human embryos given that it not only concerns embryos inside the woman's body (before and after implantation in the uterus) but also early embryos *in vitro*, i.e. outside of the human body. This issue is therefore relevant to the entire prenatal development starting with the fertilised oocyte (zygote) up until birth, which is often referred to without differentiation as the "embryonic stage" in both legal policy and ethical debates.[64] Perhaps in part due to this extremely broad concept, many people intuitively think of an unborn being during the advanced stages of pregnancy when they hear the word "embryo" rather than the cell mass of 0.1 to 0.2 millimetres in size, which is used in embryo research.[65]

This misconception could be one possible explanation why the strict position of according full moral status to human embryos from the moment of fertilisation has had such a significant influence on biopolitical discussions surrounding embryo protection, both in Germany and worldwide. This position is often ethically justified from both a religious and secular standpoint by the belief that all stages of human life are sacred or absolutely worth protecting. When it comes to extracorporeal embryos – i.e. cultured outside of the body – another frequent concern is that the ease with which these embryos can be accessed encourages third parties to instrumentalise human life. According to this position, even early human embryos would be entitled to the same protection of life and dignity as human beings after birth.[66] Generally speaking, the arguments cited to support this viewpoint include at least one of four characteristics accorded to every embryo: (i) its being part of the human species, (ii) its continuous development (i.e. the lack of ethically relevant cut-off points), (iii) its personal identity with the potential child which could develop from it, and (iv) its potential to develop into a viable, healthy child under favourable conditions. In Germany, these four arguments are referred to as "SKIP" arguments from the first letters of the German words for the four underlying principles ("**S**pezies" (species), "**K**ontinuität" (continuity), "**I**dentität" (identity) and "**P**otenzial" (potentiality)). Critics deem all four of them questionable.[67] In recent decades, this topic has evolved into a debate with a seemingly hair-splitting level of

64 In reproductive biology, the term "foetal stage" is used to describe the period from the end of the third month of pregnancy.

65 In the Anglo-American world, a distinction is occasionally made between an "embryo" and a "pre-embryo" (up to day 14), not least in an attempt to counteract such intuitions.

66 In this statement, it is only possible to touch upon some aspects of these debates, see Anselm et al. (2002) for more details. Some parts of the feminist movement have also criticised assisted reproduction techniques and embryo research, mostly due to reasons relating to the protection of women and concerns that embryos are being instrumentalised *in vitro* for medical engineering purposes, cf., for example, Braun (2003).

67 Cf., for example, the critical analysis in Kaminsky (1998), p. 73ff., and Merkel (2002), p. 117ff.

detail within both theological and secular bioethics[68] without any signs of a consensus being reached. According to many experts, the position of full human status cannot be refuted as nonsensical, but aside from a religious line of reasoning, it can barely be coherently supported.

Box 3: The Warnock Report (1984) and the 14-day limit

The bioethical recommendations made in the *Warnock Report* (1984) are a prominent example of an ethical examination of questions surrounding embryo protection in reproductive medicine and research. Chaired by the philosopher Mary Warnock, the committee of the same name concluded that – in light of the diverse range of views, which seemed irreconcilable even at the time – it was important to establish an acceptable, obvious, and objectively justifiable cut-off point during early embryonic development, which could be seen as a morally relevant threshold.[69] The committee decided on a point when, during normal development, twins could no longer form. Their reasoning was that this is the moment when individual development could begin and implantation in the woman's uterus is complete. Due to the fact that even naturally fertilised early embryos often die before implantation (see Figure 1) and the fact that implantation marks the start of pregnancy, the proposed 14-day limit was so widely accepted that it was set as the cut-off point before which research (of outstanding interest) on embryos *in vitro* could generally be approved in the United Kingdom (and subsequently in many other countries[70]). It was also readily accepted by researchers for practical reasons; at the time, technical limitations made it impossible to culture *in vitro* embryos for any longer. However, with a longer culture period becoming more and more likely,[71] discussions about revising the 14-day limit have started in many countries. An extension of the cut-off point could enable scientists to conduct more research into – and possibly find treatments for - the causes of issues such as miscarriage and of diseases that manifest themselves at later stages of development, such as congenital heart defects and disorders of the central nervous system.[72] One proposal is to extend the cut-off point to approximately 28 days. Supporters of this extension argue that embryos have still not developed any functional nerve connections or sensory systems by this point and therefore, in particular, do not have any capacity for sentience.[73]

This can be demonstrated using the example of the potentiality argument, which is the most prominent and important of the four "SKIP" arguments outlined above. A healthy embryo's potential to develop into a viable, healthy child clearly differentiates it from other cells or cell clusters – regardless of whether the embryo forms inside a woman's body or, through IVF treatment, is transferred to a woman's body with her consent and allowed to implant and develop over the course of many months in the uterus under the

68 For an overview of the ongoing stalemate, c.f., for example, Siegel (2018).
69 Department of Health & Social Security (1984), p. 66.
70 For details on the application of the 14-day limit, see Matthews & Moralí (2020).
71 See Deglincerti et al. (2016) and Shahbazi et al. (2016).
72 See Chan (2018); Matthews et al. (2021); McCully (2021); Hyun et al. (2021).
73 Tawia (1992); Hurlbut et al. (2016); Appleby & Bredenoord (2018).

necessary biological conditions. According to the potentiality argument, this potential for development obliges other people not to inhibit, or rather to actively enable, the realisation of this potential – at least as long as there are no serious moral reasons to the contrary. Therefore, in accordance with this argument, pregnancies may generally not be aborted and *in vitro* embryos may generally not be discarded or used for research.

Support for this argument may go hand in hand with the idea that under favourable conditions an embryo could develop into a baby quasi of its own account, if only it were allowed to do so. By now, it is strikingly obvious just how mistaken this line of reasoning is, especially for *in vitro* embryos. If they are to stand a chance of getting implanted into the uterus, *in vitro* embryos must first be actively transferred into a woman's hormonally prepared body. From that point on, as described above, a permanent biological interdependency between the pregnant woman and the embryo is vital for making, under the right conditions, the latter's developmental potential realise. The idea that a "mere" biological potential for development should imply a moral obligation is considered by many an unconvincing ethical postulate which does not cohere with other ethical justifications. The imprecise nature of the term "potential for development" and the extent to which it depends on external factors is made obvious by the fact that the specific "potential" of a naturally fertilised oocyte (and its subsequent stages of development) can be influenced in many ways by recent advancements in molecular biology. This is even the case before fertilisation is complete and before an "embryo" exists according to the legal definition provided in the ESchG. For example, it is possible to modify gametes so that "embryos" develop from them, which are only able to develop for a very short length of time. Moreover, scientists can produce embryoids, which show normal early development only in certain regards and can then be cultured *in vitro* over many months without being able to develop into a complete human organism. Conversely, in animal experiments somatic cells can be biochemically induced to develop into viable embryos after undergoing several intermediate stages of development. When, despite this, proponents of the potentiality argument continue to adhere to the notion that the inherent potential for an embryo to develop normally calls for its protection, this might be evidence of their argument being based on natural law ("nature does it right"), which lacks plausibility both here and in many other ethical contexts.[74]

All SKIP arguments alike are questioned by the view that ascribing intrinsic rights to protection to human embryos can only be justified by actually realised properties rather than by their partial biological preconditions as they are realised in the genome of a fertilised oocyte. This widespread view has paved the way for various alternative positions which are in favour of providing a lower level of protection. These either propose a gradual increase of the embryo's right to protection or regard certain watershed

74 Birnbacher (2006); Bayertz (2017).

moments in the embryo's development as morally important or decisive. Some of these watershed moments relate to biological aspects and some to anthropological aspects. Possible watershed moments are the formation of the real embryo (known as the "embryo proper") following its morphological separation from the tissues providing it with nutrition, its implantation in the uterus, the initial formation of neural structures, its increasing external resemblance to a born child, the foetus's ability, in principle, to survive outside of the womb (viability), and birth as the moment of separation from the mother's body at which a new independent individual comes into existence.[75] The development of sentience and, in particular, the ability to feel pain are two milestones widely supported in the ethical debate, not least because they are used to assign interests and moral rights in many other contexts.[76] Following the argument from sentience, rights to protection would not be ascribed to early embryos, given that sentience is dependent on the development of certain neural structures which, according to the current state of science, are not even present in nuce during the first few weeks. This is also a key argument in the international debate about the extension of the 14-day limit (see Box 3).

Positions in favor of a lower level of embryo protection as outlined above, diverse as they are, seem to better correspond to widespread moral "intuitions" – much better than those in favor of strict embryo protection from the moment of fertilisation. It is not without reason that under the ESchG, an embryo's survival *in vitro* is fully dependent the woman's consent to implantation, and there is no obligation to donate surplus embryos to would-be adoptive parents. It is not punishable to prevent an embryo's further development in the uterus with the help of an implantation inhibitor. After implantation, the level of protection given to both artificially and naturally produced embryos/foetuses varies depending on their stage of development.[77] During the first twelve weeks of pregnancy, women must seek counselling before having an abortion (Section 218a Para. 1 of the German Criminal Code – *Strafgesetzbuch,* StGB[78]); after week twelve, abortions can even be lawful until immediately before birth based on a medical diagnosis and a medical indication for the abortion. In all of these contexts, the right to self-determination of a woman, a pregnant woman or, as the case may be, a donating couple is given higher priority. From an ethical perspective, it seems only coherent to concede priority also to high-ranking research, especially where research in the field of reproductive medicine aims to improve the health of embryos and pregnant women.

75 Fischer (2002); Kipke (2018); Wiesemann (2008); Wiesemann (2018); Karnein (2013).

76 Cf. Hoerster (2003).

77 Taupitz (2014), III., margin number 27.

78 No noteworthy legal consequences have emerged as a result of the distinction "unlawful, but not a punishable offence", see German Ethics Council *(Nationaler Ethikrat)* (2002), p. 19; Dreier (2002), p. 377ff. Merkel (2002), p. 64ff.

4.3 Arguments beyond the question of status

The value of an embryo to its potential parents is an important factor which needs to be taken into account when considering embryo protection. In addition to the other aspects justifying embryo protection, the special nature of this social relationship substantiates the moral obligation of embryo protection, and should be honoured for the sake of these potential parents. Even going beyond concrete, individual cases, this attributes human embryos a special value already in their early stages of development. This perspective alone makes the general need to treat them with respect and not merely viewing and using them as "biological material" plausible.

Couples who are trying to have children through IVF usually want their embryos to be treated with respect, even if most of them are willing to have, in case, their surplus embryos discarded.

Beyond the currently legal options to discard surplus embryos or to have them adopted, couples in Germany could be granted greater agency by giving them the further option to donate their surplus embryos for high-ranking research. International studies have shown that the majority of couples are willing to donate their embryos to research once they do not want (any more) children, or that they would even expressly welcome this opportunity if they were informed of the nature of the research projects and approved of them.[79]

Extending a couple's freedom of choice in this way could also be justified by the objectives of embryo research. Ultimately, the aim of such research is to prevent the suffering which particularly affects people with infertility or those who have experienced repeated miscarriages. Withholding couples' freedom of choice to donate their embryos for such research also means blocking access to innovative, better researched and less harmful procedures for this particular group of people. Families affected by hereditary diseases or diseases caused by mutation also have a legitimate interest in removing obstacles to research into the causes and possible treatments of their conditions in Germany. The debate about shaping an appropriate legal framework should take all of these interests into consideration.

Some argue that embryo protection can also be justified by the fact that in a way it 'cements' the right to unconditional protection of life and dignity for human beings upon birth. The idea of embryo protection as a means of "norm protection" or as a spillover from the general attitude supporting the protection and respect of human beings upon birth can be easily reconciled with the position that the embryo's right to protection gradually increases as it develops, and it that takes the "approach" of unborn life to

79 Cf. Wånggren et al. (2013) as well as the other references discussed in detail in this article.

born human beings seriously. Conversely, it can be argued that, particularly in the early stages of development, embryos and *in vitro* embryos consisting of just a few cells are a long way off from resembling a born human being.

4.4 The use of surplus embryos and the creation of embryos for research purposes

As explained in Chapter 3.5, despite the restrictive ESchG, more embryos are created in Germany during assisted reproduction than are actually used for reproductive purposes. If it were legal, the couples from which the gametes originate, could donate these "surplus" early *in vitro* embryos for research. From an ethical perspective it seems relevant, that these surplus embryos are generally discarded, meaning that they have no chance of developing further, anyway. Thus, proponents of a gradual moral status of human embryos see their usability for research doubly justified. The same applies to embryos in which pre-implantation genetic diagnostics have identified a genetic disorder and which are therefore not transferred to the uterus.

In contrast, the creation of embryos especially for research purposes is much more controversial, even among those favouring graduated, or gradually increasing, embryo protection. For certain scientific questions, it would be advantageous if donated sperm cells and oocytes were permitted to be used specifically for research purposes to create *in vitro* embryos. Some research questions can even only be addressed using embryos produced from sperm cells and oocytes donated for research purposes, as the experimental approach concerns the fertilisation process itself (see Chapter 3.5). Here, donated embryos could not be used, because they have already undergone the initial stages of development and certain processes are already complete, such as fertilisation itself, the formation and migration of the pre-nuclei, and the replication of the parental genomes in the pre-nuclei. Understanding the errors that frequently occur during these processes could provide fundamental knowledge and possibly improve the diagnosis and treatment of infertility. Such findings could also be relevant for potential embryonic gene therapy. Finally, such embryos would allow patient-specific tests to be performed for the purpose of investigating certain pathological genetic predispositions of the gametes' donors and their effects on early embryotic development. At least the first set of issues can also be investigated to some extent using pre-nucleus stages[80] which had originally been created for reproductive purposes and subsequently cryopreserved, but which were never used for reproduction, for instances because the couple no longer wanted (any more) children. These pre-nucleus stages would need to be thawed and cultured before use, but are already available and were not "produced" specifically for

80 The pre-nuclei are formed before the maternal and paternal sets of chromosomes fuse to form a new diploid genome. The male pre-nucleus is formed from the nucleus of the sperm cell which has penetrated the oocyte. The female pre-nucleus is formed from the nucleus of the oocyte. This stage of the fertilisation process is called the pre-nucleus stage. Once it is complete, the nuclear membranes of the two pre-nuclei dissolve.

research purposes.[81] However, once they have been thawed and the fertilisation process is complete, the ESchG considers them to be embryos, meaning that they have been "produced", at least within the legal meaning of the term.

From an ethical perspective, even those in favour of giving embryos a graduated, or gradually increasing, moral status do not agree on the question of whether the creation of embryos especially for research purposes should be permitted. Some regard the primary intention for which embryos were created as irrelevant, arguing that, at least during the early stages of their development, embryos do not necessarily deserve more than a certain level of respect, which they are afforded by being used for high-level research.[82] This view thus allows for embryos to be created specifically for research purposes – as long as the gamete donors provide informed consent.[83] This position is supported by the American Society for Reproductive Medicine[84] and the International Society for Stem Cell Research, amongst others[85] and was already taken in the Warnock Report in 1985 (see Box 3 in Chapter 4.2). An alternative view holds that the extent to which an embryo is worthy of protection depends on the context in which, and the purpose for which, it was created and is used.[86] According to this viewpoint, early embryos *in vitro* must be protected for as long as they are intended to be used to bring about the birth of a child. In contrast, embryos which were never intended to be transferred to a woman have no claim to such protection.

In contrast, others strictly oppose the creation of embryos specifically for research purposes, among them even some supporters of the gradual protection position. Creating human life exclusively for research, they argue, would constitute its complete instrumentalization and thus be incompatible with the dignity of human life.

4.5 Ethical pluralism in a democratic state

The previous chapters have shown that there exists a plurality of ethical views on the embryo's intrinsic moral status, not only in Germany. This plurality has far-reaching practical consequences and seems unresolvable in the foreseeable future. In legal practice and real-life situations, however, a graduated approach towards embryo protection is applied in many cases.

81 As stated in Chapter 3.5, a large number of these pre-nucleus stages are stored in a cryopreserved state in Germany.

82 Meyer & Nelson (2001); Merkel (2002), S. 219 ff.

83 In particular, the possible side effects for egg donors need to be clarified. It could also be possible to use donated eggs which were originally cryopreserved during the donor's reproductive planning, either as a precautionary measure prior to receiving medical treatment which could be harmful to gametes or as a result of social egg freezing.

84 American Society for Reproductive Medicine (2020).

85 International Society for Stem Cell Research (2016).

86 Taupitz (2001).

Given this plurality of positions, it is worth asking whether an ethical solution to this question should not looked for on a different level. A key feature of liberal societies is that the coexistence of different ethical viewpoints is seen as legitimate and even desirable. Political compromises are sought in cases where no agreement can be reached. The basic idea of political pluralism becomes evident in the context of end of life decisions or of sexual morality, for instance. Against this backdrop, it makes sense to now shift the debate away from examining the issue in terms of personal ethics (What is the ethically correct way of treating an embryo in a specific context?) towards viewing it in terms of political ethics (What is the correct way of approaching issues surrounding embryo protection in light of the persistent philosophical and social dissent?). Discussions and decision-making processes like these are essential in a pluralist democracy. Instead of turning the most restrictive position into the general standard of the law, legal provisions should grant individuals, and in particular those concerned, leeway and the freedom to make their own decisions within certain boundaries. Regarding the internationally debated, particularly controversial question regarding the creation of embryos for research purposes, a broader public debate involving relevant stakeholders needs to be initiated.[87]

Given the ethical pluralism in the question of the status of human embryos, it stands to reason that, in terms of biolaw and biopolitics, even early embryos should not be treated as entities without any claim to protection and their creators should not be permitted to make them available for any purpose they wish. Such a farreaching liberalization regarding the protection of embryos would undoubtedly strongly violate the moral intuitions and beliefs of supporters of strict embryo protection. Even those who do not consider that human embryos have intrinsic moral rights during their very early stages of development will at least accept that they be treated with respect, for example by only allowing them to be used for research objectives of outstanding interest only and by introducing strict procedural safeguards.

A further point deserves to be mentioned in this context. In the past, Germany has often chosen to prohibit certain research based on moral grounds, but has nevertheless "imported" the results of this research from other countries. This practice was and remains common in regard to the development of IVF and also became established in the area of pre-implantation genetic diagnostics after this was allowed in Germany in 2011. Another example is research on embryonic stem cells. Although this is permitted within strict boundaries in Germany, harvesting stem cells from embryos is prohibited here, meaning that embryonic stem cells must be imported from other countries. This kind of practice, described as "moral free-riding", is ethically questionable and has received widespread criticism.

87 See also Matthews et al. (2021).

5. The legal framework governing embryo protection

5.1 Regulation concerning embryo protection in Germany

The Basic Law for the Federal Republic of Germany (*Grundgesetz,* GG) does not include any specific statements on the protection of human embryos under constitutional law. To date, even the German Federal Constitutional Court (*Bundesverfassungsgericht,* BVerfGE) has only dealt with matters relating to abortion – in other words, cases concerning embryos and foetuses in the uterus – as part of its duty to provide protection under constitutional law. In doing so, the court has explicitly left unanswered the question of whether "human life begins when an egg and sperm cell unite".[88]Above all, the court has very clearly emphasised the following: "The legislature is not obligated, as a matter of principle, to employ the same penal measures for the protection of the unborn life as it considers required and expedient for born life."[89] The regulatory freedom expressed here[90]would arguably contradict another statement made by the German Federal Constitutional Court that "Human life, wherever it exists, is inherently deserving of human dignity"[91], if indeed this latter statement meant that the protection of an embryo's human dignity – and in particular that of an embryo before implantation, since the decisions were not relating to this matter at all – were comparable to that of a person after birth. If that were the case, the legislature would hardly be authorised to make provisions contradicting this. This contradiction can, however, be resolved when one considers that – in the approach taken by the German Federal Constitutional Court[92] – the accordance of human dignity says very little about when exactly *violations* of human dignity take place. This question can clearly be answered quite differently depending on whether it concerns an embryo or a human being after birth.[93] Thus, when it comes to possible legal regulations for the protection of embryos *in vitro*, the rulings of the German Federal Constitutional Court can certainly not be used to support the strict position presented in Chapter 4.2 that argues that early human embryos are entitled to the same protection of life and dignity as human beings upon birth. In other words, in matters concerning the protection of embryos *in vitro*, it is conceivable for the legislature to stipulate completely different provisions than those laid down in the ESchG from 1990.[94]

Research on embryos is still prohibited in Germany under the ESchG. Under Section 2 Para. 1 ESchG, it is punishable by law for anyone to sell, acquire "or use" a human em-

88 BVerGE 88, 202 ff. Rdnr. 151.

89 BVerfGE 39, 1 (45).

90 For more information on this, see Dederer (2020), p. 63ff.

91 BVerfGE 39, 1ff. margin number 147; 88, 203ff. margin number 151.

92 BVerfGE 1, 97 (104); 27, 1 (6); 30, 1 (25); 72, 105 (115ff.); 109, 279 (311ff. margin number 115ff.).

93 Also, Dederer (2020), p. 63ff.: "Until such a time that generally shared values for embryos *in vitro* and other *in vitro* embryonic entities are available to the drafters of the constitution and the legislature, the legislature may (within certain limits) use its discretion and take a virtually "authoritative" approach when setting standards on how to act when it comes to the guarantee of human dignity (Art. 1 Para. 1 Sentence 1 GG) and right to life (Art. 2 Para. 2 Sentence 1 GG). This corresponds to the restricted control function (within the limits set) of the German Federal Constitutional Court."

94 See Chapter 5.3 for a more detailed analysis of constitutional law.

bryo produced outside the body (extracorporeally) or removed from a woman before the completion of implantation in the uterus when "the purpose does lie in its preservation". Accordingly, the "use" of an embryo would, at most, be allowed for the purpose of medical treatment to ensure the preservation of the embryo itself. Section 1 ESchG[95] also prohibits the fertilisation of oocytes, including the thawing and continued culture of cryopreserved pre-nucleus stages,[96] with the intention to use the resulting embryos for research purposes. Scientists based in Germany are also not permitted to participate in such international research projects involving human embryos. In accordance with Section 9 Para. 2 of the German Criminal Code (*Strafgesetzbuch,* StGB), German researchers are liable to criminal prosecution under the ESchG if they participate in research on embryos being undertaken abroad, either through counsel or actual physical research, even if research on embryos is not a criminal offence in the jurisdiction where the research project is taking place.[97]

Furthermore, under the ESchG also, as a matter of principle, interventions in the germline are a punishable offence. However, it is not clear whether the prohibition of such interventions in accordance with Section 5 ESchG also applies if such interventions someday become safe enough and can be used to preserve the embryo.[98] The distinction between an attempt to cure, a clinical study and therapy is not made clear in this context. From a legal policy perspective, it is disputed whether the prohibition of germline therapy can be justified if it is used to prevent a serious genetic disease.

Although the ESchG prohibits any kind of research on embryos, it cannot be interpreted to say that the act of letting an embryo die or of actively discarding an embryo is prohibited.[99] Furthermore, the ESchG does not include any obligation to preserve the embryo outside of the womb or to preserve it by transferring it to a woman's uterus.[100] This justifiably raises the question of whether it would actually make more sense to use surplus embryos for research of outstanding interest instead of "just" discarding them or cryopreserving them for "eternity". Since pre-implantation genetic diagnostics (PGD) was given the green light in Germany,[101] the country, in fact, has a large number of

95 In accordance with Section 1 Para. 1 No. 2 ESchG, it is a punishable offence to attempt to artificially fertilise an oocyte for any purpose other than initiating a pregnancy in the woman from whom the oocyte originated. Likewise, in accordance with Section 1 Para. 2 ESchG, it is a punishable offence 1. to bring about artificially the penetration of a human oocyte by a human sperm cell, or 2. to transfer a human sperm cell into a human oocyte artificially without the intention to initiate a pregnancy in the woman from whom the oocyte originated.

96 For more about the thawing and continued culture of cryopreserved pre-nucleus stages with a view to using the resulting embryo for a purpose other than initiating a pregnancy in the woman from whom the oocyte originated, see BayObLG (Bavarian Supreme Court), 4 November 2020, file number 206 StRR (StrafRechtsReport criminal law report) 1461/19; Taupitz (2019), 337ff.

97 See Frister (2016) and Magnus (2015), both of whom are highly critical of legal policy.

98 Cf. Reich et al. (2015).

99 In particular, Section 2 ESchG does not refer to the destruction of embryos, see BGH (German Federal Court of Justice) NJW *(Neue Juristische Wochenschrift* legal magazine) 2010, 2672 (2676 margin number 38).

100 Taupitz (2014), III. margin number 20.

101 PGD has been permitted under Section 3a ESchG since 2011 (BGBl. – Federal Law Gazette 2011 I, p. 2228) following the German Federal Court of Justice's decision (NJW 2010, 2672ff.) that the prohibition of PGD could not be inferred from the ESchG and was therefore not defined by law as a criminal offence as required under Art. 103 Para. 2 GG.

surplus embryos which are not transferred to the women for whom they were intended. These embryos are sorted out either because of a serious genetic disease or because of serious impairments that will likely lead to a stillbirth or a miscarriage. These surplus embryos in particular would be particularly suitable for researching their genetic predisposition. But, even these embryos, which will never be transferred into a woman's body anyway, are subject to the ban on conducting research on embryos.

By banning embryos from being used to benefit third parties, the ESchG also prohibits human embryos from being used for the harvesting of stem cells. Meanwhile, the German Stem Cell Act (*Stammzellgesetz,* StZG) expressly permits embryonic stem cells produced abroad to be imported into Germany for use in research under certain conditions. This legal situation in itself is viewed by many as an indication of double standards. To exacerbate matters, the restrictive regulations laid down in the ESchG (Section 2 Para. 1) only apply to embryos produced outside of the body (extra-corporeally) and therefore do not apply to embryos created naturally or to embryos and foetuses removed from a woman after implantation in the uterus. This means that the generation and use of stem cells harvested from such embryos and foetuses, which, after all, are much more developed than *in vitro* embryos, are not subject to any restrictions at all, with the exception of the general regulations on abortion – an example of unequal treatment which is less than convincing.

As the law currently stands, embryos that have been artificially produced in a Petri dish and are just a few days old can be discarded at the request of the woman for whom they were produced, but cannot be donated to research. Meanwhile, once a more developed embryo has been transferred into a woman's body, the woman may decide to allow it to be used for research. In terms of ethics, this is frequently considered as a contradictory valuation which can only be explained with the fear of uncontrolled, overly invasive research on extracorporeal embryos. However, clear procedural rules could be used to counter these concerns.

In addition to such inconsistencies in legal policy, the ESchG has been the source of further questions for a number of years. These concern novel artificial cell formations with embryo-like features of the type used in human stem cell research. Another fact to consider is that researchers have succeeded in reprogramming skin cells in mice to create artificial egg and sperm cells, which – after being fused and implanted into the female mice – developed into healthy mice capable of reproduction (see Chapter 3.6). It is likely only a matter of time before this is also possible with somatic human cells. However, artificial human gametes and embryos are not specifically considered in the ESchG. It is therefore unclear whether and to what extent they are covered by the law. This means that scientists could possibly generate them for reproductive and research purposes, genetically modify and implant them without being criminally prosecuted. This illustrates that it is high time for legal concepts such as "germline" to be redefined in more precise terms.

Even some of the ESchG's fundamental provisions, such as the definition of the term "embryo" in Section 8 ESchG, are becoming ambiguous. Researchers have used new imaging techniques during experiments on mice to demonstrate how, instead of mixing immediately after fertilisation, the parental genomes remain separate until a two-cell embryo has formed.[102] If it turns out that humans also develop in this way, the definition provided in the ESchG will be proven incorrect for having prematurely assumed that an "embryo" is formed through the "fusion of the nuclei" at the end of the fertilisation process. It would then have to be discussed whether early embryos should be given the same moral status as pre-nucleus stages or – as is often the case in other countries – whether a distinction should be made between pre-embryos and embryos.[103]

5.2 International regulations and practice in the area of embryo research

Neither the United Nations nor Europe as a whole has established uniform rules or regulations for conducting research on human embryos or on human embryonic stem cells (hES cells) derived from human embryos. However, various statements and regulatory efforts have been made in addition to the international Convention on Human Rights and Biomedicine (Oviedo Convention), all of which are relevant to the feasibility and possible objectives of research on human embryos.[104] Furthermore, the European Union's Horizon 2020 research and innovation programme explicitly excludes the funding of research projects involving human embryos.[105]

Research on early human embryos is permitted by national law under strict conditions in many countries, including Israel, Sweden, the United Kingdom, France, China, the USA and Japan.[106] Most of these countries only allow research to be conducted on surplus embryos for a maximum of 14 days following fertilisation.[107] Consent must be obtained from the individuals from whom the gametes originated and the researchers must have received authorisation from an independent ethics committee or the competent authority.[108] In addition, at least 15 countries (see Chapter 3.5) permit embryos to be created for research purposes under certain circumstances. As a general rule, the researchers involved are required to justify why the surplus embryos available are insufficient or unsuitable for the research project in question.

In the USA, the individual states have the legislative power to regulate research on human embryos and hES cells. At a federal level, the research funding provided by the

102 Reichmann et al. (2018); Hua & Mikawa (2019).

103 Cf. German Ethics Council *(Deutscher Ethikrat)* (2016), p. 114.

104 Cf. www.drze.de/im-blickpunkt/stammzellen/gesetze-und-regelungen weiterhin www.coe.int/t/dg3/healthbioethic/texts_and_documents/DIRJUR(97)5_German.pdf.

105 See European Commission (2013).

106 Cf. Araki & Ishii (2014); Taupitz & Deuring (2020).

107 See also Matthews & Moralí (2020).

108 Solter et al. (2003).

National Institutes of Health (NIH) affects the research in these areas by limiting state funding to research on hES cells from surplus embryos.[109] Privately funded research is less strictly regulated and private funds may also be used for research conducted on embryos produced especially for research purposes.

In Israel, embryos produced *in vitro* are only granted legal protection from the 41st day following fertilisation because they are not regarded as human life until this point in time. Nevertheless, research is limited to research objectives of outstanding interest and is only conducted within the 14-day limit.[110]

Research institutes which work closely with fertility clinics, such as the Karolinska Institute in Stockholm/Sweden, the Francis Crick Institute in London/UK and the Center for Embryonic Cell and Gene Therapy in Portland/USA, have been using the CRISPR-Cas genome editing technique for several years. In their research, these institutes have, for instance, been analysing molecular cellular differentiation processes which could be relevant to reproductive medicine and compared them with animal models. This revealed significant differences in gene expression and cellular differentiation between the early embryonic development of humans and that of mice.[111] Research is also being conducted into the causes of genetic predispositions to infertility or a high risk of miscarriage. Research objectives also include the creation of better hES cell lines for use in stem cell research for the purpose of regenerative medicine.[112] Researchers have also developed promising basic methodologies for correcting genetic defects in embryos. This showed that CRISPR-Cas techniques are effective on principle for these types of germline interventions[113] and revealed the first indications of a previously unknown DNA repair mechanism in early embryos.[114]

109 https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research.

110 See https://zellux.net/m.php?sid=98 and Birenbaum-Carmeli & Inhorn (2009).

111 Blakeley et al. (2015); Petropoulos et al. (2016); Fogarty et al. (2017).

112 See the Francis Crick Institute's licence renewal at the HFEA; available at: https://www.hfea.gov.uk/media/2444/licence-committee-minutes-14-january-2016.pdf.

113 Liang et al. (2017).

114 Ma et al. (2017).

Box 4: Regulatory practices in the United Kingdom

Since 1990, the national Human Fertilisation and Embryology Authority[115] (HFEA) in the United Kingdom has been granting licences for procedures in the field of reproductive medicine as well as to fertility clinics and projects involving research with human embryos which are no longer being used for reproductive purposes. As part of its work, the HFEA checks compliance with legally defined criteria. Additionally, all projects are subject to approval by an ethics committee.

In order to be permitted to use human embryos, fertility clinics and human embryo research centres must apply to the HFEA for a licence. Licences can be granted for up to four years. Before granting a new licence or renewing an existing one, the HFEA conducts an inspection to make sure that the institute concerned is operating in line with the standards set by the HFEA's Code of Practice[116].

As part of the inspection, the HFEA also checks whether changes and improvements required as a result of the licensing procedure have been met and continue to be observed. The inspectors summarise their findings in a report, which is presented to the Licence Committee before a final decision on the granting or extension of the clinic's or centre's licence is made. If the Committee has particular concerns, it may amend the licence (for example, by adding a condition to ensure improvements are made), suspend it or even revoke it in extreme circumstances. All inspection reports are publicly available on the HFEA's website[117].

According to British law, clinics and research centres must be inspected every two years to ensure that they are continuing to provide safe, legal and high-quality services and research in line with the HFEA's Code of Practice. The HFEA is authorised to inspect clinics and centres more frequently in the event of specific incidents or complaints. It also gathers feedback from patients.

5.3 Freedom of scientific research and the legislature's role in placing limits on embryo research

All of this begs the question what form a science-based, constitutional and ethically acceptable solution should take which does justice to the pluralism of considerations concerning the protection of life and human dignity in relation to embryos as well as the freedom of scientific research, the rights of potential parents and, above all, the protection of human dignity, the right of future children and patients to live a healthy life. In accordance with the essential-matters doctrine *(Wesentlichkeitslehre)* established by the German Federal Constitutional Court, one of the parliamentary legislature's original duties is to lay down basic provisions on how to adequately balance the various interests of the parties involved.[118] The details and case-by-case decisions, however, could be left up to other institutions.

115 Further information is available at: https://www.hfea.gov.uk/about-us/how-we-regulate/.

116 See https://portal.hfea.gov.uk/knowledge-base/read-the-code-of-practice/.

117 See https://www.hfea.gov.uk/about-us/news-and-press-releases/2019-news-and-press-releases/hfea-2018-19-annual-report-and-accounts/.

118 For example, BVerfGE 49, 89 (126ff.) = NJW 1979, 359; BVerfGE 34, 165 (192ff.) = NJW 1973, 133.

Art. 5 Para. 3 GG guarantees the freedom of science and research. Consequently, the burden of justification holds:[119] It is not the freedom of science and research which has to be justified, but rather the prohibition or restriction of science and research. Equally, it is not the objectives or means of the research which need to be argumentatively legitimised, but rather any reasons why they should not be permitted. It is not up to science to justify its actions or failures to act, but rather it is up to the legal system to justify why the things which science does or wants to do are illegitimate in concrete terms, rather than theoretically. Unlike other basic rights – such as the right to life – the freedom of science is not subject to a power of restriction *("Gesetzesvorbehalt")*, meaning that it cannot be restricted "by a law" or "pursuant to a law". "Taking into account the unity of the constitution and the set of values protected by it," the unrestricted basic right of the freedom of science, too, "[...] can only be limited in individual cases by colliding fundamental third-party rights and other legal values of a constitutional nature."[120] This means that the simple legislature is not entitled to limit a basic right merely in the interests of matters of reasonable public concern. Rather, it can merely disclose the regulatory limits justified under constitutional law.

In this context, the question arises how important human dignity (Art. 1 Para. 1 GG) and the right to life (Art. 2 Para. 2 GG) attributed to embryos *in vitro* are. As explained above with respect to the moral status of the embryo – and in view of the fact that this matter has not yet been clarified by the German Federal Constitutional Court to date[121] – this question is controversial in the constitutional law literature.[122] Legal scholars, however, agree that the ESchG does not accurately reflect the demands of the constitution.[123] It is already being debated whether human life in its earliest forms prior to implantation can even be viewed as having a personal right to human dignity. Some also doubt whether – assuming indeed that such a right exists – the procedures and treatments under evaluation constitute a violation of human dignity within the meaning of humiliation, disparagement, branding, stigmatisation, etc.[124] Taking into consideration the state's duties to protect – which include its obligations to protect life and physical integrity, the health of pregnant women, future children, and people with potentially treatable diseases – research on surplus embryos, which would otherwise be discarded or indefinitely cryopreserved, is not by any means excluded under constitutional law.[125]

119 For example, BVerfGE 49, 89 (126ff.) = NJW 1979, 359; BVerfGE 34, 165 (192ff.) = NJW 1973, 133.

120 BVerfGE 28, 243, 261 (on the conflict between the mandatory enlistment for military service and the freedom of conscience, which is also not subject to a power of restriction).

121 The notion that not only unborn (prenatal) human life, but also early, embryonic human life prior to implantation has a personal right to the guarantee of human dignity cannot, in any event, be based on the judicature of the German Federal Constitutional Court. This is because both relevant decisions (BVerfGE 39, 1, 37; 88, 203, 251ff.) were expressly restricted to the stage following implantation and individuation, see 4.1 above.

122 For more on the now boundless body of work on the topic, see Taupitz (2014), Section 8 margin number 4.

123 Taupitz (2014), B. I. margin number 5.

124 Dreier (2013), Art. 1 Para. 1 margin number 98.

125 Dreier (2013), Art. 1 Para. 1 margin number 98 with further substantiation.

This applies at least in those cases where the parents, on the basis of their own rights to act and choose as they see fit, provide their free and informed consent for the embryos created with their gametes to be used in research. In light of this – and given the lack of other options for these embryos – many people believe that permitting research on surplus embryos is not only moral, but is also above all justifiable under constitutional law.[126] The production of embryos specifically for research purposes is viewed more critically, however. Nevertheless, opinions here are also influenced heavily by the controversial question of whether embryos prior to implantation should be afforded the same rights to life and dignity.

5.4 Examples of the regulation of critical areas of research in Germany

Even though Germany does not currently have an institution comparable to the United Kingdom's Human Fertilisation and Embryology Authority (HFEA) (see Box 4), there are many examples of institutions which examine ethically complex research questions in interdisciplinary bodies, and which check whether research projects are permitted under the applicable laws. One such institution is the Central Ethics Committee for Stem Cell Research (ZES), which was founded on 1 July 2002 when the StZG came into force.[127] The ZES is affiliated with the Robert Koch Institute (RKI) and is comprised of members from the fields of theology, ethics, biology and medicine serving in an honorary capacity. The committee's task is to review and assess applications for conducting research on human embryonic stem cells based on the provisions of the StZG. The key criteria against which the applications are assessed include whether the research objectives are of outstanding interest, the need to use human embryonic stem cells to meet these objectives and – with this in mind – the ethical justifiability of the research projects. The ZES makes its work very transparent, and its annual reports can be viewed on the Robert Koch Institute's website.[128] The German federal government also regularly publishes reports on the application of the StZG.[129]

Another similar institution is the Central Committee on Biological Safety (ZKBS).[130] It is responsible for evaluating the production and treatment of genetically modified organisms. Part of this work includes providing safety ratings for genetic engineering operations. The committee's members, who work on an honorary basis and comprise scientists from other relevant fields as well as representatives of community groups, prepare statements and conduct risk assessments for the competent authorities. The

126 Dreier (2013), Art. 1 Para. 1 margin number 99.

127 On this and the following: https://www.rki.de/DE/Content/Kommissionen/ZES/zes_node.html.

128 See, for example: https://www.rki.de/DE/Content/Kommissionen/ZES/Taetigkeitsberichte/16-taetigkeitsbericht.pdf?__blob=publicationFile.

129 See, for example: http://dip21.bundestag.de/dip21/btd/19/100/1910060.pdf.

130 On the following: https://www.zkbs-online.de/ZKBS/DE/Home/home_node.html.

ZKBS's administrative office is located at the Federal Office of Consumer Protection and Food Safety (BVL). Like the ZES, the ZKBS works very transparently and publishes annual activity reports which provide information on its members and operations.[131]

Germany also has efficient structures in place for monitoring research on human participants involving the use of medicinal products, medical devices, radioactive substances and/or ionising radiation.[132] In each of these cases, research is subject to regulatory approval and the consent of an interdisciplinary ethics committee under the relevant laws (the German Medicinal Products Act – *Arzneimittelgesetz,* AMG, the German Medical Devices Act – *Medizinproduktegesetz,* MPG, and the German Radiation Protection Act – *Strahlenschutzgesetz,* StrlSchG). The ethics committee assesses the ethical and legal aspects of each research project against specific legal requirements. In addition to these specially regulated areas, medical professionals are required by the laws governing their profession to consult an ethics committee operating under public law if they are involved in research projects which affect a person's psychological or physical integrity, or which use data or materials from the human body. The same applies to legally permissible research using vital human gametes and living embryonic tissue. The Association of Medical Ethics Committees (AKEK) is responsible for ensuring a certain level of standardisation among evaluation practices in Germany.[133]

In light of these long-standing positive experiences with committees for evaluating critical areas of research, there is every reason to believe that a comparable institution could be effective at evaluating research on human embryos and ensure that the research objectives are of outstanding interest and legitimate, making the entire process transparent to society at large.

131 See https://www.zkbs-online.de/ZKBS/DE/UeberZKBS/Taetigkeitsberichte/taetigkeitsberichte_node.html.

132 Laufs et al., margin number 12ff., 109ff.

133 Cf. https://www.ak-med-ethik-komm.de/index.php?lang=de.

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