THE ETHICS OF CREATING HUMAN EMBRYOS FOR RESEARCH ON ARTIFICAL GAMETES

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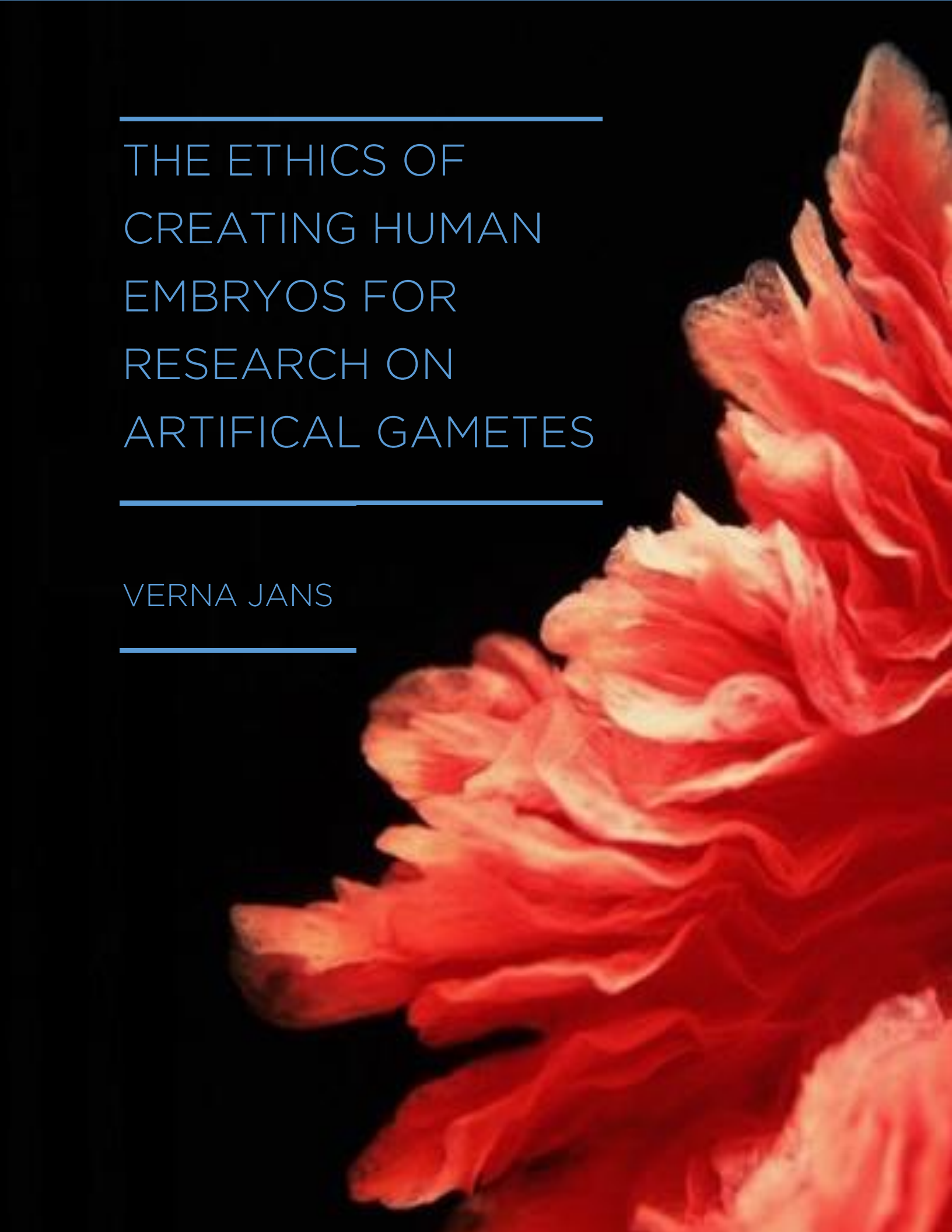

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The ethics of creating human embryos for research for the responsible introduction of artificial gametes in clinical practice

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ABSTRACT

An emerging technique in the field of assisted reproductive technologies is the use of stem-cell-derived (SCD) gametes. In the future, this technique may be used as a fertility treatment for those presently dependent on reproduction using donor gametes. History shows that all too often, assisted reproductive technologies are introduced into clinical practice on a trial and error basis. Therefore, the possible introduction of SCD gametes in medically assisted reproduction raises the question how, for this technology, the step to the clinic can be made responsibly. One element of improving assisted reproductive technology research is to systematically perform preclinical human embryo research (under the condition that it can provide additional safety information that would reduce the gap between animal studies and the first use of a new technology in humans). While some assisted reproductive technologies can be investigated using leftover embryos after IVF procedures, research on stem-cell-derived gametes can only be performed with specifically created research embryos. However, the creation of human embryos for research is regarded as morally problematic because of concerns on the moral status or value of human embryos, and/or to the risk that women will be pressured into donating oocytes against their best interest. This thesis answers the question if and how the creation of human embryos for safety research can be ethically justified, in particular in safety research concerning the responsible introduction of SCD gametes in clinical practice Using the method of wide reflective equilibrium, I argue that the creation of embryos for research can be justified, if the requirements of the principles of proportionality (meaning the research has a morally important aim) and subsidiarity (meaning the research cannot be performed with less invasive means) are met. My stance is that this is the case in embryo research concerning the responsible introduction of SCD gametes into clinical practice. Therefore, my conclusion is that the creation of human embryos for safety research concerning the responsible introduction of SCD gametes in clinical practice can be justified.

Keywords: ethics, embryo research, assisted reproductive technology, artificial gametes, stem-cell-derived gametes

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CHAPTER 1
INTRODUCTION

1.1. SCD Gametes

Current stem cell research suggests that it may be possible in the future to create eggs and sperm from human pluripotent stem cells (K. Hayashi et al., 2012; K. Hayashi, Ohta, Kurimoto, Aramaki, & Saitou, 2011; Katsuhiko Hayashi & Saitou, 2013; Marques-Mari, Lacham-Kaplan, Medrano, Pellicer, & Simón, 2009). These new cells are called Stem-Cell-Derived (SCD) gametes, otherwise referred to as artificial gametes. In contrast to what 'artificial' might suggest, these gametes are completely made out of natural body tissue. For example, gametes can be created out of skin cells. The 'artificial' element in this case, refers to the action of differentiating pluripotent stem cells to gametes.

As a new assisted reproductive technology (ART), the use of these SCD gametes would make it possible to treat several forms of infertility and would thus make donor conception redundant. To give an example, from e.g. skin cells, taken from an infertile man, pluripotent stem cells could be made, which could in turn be differentiated into sperm cells and thereafter used to fertilize an egg cell of his partner. In contrast to conception with the use of donor gametes, the conceived child would be genetically related to both parents.

Additionally, if some serious issues could be overcome, it could give same-sex couples a method to create children of which they are both a biological parent. This would mean that, for example, in a case of an all-male couple, an SCD egg cell can be created from a pluripotent cell from one of the men. The SCD gamete will thereafter be used to fertilize the naturally conceived sperm cell from the other man. However, this is more complicated then with heterosexual couples, because the derivation of oocytes from an XY stem line or even more problematic; sperm from an XX stem line, is more likely to have chromosomal problems than derivation of a sex cell from the same sex (de Sutter et al., 2015).

Although the development of SCD gametes is still at a research stage, current research suggests medically assisted reproduction using SCD-gametes is a possible scenario (particularly

for heterosexual couples) in the near to midterm future (Hendriks, Dancet, van Pelt, Hamer, & Repping, 2015). This raises the question if and how SCD gametes should be safely introduced in clinical practice. This thesis will focus on one element of safety research on SCD gametes; embryo research. The main question will be if and how the creation of human embryos[1] for safety research can be ethically justified, in particular in safety research concerning the responsible introduction of SCD gametes in clinical practice.

1.2. Background of the problem

Several authors have pointed out that all too often, the introduction of new ARTs has in the past taken place on a trial and error basis (Dondorp & de Wert, 2011; Harper, Magli, Lundin, Barratt, & Brison, 2012; Provoost et al., 2014; Van Steirteghem, 2008). According to André van Steirteghem, Editor-in-chief of *Human Reproduction*, "the recent history of reproductive medicine indicates that very few, if any, new developments have been introduced into clinical practice after thorough and rigorous clinical validation" (Van Steirteghem, 2008). Examples of innovations that have been introduced in clinical practice without much preclinical research into their effectiveness and safety are cryopreservation of embryos, ICSI, ooplasm transfer and most recently oocyte vitrification (Dondorp & de Wert, 2011). Also, in the light of the health interests of children conceived through these technologies, more research has to be performed on the possible health impacts of new reproductive technologies before they are made available for patients (Dondorp & de Wert, 2011; Pennings et al., 2007).

Similarly, Joyce Harper, expert on human genetics and embryology, argued that there are many ARTs that have been introduced in clinical practice without sufficient safety research (Harper et al., 2012). In the case of IVF for example, "developments of IVF treatments are often both money and patient-driven and the necessary research is not conducted or is conducted after the procedure has been introduced into the clinical setting" (Harper et al., 2012, p. 305). Also, "the introduction of ICSI was a revolution in reproductive medicine but was introduced into clinical practice without any proof of safety" (Harper et al., 2012, p. 309).

Apparently, the introduction of ARTs in clinical practice often lacks (sufficient) research on their effectiveness and safety. Therefore, ART research should be improved. Although there are several good recommendations to improve research on the effectiveness and safety of ARTs

[1] For economy's sake I use the term 'embryo' as a shorthand for 'human embryo' throughout this thesis

(ACOG, 2006a; ASRM, 2014; Pennings et al., 2007), these are most of the time not followed in practice. This can have various reasons, such as patients pressuring to introduce the treatment, the desire to receive money from patients at the earliest convenience, or ethical and legal issues withholding research. Without appropriate safety and effectiveness research it would be irresponsible towards patens and potential children to introduce new ARTs. This means that also safety and effectiveness research for the responsible introduction for SCD gametes into clinical practice needs improvement.

1.3. Embryo research as a possible element of safety research

European Society of Human Reproduction and Embryology (ESHRE) suggests that appropriate ART research would have to consists out of a threefold of steps (Pennings et al., 2007). It needs to start with preclinical research in animal models, then to use human preimplantation embryos for additional research and last to make sure that clinical studies are performed with collecting sufficient data about effectiveness and safety (Dondorp & de Wert, 2011). This thesis will focus on the second step; embryo research.

Embryo research can be the step between animal studies and actually using SCD gametes in clinical practice, which would decrease the yet unknown safety risks for patients in clinical practice (Dondorp & de Wert, 2011; Hinxton, 2008; Pennings et al., 2007). Of course, inserting embryo research as a step in the chain of safety procedures is only a good idea when it is expected that it would actually contribute relevant and useful information on the safety of the technology. In a consensus statement, scientists working on the development of SCD gametes have suggested that such preclinical safety studies using embryos would indeed be an important condition for the responsible introduction of this new technology (Hinxton, 2008). To perform such research on embryos, would mean that instead of transferring the SCD embryos to the womb of a woman, they would be subjected to research. All cells will be taken apart to analyze several biological processes, like mitoses and several forms of (epi-)genetic expression which are relevant for the normal development of the embryo. Subjecting the embryos to research would thus mean to destroy them.

1.3.1. The ethics of embryo research

Although research has argued that using embryos for safety research can be of significant importance, it nevertheless leads to several ethical issues. The first issue questions if the use of embryos for research is actually acceptable. Because the benefit of performing safety research should be balanced against the harm of using embryos, it is key to define the moral status of the embryo. To define the moral status of the embryo is important, because the higher the moral status of an embryo is considered, the greater the benefits that would be necessary to justify the use of the embryo.

The Health Council of the Netherlands identified three views considering the moral status of the embryo (Gezondheidsraad, 1998, p. 60). According to the first view, the moral status of the embryo is the same as the moral status of a grown human being. Therefore, embryos should be protected at the same level as grown human beings should be protected (Gezondheidsraad, 1998, pp. 60-61). Another view argues that embryos do not have a moral status on which ground they should be protected. They should not be treated any differently than the gametes from which they derive. A third view considers embryos to have a limited worth of protection. This view does not consider the embryo a human being, but still thinks that there can be granted moral relevance because the embryo can grow into a human being. Thus, the embryo does have a moral status, however this status is not equal to the moral status of a grown human. Often, it is added that the worth of protection increases the more the embryo develops (Gezondheidsraad, 1998, pp. 61-62). Following this view, it can be argued that embryo research can be justified if the research (and the way of conducting the research) is commensurable with the embryo's limited moral status.

There is a lack of consensus on the acceptability of embryo research at European level (ESHRE, 2001). It has been suggested that the beliefs on the moral status of the embryo and embryo research are often shaped by several cultural traditions, such as scientific advances in biology and medicine, and especially by religion (Pardo & Calvo, 2008). However, several commentators argue that there is actually a broad consensus on the relatively low moral status of the embryo, because the justification of IVF in many European countries presupposes such a limited moral status (Devolder, 2005; Dondorp & de Wert, 2007).

1.3.2. The ethics of creating embryos for research

If embryo research would be considered acceptable, would it also be justifiable to create embryos for the purpose of research? Currently, in most countries in Europe, including the Netherlands[2], the creation of embryos for research is not allowed. The use of spare embryos (leftover embryos after IVF treatment) is in most countries authorized. However, for safety research on SCD gametes, the creation of embryos is necessary. The safety of using SCD gametes can only be investigated in embryos developed by using SCD gametes. This means that safety research cannot use spare embryos that stem from IVF, and that will therefore not be made using SCD gametes. If embryo research is argued for to be a contribution to safety, then what are the arguments for prohibiting it? Moreover, do the moral arguments behind the legal prohibition weigh up against the predicted improvement of safety research?

I argue that the moral debate on the creation of embryos for research focuses on whether a moral difference can be made between using spare embryos for research and creating research embryos. If there is no moral difference between using spare and creating research embryos, it could be argued that the creation of research embryos should be allowed just like the use of spare embryos is. This issue has been a longstanding topic of debate in the field of embryo research, whereby one position uses the distinction to defend the prohibition on research embryos (FitzPatrick, 2003; Murphy, 2012; van Beers, 2016), while others argues that such moral distinction is invalid (Brock, 2010; Devolder, 2005, 2013).

1.3.3. The ethics of donor egg cells

The creation of embryos does not only cause ethical issues concerning embryos, but also concerning women. To create embryos for research, a great amount of gametes is needed. Sperm cells are relatively easy to acquire, but egg cells are much more difficult to obtain. Several authors have argued that the need for oocyte donors can increase the risk of coercion and exploitation of women, since oocyte donors have to undergo hormone therapy and an invasive IVF procedure without receiving any physical, personal or financial benefits (Baylis, 2000; Gerrand, 1993). Moreover, the need for egg donation can threat women´s autonomy (Gerrand,

[2] However, Dutch Minister Schippers has recently suggested, in reaction to the Pallas report (Eeuwijk, Kochems, van den Bosch, & Smilde-van den Doel, 2015), to broaden the current embryo law. This means that the creation of embryos for 'very important 'research purposes would be allowed in The Netherlands. An example of such 'very important' research, would be specific research concerning infertility, assisted reproductive technologies and hereditary or congenital disorders (Schippers, 2016).

1993). Because the long-term effects of IVF are not fully understood yet, it is impossible for women to make a fully informed choice about egg donation (Brison, Roberts, & Kimber, 2013; Gerrand, 1993).

Additionally, it has been argued that ARTs can cause several social concerns, such as the possibility that women would be perceived as just reproductive vessels (Arditti, Klein, & Minden, 1984; Corea, 1985; Rowland, 1992). When women are used for harvesting eggs in order to create embryos for research, this could lead to exploitation of women (Dickenson, 2002; Gerrand, 1993)

1.4. Embryo research on SCD gametes

Although it is argued that embryo research is important in the responsible introduction of SCD gametes in clinical practice (De Rycke, Liebaers, & Van Steirteghem, 2002; Eeuwijk et al., 2015; Gezondheidsraad, 1998; Hinxton, 2008; ZonMw, 2012) literature on the moral justification of embryo research on SCD gametes in specific is lacking. Under the condition that embryo research is useful and the creation of embryos is acceptable for safety research on several ARTs, can the creation of embryos also be justified for the purpose of safety research on SCD gametes? Therefore, the possible justification of research embryos for the purpose of safety research on SCD gametes in specific should be investigated.

Two conditions under which the creation of embryos for research on artificial gametes could be justified are proportionality and subsidiarity (Isasi & Knoppers, 2006). To meet the proportionality condition would mean that the importance of the development of SCD gametes and the profit of embryo research weights up against the harm involved in the destruction of embryos. To meet the subsidiarity principle, it would mean that the knowledge that embryo research would provide cannot be performed with spare embryos or other research methods.

1.5. Roadmap

This thesis will investigate the ethical arguments that are made regarding the creation of embryos for research. The main research question will be if the creation of embryos for safety research can be ethically justified, in particular in safety research concerning the responsible introduction of SCD gametes in clinical practice. I will start with examining the current research in the ART field. It will be argued that there are shortcomings considering the safety of introducing ARTs in

clinical practice. Second, I will examine SCD gametes and its safety research. An introduction on SCD gametes will be given. I will investigate its safety research and examine what embryo research on artificial gametes would mean and why it is recommended. Thereafter, the ethical perspectives on embryo research will be analyzed. I will first briefly analyze the current moral perspectives on embryo research. After that, I will focus on the arguments considering the distinction between spare embryos and research embryos. Then, the moral implications of egg cell donation will be investigated. In the following chapter, the arguments on embryo research in general will be assessed and consequently be applied to SCD gametes in specific. The aim is to examine if the creation of research embryos for safety research on SCD gametes can be justified.

1.6. Method

1.6.1. Literature Research

For this thesis, English and Dutch journal articles have been selected, the majority of which is published in the last twenty years. This thesis aims to perform a normative ethical assessment in the field of ART and embryo research. Therefore, literature is chosen from mainly scientific journals focusing on normative aspects of biotechnology, ARTs and embryo research. This means that alternative approaches to examine the justifiability of embryo research have not been taken into account extensively. For example, approaches concerning the effect of social, political and cultural values on technological innovation and their effect on society, politics and culture are not widely expanded.

1.6.2. Wide Reflective Equilibrium

To investigate the possible justification of embryo research on artificial gametes, I will make use of *Wide Reflective Equilibrium* (WRE) (Daniels, 1979, 2011; Rawls, 1971). This procedural ethical approach (and at the same time a theory) is developed by John Rawls (Rawls, 1971) and later interpreted by Norman Daniels (Daniels, 1979, 2011). In Rawls' *A theory of Justice* (Rawls, 1971), Rawls proposes that we can only determine what principles of justice we should adopt by broadening our circle of beliefs, on condition that this circle is coherent. This means that WRE does not take an extreme position or gives authority to certain moral theories or empirical data, but includes a wide range of moral theories and empirical data in order to reach a normative conclusion (Molewijk, Stiggelbout, Otten, Dupuis, & Kievit, 2004). Rawls argues that we should

include intuitions, normative frameworks and background theories in the assessment. Examples of such theories, or crucial beliefs, concern the nature of persons, psychology or beliefs about justice (Daniels, 2011). In later work from Rawls, he emphasizes that WRE is not an account of truth, but only of justification (Rawls, 1993).

The advantage of using WRE is that it enables me to evaluate moral judgements in a broader field of moral principles and background theories on embryo research (Daniels, 2011). By including a broad range of considerations, WRE distinguishes itself from more foundationalist approaches, such as consequentialist ethics and deontology, which only focus on a narrow range of particular cases and moral principles. With 'foundationalist', I mean that such approaches are based on an account of morality as rooted in what are claimed to be universally valid rules, or in a universally valid understanding of the meaning of moral terms (e.g. categorical imperative, hedons over dolors, etc.). In contrary to WRE, foundationalist approaches do not take practice-based principles and intuitions into account, which leads to an ethical assessment distancing itself from current practice. Since the described ethical debate on embryo research is so closely connected to scientific and medical practice, it is important to take all (practice-based) considerations into account. Therefore, WRE is a better fit to the ethical assessment of this thesis than the rather narrow foundationalist approaches. WRE makes it is possible to include all possible moral theories in the assessment without leaving important elements out. This means that e.g. the moral value of the embryo and theories on personhood as well as the consequences of safety research are part of the evaluation.

Furthermore, the outcome of the procedure of WRE is in all cases fair to all parties, because it is the result of a procedure of which the considerations of all parties have been taken into account (Rawls, 1971, p. 104; 1993, p. 72). Instead of evaluating ethical issues in terms of a foundationalist framework, WRE examines the consistency of ethical arguments within the overall ´equilibrium´ of intuitions and theories and supplements arguments with general practice-based principles and intuitions. It is important that the considerations of all relevant actors are involved, which is called the *inclusiveness criterion* (Doorn, 2011, p. 76). Since the considerations of all parties are included in the ethical assessment, the result of the WRE procedure is fair to all parties. This is called *pure procedural justice*: "what is just is specified by the outcome of the procedure, whatever that is" (Doorn, 2011, p. 70). WRE is therefore ideal to

reach moral agreement between various parties in ethical diverging debates such as the debate I identified on embryo research.

Additionally, by using WRE, it is possible to distinguish moral disagreements from disagreements resting on non-moral disagreements, such as background theories. Disagreements about background theories are more tractable than disagreements about moral judgements or principles (Daniels, 1979). For example, the moral disagreements concerning the use of embryos for research rest on several background theories, such as theories concerning personhood and potentiality. WRE enables us to understand the reasons behind considerations in people's arguments (Daniels, 1979).

The WRE assessment of this thesis will include considerations on research embryos in general as well as on the supposed distinction between spare embryos and research embryos and the moral concerns on oocyte donation. In chapter four, I will first study different ethical perspectives on embryo research and discuss their adequacy to deliberate ethical questions on the creation of embryos for safety research. These views include the moral status of the embryo and the difference it makes to evaluating if embryos could be used for safety research. Furthermore, the difference between using spare embryos and the creation of embryos for research will be examined. Additionally, I will study the moral implications of egg cell donation, focusing on the risk of exploitation of women. In chapter five, I will first explain the procedural method of WRE. Thereafter, I will apply WRE to assess the arguments on the creation of embryos for research, in particular on SCD gametes, by evaluating their consistency with the broader ethical intuitions, principles and theories that I will examine. In addition to considering the ethical acceptability both of embryo research as such and of the creation of embryos for research, I will focus on the principles of proportionality and subsidiarity, because they enable me to evaluate if embryo research can be justified on SCD gametes research in particular.

CHAPTER 2
ASSISTED REPRODUCTIVE TECHNOLOGY AND SAFETY RESEARCH

Many ARTs are introduced into clinical practice without sufficient safety research. Several authors have pointed out that all too often, the introduction of new ARTs has in the past taken place on a trial and error basis (Brison et al., 2013; Dondorp & de Wert, 2011; Harper et al., 2012; Pennings et al., 2007; Provoost et al., 2014; Van Steirteghem, 2008). This means that the research that is necessary to examine the safety of a technology is often not performed before introducing it into clinical practice.

In the light of the health interests of children conceived through these technologies, as well as of the health interests for the parents, current safety research should be improved. Pointed out by the European Society of Human Reproduction and embryology (ESHRE), "Technology and research must always be subordinate to the welfare of the future offspring" (Pennings et al., 2007, p. 2587). Sadly, history shows that new ARTs were (and are) regularly introduced without such subordination. Therefore, in this chapter, I will first investigate three examples of ART safety research. Thereafter, I will examine what the current recommendations on ART innovation are, and last, I will show that these recommendations are generally not followed in practice.

2.1. The lack of safety research on ARTs in today's clinical practice

2.1.1. In Vitro Fertilization

One of the ARTs that are used in clinical practice is *in vitro* fertilization (IVF). IVF is a procedure where the egg cell of a woman is fertilized by a sperm cell outside the woman's body. *In Vitro*, which means "in glass", refers to the early biological experiments that were performed in glass containers, like petri dishes or test tubes. Nowadays, it refers to any biological procedure that is performed outside the organic body, which originally occurs inside the organic body. The

treatment is often used when women cannot (easily) get pregnant. This has several possible causes, such as hormonal dysfunctions or closed or removed oviducts of the woman, or deviations in the production or ejaculation of the sperm of the man.

In IVF procedures, one egg cell and multiple sperm cells are brought together in a laboratory, completely outside the body. The procedure consists of several steps. First, the woman is given fertility drugs to increase her egg production. Whereas a woman normally produces one egg a month, these drugs enable her to produce several eggs. Thereafter, all of the women's eggs are removed from their ovary with a long, thin needle. Then, the eggs with the best quality are brought together with sperm cells in the laboratory to allow the fertilization process to start. The ensuing embryo development will be monitored for several days. After successful fertilization the resulting zygote starts a process of cell division. Three or five days later, the resulting embryos will be selected for transfer to the uterus of the woman. If an embryo implants in the lining of the womb of a woman and grows, this results in pregnancy. Unless a priori chances that the procedure will lead to a child are low, only one embryo is placed into the womb of the woman at the same time. This policy aims to reduce the risk of twins and to avoid higher multiples as much as possible, given that multiple pregnancies have a higher rate of complications and outcomes (such as preterm birth, low birthweight) that may also affect the long term health of the child. Good quality embryos that are not used in the same cycle may be frozen for use in a next attempt or for donation, either to other infertile couples or to scientific research (Goldberg, Falcone, & Attaran, 2007).

In the mid-seventies, when IVF was not yet successfully used in humans, it was proposed that the safety of IVF methods should first be sufficiently verified in monkeys before exposing it to women (Dondorp & de Wert, 2011, p. 2). Despite this recommendation, those working on the technology thought that such research would be too expensive and time consuming. John Biggers, who made a great contribution with mouse research on IVF, said during an interview on an early debate on possible funding of clinical IVF: "I knew enough about working with monkey embryos to state that the order of fifty years would be needed to get these answers using monkeys, as well as the need of enormous expenditure of research money. I felt that we already had enough information to proceed with caution"(Summers & Racowsky, 2008).

Some years earlier, in 1971, Cambridge physiologist Robert Edwards and Oldham gynecologist Patrick Steptoe applied for long-term funding from the British Medical Research

Council (MRC) for a program of scientific and clinical 'Studies on Human Reproduction'. Their application was rejected because the MRC did not consider infertility high priority and set the bar for safety very high (Johnson, Franklin, Cottingham, & Hopwood, 2010). Alternative funding came from private donors leading to further experimentation as a result of which in 1978 the first IVF baby, Louise Brown, was born. Instead of performing systematic research like the rejected application aimed at, the research was rather performed as innovative treatment (Dondorp & de Wert, 2011, p. 3). After the birth of Louise Brown and another healthy baby, the MRC changed its viewpoint and started to support IVF enthusiastically (Johnson et al., 2010).

Both cases describe the trial and error introduction of IVF and seem to support the view of Joyce Harper, who argues that "developments of IVF treatments are often both money and patient-driven and the necessary research is not conducted or is conducted after the procedure has been introduced into the clinical setting" (Harper et al., 2012, p. 305). As shown in the first example, additional safety research was considered 'too expensive' and 'too time-consuming'. Therefore, research was mainly performed with mouse models. Jason Biggers declined the recommendation to perform monkey research for these reasons. In the second example, the MRC first supported a high standard for safety research and therefore declined the application of Edwards and Steptoe. However, when the project continued with private funding and two patients were given healthy babies, the council suddenly started to support IVF. In both cases, the safety research that some considered necessary was not performed before introducing IVF as a treatment.

2.1.2. Intracytoplasmic Sperm Injection

Another ART used in clinical practice is intracytoplasmic sperm injection (ICSI). ICSI is an assisted reproductive method whereby one sperm cell is directly injected into an egg cell. The treatment was first used in cases of severe male infertility where the sperm is of low quality and/or quantity. The procedure is also used in cases where IVF is combined with preimplantation genetic diagnosis (PGD) and in many centers worldwide more generally as a substitute for classical IVF.

Technically, ICSI is an addition to the normal IVF treatment. Instead of bringing eggs and sperm together, one sperm cell is ejected into one egg cell *in vitro*. A normally build, moving sperm cell is isolated and its tail is made immotile. The egg cells are also investigated with a

microscope and their cumulus cells (collection of cells around a mature egg cell) are removed. After preparing both gametes, the sperm cell is injected in the egg cell.

An early form of ICSI was developed in 1962, where sea urchin sperm was microinjected into sea urchin eggs by a research team led by Hiramoto (Hiramoto, 1962). In the 1970s and 1980s, this method was developed in rodents. However, in rodents as well as in larger animals such as the bovine later on, it resulted in a low pregnancy rate (Goto, 1993; Keefer, 1989; Thadani, 1979). Despite these low pregnancy rates in animal models, a similar technique, subzonal injection (SUZI), was discovered by research in humans. Although SUZI led to a human pregnancy in 1988 (S. C. Ng et al., 1988), the technique was very quickly replaced by a more promising treatment: ICSI. ICSI was applied in humans in 1988, which resulted in the first reported human ICSI pregnancy in 1992 (Lanzendorf et al., 1988; Palermo, Joris, Devroey, & Van Steirteghem, 1992). Thereafter, the majority of fertility centers adopted ICSI (Harper et al., 2012, p. 305). ICSI can be performed in three different forms. The first form is as we use ICSI regularly today, by injecting ejaculated sperm into an egg cell. The other two forms, MESA and TESE, consist of medically extracting sperm from the epididymis or testicles. In 1996, Dutch IVF professionals decided to withdraw MESA and TESE from clinical application because of the lack of safety evidence and effectiveness in humans. The Minister of Health asked the Health Council to advice on the matter. The Council concluded that animal research was needed to provide sufficient evidence of safety. Because 'regular' ICSI was already successfully applied to humans that much, it remained allowed in clinical practice, but under strict conditions (Gezondheidsraad, 1996).

At the time, there was no adequate animal model to investigate the safety of ICSI, but the technique was introduced into clinical practice anyhow. This means that with the introduction of ICSI, hardly any adequate safety research was performed and if any precaution was taken, it "was to prepare a specific informed consent to make patients aware of the lack of data supporting the safety of this micromanipulation technique" (Harper et al., 2012, p. 305). This means that the clinicians were aware of the lack of safety evidence at that time. Considering the fact that there was so little safety proof at that moment, it would have been better if "more basic research and follow-up studies in the embryo, such as monitoring development and analysis of aneuploidy, metabolism and methylation and paediatric follow-ups…" were performed (Harper et al., 2012, p. 305).

2.1.3. Mitochondrial Supplementation / Augment treatment

If anyone might think that trial-and-error safety research is only a matter of the past, he or she could not be more mistaken. In December 2014, the US company OvaScience announced that they would introduce their new treatment, 'Augment', commercially. This mitochondrial supplementation treatment would enable older women to supplement the energy of their egg cells and improve pregnancy chances when previous IVF treatment is failing.

The *Augment* treatment consists of extracting mitochondria (which generate the energy of a cell) from the ovarian stem cells of a woman and injecting them during IVF into her own egg cells. This means that before fertilization, the woman has to undergo an ovarian biopsy. Here, pieces of the ovary's outer layer are extracted. In this tissue reside ovarian stem cells that are harvested, counted and frozen. When the egg cell is retrieved, the mitochondria of the ovarian cells are isolated from the thawed stem cells. Thereafter they are prepared and injected in the egg cell during IVF together with the sperm (Motluk, 2015). The treatment uses techniques that are similar to IVF and ICSI, although the insertion of the woman´s own mitochondria into her egg cell is a relatively new element to the 'traditional' treatments. The technique is a variant of an older technique that used donor mitochondria. The older technique was however not continued, because of the lack of safety research. (Fakih et al., 2015).

Regarding the success and safety of Augment, Michael Fakih, owner of one of the few centers that offers *Augment* treatment, and his team, argue in an article on the treatment that "the support and use of the *Augment* treatment is based upon case reports of clinical success using human donor egg cytoplasm injection as well as multiple published animal studies that have demonstrated that the addition of mitochondria during IVF treatment is safe, improves the quality of the embryos, and increases the success of IVF". This seems however a very weak claim, because the research they refer to considers a similar, but different technique to perform the same treatment as the 'new' technique. This technique was first practiced in the 1990s and was introduced into clinical practice without safety research. It consisted of using the cytoplasm (where the mitochondria are located) of young, healthy, donor eggs and injecting that into patient's egg cells to improve the quality of the egg and embryo. Although 50 babies were born, the treatment was not continued because more research on the safety of the technique was required (Fakih et al., 2015). The safety and success of *Augment* is thus based on the cytoplasm

treatment of the 90's, which is first; a different technique than *Augment* uses, and second; has been argued for that it needed more study.

Apparently, *Augment* builds its safety evidence on the fact that 50 babies without significant deviations were born after the old treatment. However, the lack of safety research remains a fact. The old treatment that the developers of *Augment* refer to has been proven to not guarantee sufficient evidence of safety. This means that the old treatment cannot be used to serve as safety evidence for the new treatment. First of all, the research performed on humans concerned ooplasmic transplantation (J. Cohen et al., 1998), which differs from the technique used in Augment. In a case of ooplasmic transfer, ooplasm from the eggs of a donor are injected into the eggs of the patient. The injected egg is then fertilized with sperm and implanted into the womb of the patient. This is different from the process the contemporary *Augment* treatment entails. It is therefore insufficient to use this example to argue for the safety of the *Augment* treatment. Furthermore, the same study concerns treatment with egg cell donors, whereby the *Augment* treatment concerns tissue from the patient herself.

Then, in the case of animal studies, the reference Fakih uses only refers to unpublished animal studies. Apparently, although *Augment* treatment was introduced commercially in 2015 (Fakih et al., 2015), it was not until a year later, in 2016, that animal research in pigs suggested that the treatment might actually be successful and safe (Cagnone et al., 2016).

Last, what is maybe most surprising, is the fact that the research Fakih refers to concludes with: "In our opinion, the presented technology is highly experimental and it would be wise to delay its widespread medical application until further studies in animal models and donated human material indicate the best approaches" (J. Cohen et al., 1998, p. 279). The reason for its delay is the fact that the treatment raised safety concerns to use donor's mitochondria (Motluk, 2015). Although current *Augment* treatment uses the patient's own tissue, this does not mean that all safety dangers regarding the mother and the potential child are automatically avoided. Therefore, *Augment* is forbidden in the United States (Motluk, 2015).

It seems that OvaScience introduced Augment treatment into clinical practice without sufficient evidence on safety or effectiveness. While IVF as well as ICSI had proven their effectiveness, when OvaScience announced that they were introducing the treatment: "No clinical data on efficacy were provided, though they noted that 150 women had been enrolled in

experimental trials at four sites worldwide. These include the Toronto Centre for Advanced Reproductive Technology (TCART) and clinics in London, Istanbul and Dubai" (Motluk, 2015).

The question then remains; why did OvaScience introduce the technology without sufficient safety research? When OvaScience voluntarily suspended their US trial with the Food and Drug Administration (FDA) in September 2013, they claimed that they were not aware that *Augment* treatment needed regulatory approval. They argued that since the treatment consists of injecting a woman's own tissue into her own egg using ICSI, the method is similar to using ICSI with only sperm. Instead of meeting terms with the US regulations, the company decided to move their headquarters to the UK (Motluk, 2015). *Augment* is currently practiced in a few selected clinics in Canada, Panama, Spain, Turkey, the United Arab Emirates, and Japan (OvaScience, 2016).

In relation to the example of IVF, the regulations in this case might also be perceived as 'too' strict by OvaScience, which can explain the company's choice to avoid the regulation issue by moving to another country. Anyhow, it resulted in the fact that there was no to little preclinical testing before introducing it into clinical trial. Also, in relation to ICSI, the developers of *Augment* knew (after the FDA trial) that there was no sufficient safety evidence. Just like in the case of ICSI, researchers ignored the request of the FDA to improve research procedures. Instead of improving their research, they continued their business by moving the treatment to other countries.

2.2. Recommendations

As discussed, several ARTs have been introduced without sufficient preclinical safety research. But as also follow-up studies or clinical practice have been scarce, it is still unclear to what extent fertility treatments may have long term health consequences for mother and child. For the mother, because of the risks of the medical procedure and for the child, because of potential procedure-related abnormalities. According to Michèle Hansen and her team, it is widely acknowledged that "infants conceived following in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are more likely to be born preterm, of low birth weight and to be a twin or higher order multiple than spontaneously conceived infants" (Hansen, Bower, Milne, de Klerk, & Kurinczuk, 2005, p. 328). In their research to find evidence supporting this claim, Hansen et al. found out that indeed infants that are born following ART treatment have an increased risk of

birth defects, in comparison to 'naturally' conceived infants (Hansen et al., 2005, p. 336). Although it is unclear if these abnormalities are a result of the medical procedure or of the subfertility of the parents, it remains a fact that the technologies need more study to investigate the (origin of the) risks. The fact that until now no serious health problems related to fertility treatments have come to light, should not be taken as a ground for complacency. Clearly, introducing new ARTs into clinical practice without adequate safety research, including preclinical studies and long term follow-up, would be irresponsible towards the primary stakeholders: the women exposed to the relevant technologies and the children born as a result.

This section will build further on the argument that safety research in ART should be improved (Dondorp & de Wert, 2011; Harper et al., 2012; Pennings et al., 2007). In medicine there are two forms of innovation; formal research and innovative treatment. Formal research refers to a systematic research process, mostly consisting of preclinical research, clinical trial and follow-up research. Innovative treatment is "what clinicians do when they try something new that has not yet been thoroughly tested in a research setting"(Dondorp & de Wert, 2011, p. 1). This section examines European and American recommendations on both forms of innovation to improve this research.

2.2.1. ESHRE

In 2007, the Task Force on Ethics and Law of the European Society of Human Reproduction and Embryology (ESHRE) published a statement on the welfare of the child in medically assisted reproduction. ESHRE points out that "the widespread adoption of new techniques frequently takes place without the necessary evaluation of their efficacy, effectiveness, safety and social and economic consequences" (p. 2587). This leads to possible risks inherent in the technologies and medical treatments themselves. Therefore, sufficient safety research should be performed to provide the welfare of the child (e.g. preventing malformations), public health (e.g. preventing multiple pregnancies) and to inform potential parents to enable them to make better informed decisions (p. 2587).

To ensure sufficient safety research, four steps are recommended; a) animal studies, b) preclinical embryo research, c) clinical trials and d) follow-up studies. As this thesis concerns embryo research, I will focus on the second step. Preclinical embryo research should be considered where there is reason to believe that such research would enable to study "the

influence of different factors and interventions on the development and growth of the embryo, epigenetic processes, genetic health, etc." (Pennings et al., 2007, p. 2587). If this is the case, then such research is crucial to arrive at a better understanding of the consequences of altering the fertilization process of the embryo, thus reducing the uncertainty inevitably involved in the step from animal research to human experiments. Withholding preclinical embryo research would then mean that women and children are exposed to potentially greater risks than necessary (Pennings et al., 2007, p. 2587). In the light of the need to take account both of the interests of the would-be parents and of the welfare of the future child, this would be morally problematic.

2.2.2. ACOG

The American College of Obstetricians and Gynecologists (ACOG) supports the necessity for safety research on embryos by using another argumentation than ESHRE (ACOG, 2006b). Instead of arguing that such research is necessary because of the welfare of the future child, they argue for its necessity in view of the patients' right to be properly informed about the benefits and risks of medical treatment as part of 'informed consent'. According to them, "in some cases […] innovative practice that appears to be safe and effective may become accepted practice, even if it has never been subjected to formal research and an evidence base has never been developed to support efficacy and safety. When this happens, patients and practitioners are left without the data they need to make adequately informed decisions"(ACOG, 2006a, p. 1590). According to ACOG, research should be performed to make sure that patients and clinicians can be well informed about the treatment they are going to engage with. Without sufficient data on the safety of the treatment, it is not possible to fully provide informed consent. This means that except for the reason to provide a safe treatment to patients, there is also the argument that safety research is necessary to provide informed consent. Without a sufficient evidence base, it is impossible for them to make an informed decision.

Although the introduction of innovative practices and techniques is necessary for medical progress, they should be subjected to systematic formal research in the following conditions; (1)"in the absence of formal research", (2)"without an adequate evidence base" and (3)"without adequate data on the risks and benefits of new treatments" (ACOG, 2006a, p. 1594). The first case addresses the necessity to have data for assessing the risks and benefits. When innovative practices and techniques are introduced without systematic formal research, the data to assess the

risks and benefits are lacking. In the second case, practioners do not have the knowledge to decide if an innovative technique is safe and effective enough to treat their patients. This means that without adequate data practioners cannot make a responsible decision towards their patients. In the last case, patients are unable to make an informed decision without the adequate data. This makes it impossible to provide informed consent (ACOG, 2006a, p. 1594).

For a practioner to decide if innovative practice should be subjected to formal research, one of three criteria should be satisfied. First, when the innovation is significantly different from standard practice. Second, when the innovation has risks that are not known or that do not weigh up against the potential benefits. Last, when the innovation is likely to result in generalizable knowledge and depend on results of formal clinical trials (ACOG, 2006a, p. 1594).

2.2.3. ASRM

The American Society for Reproductive Medicine (ASRM), builds further on the recommendation to perform safety research on embryos. Instead of making recommendations on the necessity of such safety research themselves, they argue that such research should be proven necessary by the investigator. According to them: "In view of the level of interest in embryo and gamete research, this Committee advises that the investigator bears the burden of demonstrating that the proposed studies merit using human gametes or embryos, that there is no adequate alternative research methodology, that the study is likely to yield important scientific or clinical data, that the number of gametes or embryos will be the minimum required for adequate study design, and that risks to donors will be minimized"(ASRM, 2014, p. 333). Furthermore, there always must be an approval from an ethics committee for the research project and informed consent from every prospective participant before any research is performed on his or her donated cells, embryos or tissues (p. 333).

2.3. Recommendations in practice

Although there are several good recommendations on how to safely introduce new ARTs (ACOG, 2006a, 2006b; ASRM, 2014; Pennings et al., 2007), these are often not followed in practice. As seen in the cases of IVF, ICSI and recently *Augment* treatment, recommendations were ignored and the necessary research was not performed. Harper points out that "as time is money, many of these new techniques have not been shown to be safe, to have a clear clinical

benefit and/or not been properly validated. This is a very worrying situation that may become even more common as new technologies are developed" (Harper et al., 2012, p. 303).

Some might argue, that it takes a long time to perform the necessary research and withhold medical development. Systematic formal research can be very time consuming. As seen, time was for Jason Biggers the reason to reject the recommendation to perform research on monkeys (Summers & Racowsky, 2008). Spending more time on research can be very expensive and also means not receiving money from patients during this period. This might also explain why ICSI was introduced despite the failing animal models. Also in the case of *Augment*, OvaScience seemed to introduce the treatment as soon as possible. When the trial would almost hold the company back, it just decided to move and offer their treatment in the countries where regulation did not hold them back. Derived from the fact that OvaScience voluntarily suspended their trial and only provides their treatment in a few selected countries, companies like OvaScience might try to avoid the regulations and move to counties with softer regulations to continue their treatment. The message on their website that their treatment is not offered in all countries due to difference in regulation only supports this (OvaScience, 2016).

Time consuming safety research does not only bring negative financial effects to introducing a technology, but also has to face the pressure of patients. Implementation of innovations is often patient-driven. There can be pressure of patients to introduce the treatment as soon as possible. Especially after positive media attention (Dondorp & de Wert, 2011, p. 4).

In the example of IVF, Edwards' and Steptoe's application was declined by the MRC because the proposed preclinical research could not be ethically justified according to the council. Because the council did not recognize the importance of treating infertility, they set the bar for safety very high. The council wanted Edwards and Steptoe to perform primate studies first and considered their proposed research too 'experimental', since it would subject woman to a still experimental technique (laparoscopy) (Johnson et al., 2010). When their application was denied, Edwards and Steptoe had to rely on private funding, which led to improper safety research. Also in the case of embryo research, it appears that ethical issues withhold proposed research. While embryo research is pleaded for by many authors (Brison et al., 2013; Dondorp & de Wert, 2011; Pennings et al., 2007), it cannot always be sufficiently performed. While the use of spare embryos is accepted by a lot of countries, these embryos cannot always be used, because for some ART research, specially created embryos are needed. In the case of SCD Gametes for

example, embryos need to be created with these artificial gametes to investigate the safety and effectiveness of the technology. This is problematic, because creating embryos for research is in a lot of countries in Europe prohibited. Therefore, it is impossible to perform embryo research on ARTs with specially created embryos in these countries.

However, Harper argues, "with so many examples where data now show that the techniques that have been applied to thousands of patients have no clinical significance […], we have to be fair to the patients" (Harper et al., 2012, p. 309). Without the evidence of the effectivity of a technique, it is irresponsible to subject patients to the safety risks of new treatments. The recommendations from ESHRE, ACOG and ASRM explicitly underline the importance of responsibility towards the patients and future children (ACOG, 2006a, 2006b; ASRM, 2014; Pennings et al., 2007). Although the introduction of IVF and ICSI were very significant in reproductive medicine, both were introduced into clinical practice without any safety evidence. As seen with *Augment* treatment, effectiveness as well as safety were not proven before OvaScience introduced it in several clinics.

In conclusion, while many researchers emphasize the fact that there is a lack of sufficient preclinical research on the safety and effectiveness in ARTs (Brison et al., 2013; Dondorp & de Wert, 2011; Harper et al., 2012; Pennings et al., 2007), the current practice of introducing new technologies generally does not respond to this observation[3]. Although this can have various reasons, responsibly introducing a new technology does need sufficient research on the safety and effectiveness before exposing it to patients. As seen in the introduction of *Augment* treatment, new technologies are, despite all the recommendations, still introduced into clinical practice without sufficient evidence of safety and effectiveness. This means that introducing new ARTs in clinical practice with the current way of safety research procedures would be irresponsible towards would-be parents and potential children. Therefore, safety research procedures should be improved and applied in practice. This concerns also the safety research for the responsible introduction for SCD gametes in specific.

[3] One exception is the introduction of Mitochondrial Replacement Therapy (MRT) in the UK. MRT is subjected to a systematic process of preclinical research and regulation. One important element of regulation considers the restriction to only transferring male embryos. Because the long-term effects of MRT are not known yet, currently transferring only male embryos avoids germ-line issues, since mitochondria are normally inherited exclusively from the mother (National Academies of Sciences Engineering and Medicine, 2016).

CHAPTER 3
STEM-CELL-DERIVED GAMETES

The creation of SCD Gametes is an emerging development in the field of ART. Although the development is still at a research stage, current research suggests medically assisted reproduction using SCD-gametes is a possible scenario (particularly for couples currently dependent on donor gametes for reproduction) in the near to midterm future (Hendriks et al., 2015; Hinxton, 2008; Marques-Mari et al., 2009). In an environment where ARTs are often introduced without sufficient safety research, the possible introduction of SCD gametes in medically assisted reproduction raises the question how this introduction should be safely performed. Therefore, embryo research as a possible element of safety research on SCD Gametes will be investigated. In this chapter I will first discuss the envisaged reproductive application of SCD gametes. Thereafter, I will give an overview of the current state of research. Last, I will investigate the utility of preclinical safety studies using embryos, for which embryos will have to be created from donated gametes.

3.1. Envisaged applications of SCD gametes

As a new ART, SCD gametes can have many applications. One can think of SCD Gametes as a fertility treatment for those presently dependent on reproduction using donor gametes. Furthermore, in addition to reproductive goals, SCD gametes can be useful in research. It has been argued that SCD gametes can help in fundamental research to understand the development of sperm- and egg cells and of early embryos (Hinxton, 2008; ZonMw, 2012).

The introduction of SCD Gametes in medically assisted reproduction would make it possible to treat multiple patient groups facing problems with reproduction. People who were born with a condition that would render them infertile or who became infertile during their lives could be helped with this technique. When ‘traditional’ IVF and ICSI treatments cannot offer a solution to their problems, the use of SCD gametes to produce embryos with those techniques

possibly can. Now, people with such infertility problems are dependent on donor conception. Medically assisted reproduction using SCD gametes would make donor conception redundant. In contrast to conception with the use of donor gametes, the conceived child would be genetically related to both parents (ZonMw, 2012, p. 31). To give an example, from e.g. skin cells taken from an infertile man pluripotent stem cells could be created, which could in turn be differentiated into sperm cells and thereafter used to fertilize an egg cell of his partner. This way, the child would have half of the genetic material of both parents.

An example of another patient group are women and children needing fertility threatening medical interventions. They are now dependent on gamete vitrification and egg- and sperm maturation technologies (Loren et al., 2013). When the medical interventions would cause fertility problems, they could use their preserved gametes. With the introduction of SCD gametes, patient-specific gametes can be created after they are cured (ZonMw, 2012, pp. 31-32). This would mean that gamete preservation would not be necessary anymore, because when the medical intervention would cause fertility problems, SCD gametes could always be created.

Post-menopausal women would also be a potential patient group for SCD gametes. Sometimes women get into menopause at a really young age. This way, they could still have genetically related children. Of course, the age up to where post-menopausal women should be helped to get pregnant is still considered highly debatable (Leridon, 2004; Mertes & Pennings, 2010).

Additionally, if some serious issues could be overcome, it could also give same-sex couples a method to create children of which they are both a biological parent (Mertes & Pennings, 2010; Testa & Harris, 2004, 2005). This would mean that, for example, in a case of an all-male couple, SCD egg cells can be created from a pluripotent cell from one of the men. An SCD egg cell will thereafter be used to fertilize the naturally obtained sperm cell from the other man (ZonMw, 2012). This way, with the help of a surrogate mother, all-male couples can receive their own biologically related child. However, this is more complicated than with heterosexual couples, because the derivation of oocytes (XX) from an XY stem line, or even more problematic sperm cells (XY) from an XX stem line, is more likely to have chromosomal problems than derivation of a sex cell from the same sex (Hinxton, 2008; Mathews et al., 2009; Testa & Harris, 2005).

Also, the use of SCD gametes can improve IVF treatment, because the technique requires in vitro growth and maturation procedures that will make hormone stimulation redundant. In IVF, hormone stimulation is used to make women produce more than one egg cell per cycle, which makes it possible to retrieve more egg cells for treatment. Women who are now dependent on hormone stimulation to undergo IVF treatment, can use SCD gametes to create the necessary amount of grown egg cells.

Another application of SCD gametes would be the ability to make the donation of egg cells for research and therapy redundant. The demand for donor egg cells could put women under pressure to donate (Beeson & Lippman, 2006). The use of SCD gametes could make the argument that the creation of embryos for the purpose of research or therapy would put too much pressure on women less relevant, because the demand of donor egg cells would be decreased (ZonMw, 2012). As for research purposes, researchers would not be dependent on donation of egg cells anymore to perform research with specially created embryos. In stem cell research, the amount of egg cells needed to develop only a small amount of stem cell lines is extremely large (Newson & Smajdor, 2005). If it is possible to create egg cells out of pluripotent stem cells, these 'artificial egg cells' can be used for research purposes (ZonMw, 2012, pp. 29-30). This possibility to obtain a large amount of egg cells, could boost stem cell research and its envisioned applications like treatment of Parkinson's disease or cancers enormously (Newson & Smajdor, 2005).

In addition to research purposes, SCD gametes can thus also be used in therapy for the treatment of e.g. Parkinson's disease or cancers. In each case where non autologous (not derived from the patient's own stem line) embryonic Stem Cells (ESC) are needed, the use of donor gametes for the necessary Somatic Cell Nuclear Transfer (SCNT) procedure would be needed. If these donor gametes could be replaced by SCD gametes, the need for donor gametes (in specific egg cells, which are difficult to obtain in contrary to sperm) would decrease even more. On the long run, SCD Gametes could make the use of donor gametes redundant. However, until SCD gametes are sufficiently tested on efficiency and safety, donor gametes (e.g. egg cells) will be needed for research on SCD gametes.

3.2. Current state of research

Multiple strategies to create gametes in vitro are explored (e.g. K. Hayashi et al., 2012; K. Hayashi et al., 2011; Katsuhiko Hayashi & Saitou, 2013). These procedures are described in a systematic review by Hendriks et al in 2015 (Hendriks et al., 2015). Hendriks et al describe eight biologically plausible strategies to create human SCD gametes in males, and nine plausible strategies in females. Furthermore, they describe nine biologically plausible strategies to create SCD oocytes in males and nine plausible strategies which could result in SCD sperm in females (Hendriks et al., 2015). The procedures are divided into three different kind of pathways following the type of cells that are used; germline stem cells (GSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). GSCs are stem cells that are produced in the ovaries or testicles and can only differentiate into gametes. These cells are multipotent and not pluripotent. I will not discuss this pathway, because this thesis envisions a broader application beyond the maturation of GSCs. When using GSCs, only subfertile people with problems considering the maturation of their gametes could be treated. Therefore, in this thesis, the focus will be on gametes derived from PSCs, of which the use can potentially help people to have children who do not even have anything in terms of early germ cells to start a growth and maturation process with. Currently, there are two promising pathways for deriving SCD gametes with PSCs; to use Embryonic Stem Cells (ESCs) or to use induced pluripotent stem cells (iPSCs).

3.2.1. Embryonic Stem Cells

After four to five days after fertilization, embryos reach the blastocyst stage. A blastocyst is an early-stage preimplantation embryo. Embryonic Stem Cells (ESCs) can be derived from the inner cell mass of the blastocyst. These cells are pluripotent, which means that they can develop into any type of body cell, and may thus yield tissue for different kinds of regenerative medicine (think e.g. of deriving dopamine producing cells to treat patients suffering from Parkinson's disease, or heart muscle cells for patients with cardiomyopathy), potentially also including the derivation of gametes for medically assisted reproduction.

A necessary method to create patient-specific ESCs is the use of Somatic Cell Nuclear Transfer (SCNT). The ESCs need to be patient-specific if you want to prevent rejection after transplantation procedures. Moreover, in SCD gamete procedures, the patient-specific ESCs are needed to make sure that the potential child is genetically related to the parents. In SCNT an

embryo is generated by replacing the nucleus from the egg cell by the nucleus of a somatic cell. This procedure is often called 'therapeutic cloning' (Lanza, Cibelli, & West, 1999; X. Yang et al., 2007). Although SCNT has not yet been successfully conducted in humans and is still in a fundamental research phase (Dondorp & de Wert, 2007), it could theoretically be used for patient-specific therapeutic applications like treating Parkinson's disease or cancer (Barberi et al., 2003; Byrne et al., 2007; Lanza et al., 1999). In such a case, genetically identical ESCs derived from the created embryo would be used for cell replacement therapy. Because the embryo from which the cells are derived has the same genetic material as the patient, this results in patient specific PSCs, which are very unlikely to be rejected. The same technique can also be used for reproductive purposes. In that case, it results in patient-specific PSCs from which gametes will be created that are genetically identical to the patient.

Human SCD Sperm from males and SCD eggs from females have been only successfully derived from non-patient-specific ESCs (Hendriks et al., 2015). Despite close attempts (Tachibana et al., 2013; Yamada et al., 2014), creating human patient-specific ESCs using SCNT still has not been achieved without significant drawbacks (e.g. considering the development of the embryo). However, although not yet successful in humans, fertilization and live-birth offspring has been achieved in animals using recipient-specific ESCs (Hendriks et al., 2015). One of the leading research groups using SCNT succeeded to produce SCD gametes from mouse ESCs in 2012 (K. Hayashi et al., 2012). They did so by acquiring naïve mouse ESCs from an intermediate epiblast-like state after SCNT. Additionally, ESCs resulted in deriving eggs from male mouse cells and were fertilized with SCD sperm from the same male mouse (Kerkis et al., 2007).

A potential issue with this procedure (SCNT) is that the cells may retain a somatic epigenetic memory (R. K. Ng & Gurdon, 2005). Such memory could lead to biases or limitations concerning the differentiation into cells of a particular lineage. Gene expression and therefore the properties and behavior of the cell may be altered. As a result, the altered gene expression would be passed on to the future child, which could lead to imprinting disorders or subtler health-related consequences not manifesting until after adulthood (Grace & Sinclair, 2009). For example, research in mice has shown that human overgrowth syndromes, such as the Beckwith-Wiedemann syndrome (BWS), are associated with errors in an imprinted cluster of genes on human chromosome 11 (Sinclair, Young, Wilmut, & McEvoy, 2000).

Furthermore, SCNT has two additional ethical concerns. First, isolating the inner cell mass of the blastocyst to create ESCs means the destruction of the embryo, which is ethically sensitive. Second, to perform SCNT donor egg cells are needed, at least in the research phase. After that, non-patient specific SCD egg cells might be used for therapeutic applications, including for the creation of patient specific SCD gametes for reproduction through SCNT. The need for donor egg cells could pressure women to donate egg cells, which concerns collaborating in the riskiest element of IVF procedures; the hyper stimulation and extraction of egg cells. Both issues will be addressed in chapter four of this thesis.

3.2.2. Induced Pluripotent Stem Cells

The second procedure, iPSCs will directly lead to patient-specific gametes without the in-between step of creating an embryo through SCNT. The procedure concerns the reprogramming of differentiated somatic cells (any kind of body cell) to induce pluripotentiality (S. Yang et al., 2012). This is performed by introducing a set 'reprogramming factors' to the body cell. The four factors, discovered by Shinya Yamanaka, are forced over-expressions of pluripotency genes and reprogram the somatic cell into an iPSC (Takahashi & Yamanaka, 2006).

In animals, artificial sperm and artificial oocytes generated from iPSCs have been created (Hendriks et al., 2015). Furthermore, research has succeeded to create fertile mouse offspring from oocytes derived from skin cells using this procedure (K. Hayashi et al., 2012).

Just like the procedure using ESCs following SCNT, there is the possibility that iPSCs retain a somatic epigenetic memory, which could lead to health-related consequences for the future child. The procedure using iPSC has the advantage over SCNT in that there is no need to create an embryo as an in-between step. This makes the procedure less technically difficult than SCNT and also less ethically sensitive. In the case of ESCs, there is the moral issue of creating embryos that will not be used for pregnancy each time SCD gametes would be created. This means that next to possibly creating embryos in the context of safety research, also the treatment itself would involve the creation and destruction of embryos. In addition, using iPSCs also excludes the possible pressure on egg cell donors for the reproductive procedure, since no donor egg cells would be needed.

3.3. Utility of preclinical safety studies using human embryos

Although it is still difficult to predict the time frame when clinical application of SCD gametes would be possible, Hendriks et al. expect the introduction to be possible in the intermediate future. However, the safety and functionality of SCD gametes in humans is still to be proven, since the first human SCD gametes still have to be produced (Hendriks et al., 2015).

It is argued that the procedure with SCD gametes, like several ARTs, can disrupt the process of genetic imprinting (Grace & Sinclair, 2009; R. K. Ng & Gurdon, 2005; Sinclair et al., 2000). Because the safety concerns, the UK allows the use of SCD gametes for safety research, but banned their use for human reproduction (HFEA, 2009). There first needs to be more data on the possible health risks before the treatment can be introduced into the clinic (ZonMw, 2012).

3.3.1. Systematic Formal Research

Research has recommended a process of animal research, preclinical embryo research, clinical trial and follow-up studies to investigate the safety and effectiveness of ARTs, and specifically of SCD gametes (Brison et al., 2013; Dondorp & de Wert, 2007, 2011; Hinxton, 2008; Pennings et al., 2007). As described in the previous chapter, the history of ARTs shows that such research was and still is often neglected. However, these steps are crucial to determine the safety of SCD gametes. Animal research can give insight in potential transgenerational effects by performing follow-up research on multiple generations (Brison et al., 2013; Dondorp & de Wert, 2011). Non-human primates would be ideal for this research, because of their close resemblance to human beings. However, such research is very expensive, time-consuming and ethically sensitive (ZonMw, 2012, p. 37). To narrow the gap between animal research and clinical research, preclinical embryo research can be performed (Dondorp & de Wert, 2011; Hinxton, 2008). After positive results, the treatment can move to clinical trial. If it has been proven to be sufficiently safe and effective, the technology can be introduced in the form of clinical studies determining efficiency and investigating the conditions under which the procedure can best be offered. Follow-up research helps to keep track of the effects of the treatment (including long-term safety) and may lead to its adaptation.

3.3.2. Preclinical Embryo Research

Since the aim of this thesis is to investigate the ethical justifiability of embryo research on SCD gametes, I will focus on this part of the safety research procedure. As already briefly explained in the previous chapter, preclinical embryo research forms an important step in safety research on ART. To follow the internationally recommended 'chain' from experimental procedures to follow-up research (ACOG, 2006b; Pennings et al., 2007), safety research on SCD gametes ideally should include preclinical embryo research. In this section, I will explain the necessity of embryo research in safety research more extensively.

In 2013, professor of clinical embryology and stem cell biology Daniel Brison, published an article on how to assess the safety of IVF technologies. According to him, a very important part of preclinical testing should be embryo research: "much of our knowledge of the impact of assisted reproduction treatment on the embryo comes from assessments of embryo developmental progression in culture and embryo morphology" (Brison et al., 2013, p. 714).

Brison is not the first to recommend embryo research on new ARTs (Dondorp & de Wert, 2011; Hinxton, 2008; Pennings et al., 2007), but he makes its benefits to safety research very explicit. He explains that it is very important to examine the gene expression patterns of preimplantation embryos. In the gene expression of the embryo, maternal as well as paternal genes are reorganized. The process by which an embryo begins to transcribe its newly formed genome is called embryonic gene activation. Following Brison, "embryonic genome activation is essential to the development of the embryo and can thus be used as a global marker of embryonic health" (Brison et al., 2013, p. 715). Furthermore, gene expression of embryos is affected by epigenetic regulation (Chason, Csokmay, Segars, DeCherney, & Armant, 2011), that can result in 'environmental cues' (Brison et al., 2013, p. 715).

According to Brison, as a result after gene expression research, embryo development highly differs between one embryo and the other. While large numbers of embryos are used in animal models like mice, performing large embryo studies are constrained by several issues, like scarcity and ethical difficulties. This results in embryo research with embryos from couples with problems concerning fertility. Therefore, it cannot be assumed that the development of embryos in the laboratory represents 'normal' embryo development (p. 715). Therefore, Brison et al. argue that it is "essential to study the impact of new technologies on embryo development using embryos donated to research as fresh embryos, cryopreserved embryos, fresh or cryopreserved

oocytes which can be activated to generate embryos for research and human ESC lines generated from equivalent embryos" (Brison et al., 2013, p. 717).

3.3.3. The creation of embryos for research

Like with all new ARTs, the safety of SCD Gametes should be investigated before introducing it into clinical practice. Since preclinical embryo research is essential in safety research on new ARTs (Brison et al., 2013; Dondorp & de Wert, 2007, 2011; Pennings et al., 2007), it can be argued that preclinical safety research should also be included in the safety research on SCD Gametes. Recent research has shown the effectiveness of using specifically created embryos to preclinically investigate the safety and effectiveness of mitochondrial replacement therapy (Hyslop et al., 2016) and the Hinxton Group explicitly recommends preclinical embryo research on SCD Gametes as this would narrow the gap between animal research and first clinical studies (Hinxton, 2008).

In some cases of research on ARTs, spare embryos after IVF can be used for preclinical embryo research. However, research on the safety of SCD gametes needs to be performed with specially created research embryos. After all, the research concerns primarily the process before fertilization. Therefore, to test the safety of SCD Gametes, the embryos need to be created by using these gametes. The use of spare embryos after IVF would thus be ineffective, since they are generated with 'normal' gametes.

This chapter examined the possible advantages of introducing SCD Gametes, its technical pathways and limitations, and the necessity to perform preclinical embryo research to responsibly introduce the technology into clinical practice. The next chapter explores the arguments of those rejecting either all forms of (instrumentalizing) embryo research as well as of those only rejecting research for which embryos would need to be created. Furthermore, the arguments of those supporting embryo research in general as well as the arguments of those supporting the use of specifically created embryos for research will be investigated.

CHAPTER 4
THE ETHICS OF EMBRYO RESEARCH

Many researchers have argued that using embryos for safety research can be of significant importance (Brison et al., 2013; Dondorp & de Wert, 2011; Pennings et al., 2007), it nevertheless leads to several ethical issues. The use of specifically created embryos for research is regarded as problematic by several commentators. Arguments against the creation of embryos for research refer to the status or value of embryos and/or to the risk that women will be pressured into donating oocytes against their best interest or exploited (Baylis, 2000; Dickenson, 2002; FitzPatrick, 2003; Gerrand, 1993; Hoedemaekers, 2003; Murphy, 2012; van Beers, 2009). Some of those opposing the instrumental use of embryos see no difference between the use of spare embryos or embryos that are specially made for the purpose, rejecting all research not intended to benefit the embryo in question (Hoedemaekers, 2003). However, others accept the use of spare embryos for research, but find the intentional creation of embryos as research material unacceptable (FitzPatrick, 2003; Murphy, 2012; van Beers, 2009). This distinction is reflected in the fact that many countries with legislation regulating embryo research reject the creation of embryos for research, but allow the use of spare embryos under conditions of proportionality and subsidiarity. In this chapter, I will describe the ethical debate, identified in the selected literature, concerning the use of embryos for research and the creation of research embryos. I argue that this debate can be structured around three main ethical issues.

First, general moral arguments considering the acceptability of embryo research will be mapped. The debate will be illustrated by three views on the moral status of the human embryo. It will be shown that the perspective on the moral status of the embryo is determining the perspective on the acceptability of embryo research. The second section concerns the ethical debate on the creation of embryos for research. If embryo research can be justified in general, can then also the creation of embryos for research be justified? Building further on the second

section, the last section will describe the ethical debate on how to responsibly obtain the required oocytes. If embryo research, and the creation of embryos for research, can be justified, how should we deal with obtaining donor oocytes? It will be argued that the necessity of obtaining donor oocytes can also be used as a moral difference between using leftover embryos for IVF and creating embryos for research.

4.1. Ethical perspectives on embryo research

Is embryo research acceptable? To investigate this essential basic question, the safety benefits of embryo research are balanced against the moral harm of destroying early stage human embryos. It is also possible to perform research on embryos benefiting the embryo and without destroying it. This is known as therapeutic embryo research. This thesis will focus solely on embryo research that involves destroying the embryo, as this would also be the case in embryo research on SCD gametes. The benefits of embryo research are already explained in chapter two and three (21-42). We have seen that embryo research would improve safety research on ARTs, so that they could be responsibly introduced into clinical practice. Also briefly discussed in chapter two and three is the drawback of embryo research concerning the destruction of the embryo, which is necessary to perform the research.

Can the destruction of embryos be balanced against the benefits of preclinical embryo research? To measure if the benefits outweigh the harms, it is key to define the moral status of the embryo. An entity has a moral status if it has moral interests that matter for that entity's own sake and which can be wronged (Jaworska, 2013). If a being has a moral status, we are obliged to consider its needs, interests, or well-being when we are making decisions towards it (Warren, 1997). Some philosophers have argued that moral status comes in degree, of which full moral status is the highest (DeGrazia, 2008; Sumner, 1981). Their hypothesis that "the moral status of a being is proportional to its degree of sentience helps to explain why it is reasonable to distinguish between the moral status of (for instance) fleas, sparrows and human beings" (Warren, 1997, p. 87). It is important to define the moral status of the embryo, because it determines the moral weight of using and destroying it. To give an example, if an embryo would have the same status as a human being, destroying the embryo would mean the same as to kill or perhaps murder a human being. Would it have no moral status at all, there would be no harm in using it for research. Therefore, the ethical justifiability of embryo research is centered on the moral status of

the embryo. The relation between moral status and justification of embryo research will get more clear in the next paragraphs.

The Health Council of the Netherlands published a report in 1998 summarizing the three main views considering the moral status of the embryo (Gezondheidsraad, 1998, p. 60).

4.1.1. The moral status of the embryo is the same as the moral status of a born human individual

According to the first view, the moral status of the embryo is the same as the moral status of a human being. Therefore, embryos should be protected to the same level as born human individuals should be protected (Gezondheidsraad, 1998, pp. 60-61).

This view can be identified in the work of e.g. philosopher Stephen Buckle, who has argued according the *respect for the capacities of individuals argument* that "respect is due to an existing being because it possesses the capacity or power to develop into a being which is worthy of respect in its own right; and respect is due to such a being because it is the very same being as the later being into which it develops. The already-existing being is a being which has the potential to become a being worthy of respect in its own right" (Buckle, 1988, p. 230). Because the zygote can be identified with the later person, Buckle argues that it is entitled to the same respect as the later person. This however does not apply to separate egg cells or sperm cells, because they are not an 'individual' yet. They cannot be identified with the later person and therefore do not have to potential to develop into that specific individual (Buckle, 1988).

The view that embryos deserve the same respect as human beings, or something close to it, can also be seen in the regulation on embryo research in Germany, as well as in the view on embryos of the Catholic Church and orthodox Protestants. The German Law forbids nearly (e.g. abortion is allowed) all actions with embryos that may harm the embryo. Also oocyte and embryo donation are forbidden (ZonMw, 2012, p. 77). To harm the embryo for a purpose other than its own means to fully instrumentalize it. Instrumentalization of the embryos means that the embryo is not seen as an end in itself, but only as an object for us to use to reach a specific goal. Key of the argument behind the German Law is that such instrumental use of an embryo is not commensurable with their high moral status. Therefore, the German Law forbids every instrumental use of an embryo (ZonMw, 2012, p. 81).

Furthermore, in the 1988 report of the scientific bureau of the Dutch democratic Christian party (CDA), it has been argued that embryos leftover after IVF may not be destroyed nor used

for research (CDA, 1988). According to the report, human life deserves protection regardless the stage of development. This means that born as well as unborn individuals deserve the same level of protection. To destroy a spare embryo after IVF would mean to instrumentalize human life, because life is destroyed when it is no longer perceived as useful anymore (CDA, 1988, p. 93). This applies as well to using spare embryos for research, since this would also mean to instrumentalize the embryo and to deny its high moral status (CDA, 1988, p. 93). Supporters of this view consider the embryo to have the potential to grow into a human being and to interrupt this process cannot be justified.

In my view, the argument by proponents of this view consists out of two parts. The first part considers the argument that early stage embryos are the same individuals than the later persons they (potentially) grow into. Because of the potential the embryo has to develop into the later person, embryo and born human individual should be protected equally. To interrupt the process of development of the embryo is thus perceived impermissible. The second part of the argument considers the instrumentalization of human life. According to this argument, it is impermissible to use human life for a purpose other than its own. Since the use of embryos for research means to destroy them, the embryo is used without any interest for its own. Because the embryo is considered equal to the later person it can develop into, instrumentally using embryos is equally impermissible than instrumentally using (and destroying) grown human individuals.

4.1.2. Embryos have symbolic worth at best

Another view is that embryos do not have a moral status on which ground they should be protected. This view is more theoretical than that it can be found in practice. According to this view, embryos should not be treated any differently than the gametes from which they derive.

However, not having an intrinsic moral status does not mean that embryos should not be protected at all. For instance, the symbolic worth of an embryo can be used as an argument to protect it. The symbolic worth refers to the social connection the embryo has with all humans (Gezondheidsraad, 1998, p. 61). The embryo is in this case not protected because of its intrinsic moral value, but because of the community ascribing it meaning as a starting form of human life (Sandel, 2004). This means that such a given meaning can differ between cultures and time periods. Contrary to the division of the Dutch Health Council, the position of symbolic worth can be better classified as a category of the next view where embryos also have a limited worth of

protection. Therefore, from now on, I will use the view on symbolic worth of the embryo as a category of the next position.

4.1.3. Embryos have a limited worth of protection

A third view holds the middle between high and no protection and considers embryos to have a limited worth of protection. This view does not consider the embryo a human being, but still thinks that it can be granted moral value because the embryo can potentially grow into a human being. In contrary to the first view, that used potentiality to argue for no difference in moral status, authors supporting this view have argued that the potential to grow into a human being that embryos have, grants them a degree of, but not full, moral status (Harman, 1999, 2003) or enhance their moral status (Steinbock, 2011). This means that the embryo does have a moral status, but this status is not equal to the moral status of a born human individual. Often, it is added that the embryos have an increasing worth of protection. This means that the worth of protection increases the more the embryo develops (Gezondheidsraad, 1998, pp. 61-62).

Also the previously discussed symbolic worth of the embryo can grant the embryo limited worth of protection. Only in that case, the worth of protection is not granted because of its intrinsic value, but because of the fact that it has a social connection with the human species, since the meaning of the embryo is ascribed by the community.

The view that embryos deserve limited protection can be seen in e.g. the Dutch embryo law (CBO, 2003). According to this law, it is permissible to use embryos for research only when specific criteria are met. For example, in article 10, it is written that embryo research is only acceptable when it is very likely that the research will lead to new insights in medical science. Furthermore, the research using embryos is only permissible when it cannot be performed using other methods of scientific research (CBO, 2003). The fact that these criteria need to be met in order to justify the use of embryos for research, means that it is unacceptable to use embryos for every arbitrary purpose. This means that embryos deserve protection according to this view. Yet, if these criteria are met, the use of embryos for research is acceptable, which means that embryos do not deserve full protection. The Dutch embryo law thus proclaims the view that embryos have a limited worth of protection.

4.2. Ethical perspectives on creating embryos for research

In some cases of embryo research on ARTs, using spare embryos is insufficient; to obtain a result it is necessary to specially create embryos for research (e.g. on SCD gametes). In this thesis, I will only focus on the arguments considering the acceptability of the use of research embryos in a case where spare embryos are insufficient for research. This leaves the waste principle (using spare embryos because it is better to use them than to do nothing with them) out of account. Also the subsidiarity principle, stating that embryos should not be created for research when spare embryos can be used, is thus not relevant.

Following the previous section, proponents of two out of the three views (potentially) accept the creation, use and destruction of embryos for research. The first view, which considers embryos to have the same moral status as human persons, clearly is against all deliberate harm and destruction of embryos. Proponents of this position leave no room for the use of embryos for research, regardless of whether the embryos are surplus after IVF and donated for research (spare embryos) or created solely for research purposes. Therefore, there is no need in examining this view any further in this chapter.

The second view considers embryos to not have any moral status on which ground they should be protected. This view does not make a difference in moral status between spare embryos and research embryos as well, since both types of embryos should not be treated any differently than any other body tissue. Because this position is generally non-existent in practice and does not oppose embryo research more than any other research containing human body tissue, there is no need for a further examination of this view in this chapter either.

The middle view however (including symbolic worth of embryos), does leave room for discussion on the moral acceptability of creating and destroying embryos for research purposes. Since proponents of this view consider embryos to have a limited worth of protection, some purposes (e.g. research concerning the treatment and prevention of serous human diseases and suffering) using embryos could be justified (Brock, 2010). If embryo research can be considered acceptable following this view, can it also be justified to create embryos for the purpose of research?

Currently, in most countries in Europe, the creation of embryos for research is not allowed. The use of spare embryos for specific research (serving an important purpose) is in most countries authorized. Apparently, a moral difference is made using spare embryos (accepted) and

creating embryos for research (forbidden). If there would be no moral difference between using spare embryos that already exist and intentionally creating embryos for research, it could be argued that the use of research embryos should be allowed just like the use of spare embryos is, or that the use of both type of embryos should be forbidden. The moral distinction between spare embryos and research embryos has been a debate in the field of embryo research identified in the selected literature, in which one position suggests that there is indeed a moral distinction between spare embryos and research embryos that would require prohibiting the creation of research embryos (FitzPatrick, 2003; Murphy, 2012; van Beers, 2009), while others argue that there is no moral difference between using spare embryos and research embryos (Brock, 2010; Devolder, 2005, 2013). This section will focus on the ethical arguments opposing and supporting the creation of embryos for research.

4.2.1. Inherent moral status

Is it possible that the authors arguing for a difference in moral acceptability between using spare embryos and creating embryos for research mean that there is a difference between inherent moral statuses of both types of embryos?

Following the middle position (that considers embryos to have an increasing worth of protection) an embryo does not have the same moral status as a full human person, but it nevertheless has a certain moral status on which ground it should be protected. This status is, as described above, related to the potential or symbolic worth of the embryo. According to this view, embryos morally deserve a certain respect, because they are a human species or can potentially develop into a person (Brock, 2010; Gezondheidsraad, 1998).

Supporters of the potentiality argument of the middle position grant a moral status to the embryo based on *internal* characteristics, because they consider the embryo more valuable than other human tissue (Devolder, 2005). These internal characteristics can be described as biological properties allowing the embryo to grow into a human being. The embryo is thus considered a biological entity, yet also a potential human being. Following the view of limited value based on potentiality there cannot be found a moral difference in status between spare embryos and research embryos. Both types of embryos have the intrinsic biological properties to grow into a human being. Whether the embryo actually becomes a person is considered not relevant to the protection we have to give it. In both cases they have the capacity to become humans, and in both

cases they are destroyed when they are used for research. Thus, there is no moral difference between spare and research embryos based on their intrinsic potential (Gezondheidsraad, 1998).

Also in the middle position based on a symbolic, social value of the embryo, there cannot be found a difference considering inherent moral value between spare embryos and research embryos. Both spare embryos and research embryos have the biological properties that make them socially seen part of the human species.

Furthermore, the fact that the middle position acknowledges increasing protection of the embryo the more it develops, emphasizes the focus on the internal biological characteristics of the embryo. Following the element of increasing worth of protection, there can be found no difference between both types of embryos, since both embryos are used for research at the same stage of development. Thus, one type of embryo is not further developed than the other, leaving both kinds of embryos with the same level of protection worthiness.

The literature does not mention a moral difference between spare embryos and research embryos based on a difference in moral status of the embryo as entity. I have not found any author arguing for such difference in moral status. If the authors did not argue for a difference between the intrinsic moral value of spare embryos and embryos created for research, what could then be their argument for allowing research with spare embryos but not allowing creating embryos for research?

4.2.2. Intention

Clearly, the authors who point out a difference between using spare embryos and specially created embryos for research do not aim at a difference in moral status considering internal factors. An alternative option that has been argued for is that a moral difference can be made between the *intention* of creating spare embryos and creating research embryos (FitzPatrick, 2003; Murphy, 2012; van Beers, 2009).

Britta van Beers, professor in the department of Theory of Law and Legal History at the University of Amsterdam, has pointed out a difference in intention of creating IVF embryos and research embryos (van Beers, 2016). She argued that the creation of embryos for the purpose of research introduces a new category of human life that is only intended for instrumental use instead of serving a ‘relational value’, such as reproductive purposes (van Beers, 2016). Van Beers argues that research embryos are intentionally created as a subcategory of human life that

will never grow into human beings, which in her view is at odds with the protection that embryos deserve. In the case of spare embryos, the embryos were at least created with a relational value in mind, namely helping a couple with reproduction.

Biomedical philosopher Timothy Murphy has argued for a moral difference in intention as well (Murphy, 2012). Murphy supports his statement by arguing that the *principle of double effect* can justify embryo deaths in natural reproduction and IVF, but not for research. Following the principle of double effect, it can be justified to bring about harm when it is a foreseen but unintended side effect of an action that is aimed at some good end (McIntyre, 2004). An action thus has two effects; one that is intended and one that is a side effect, or "double effect". The principle of double effect stresses that "if the evil effect is brought about as a means to the good effect, then the evil effect must be intended, and the bringing about of the instrumental state of affairs is morally impermissible" (Boyle, 1980, p. 531). This means that bringing about harm can only be justified when it is not the means for an end, but a side effect that accompanies getting to that end. The principle of double effect will be further explained in chapter five. For now, this brief explanation will be sufficient.

According to Murphy, embryo loss in fertility medicine using IVF is not intended, but only foreseen. This differs from the intentional destruction of embryos that occurs in research (Murphy, 2012, p. 531). Embryos leftover from IVF were not created with the intention of destruction, because their deaths are not the means for reproduction. In the case of research embryos however, destruction of the embryos is intended, because the research performed on the embryos necessarily involves the destruction of the embryo. Therefore, the intention of destruction is already present when creating the embryo. The destruction of the embryo is the means for research.

Murphy's argument thus states that morality depends on intention. He gives the example of natural reproduction, where many embryos fail to implant or lead to embryo-loss or miscarriage; "conception in vivo does not require any intent to expose embryos to the risk of death, the embryo loss that occurs is not the means by which successful conception occurs, and the effect of having children is as important as any to be found in human life" (Murphy, 2012, p. 532). The moral difference lies in the 'means' as intention. While in IVF and natural reproduction embryo deaths are not the means for new life, embryo deaths are necessarily the means to perform embryo research.

Also using double effect reasoning, moral philosopher William FitzPatrick has argued that the moral difference between using spare embryos and creating embryos for research lies in the *intent/foresee distinction* (FitzPatrick, 2003). According to FitzPatrick, IVF clinicians *foresee* that probably not all embryos will result in a child. However, they do not create embryos with the *intention* to destroy them. On the contrary, when creating embryos for research, we are "creating embryos with such an intention, exhibiting the distinctively exploitative and opportunistic attitude bound up with such a practice"(FitzPatrick, 2003, p. 31).

Emphasizing the intentional destruction in the creation of research embryos, FitzPatrick argues that since the research necessarily involves the destruction of the embryo, performing the research and destroying the embryo are in a *constitutive relation*. In other words, the relation between the creation of embryos for research and their destruction is of excessive closeness (FitzPatrick, 2003, p. 32). According to FitzPatrick, the possible destruction of embryos in IVF is merely a *causal* relation, in which it is possible to aim at the one without aiming at the other. This is different to the *constitutive* relation between creating embryos for research and destructing them, because these two things are "too intimately connected to speak of aiming at the one without aiming at the other" (FitzPatrick, 2003, p. 32). Because of this constitutive relation, to create an embryo for research thus means to create an embryo for intentional destruction, which cannot be justified.

Thus, using spare embryos for research is perceived to be more commensurable with the value of the embryo than creating embryos for research. FitzPatrick argues that in creating embryos for research, we are taking an intrinsically inappropriate attitude towards early human life (FitzPatrick, 2003). Because of the constitutive relation between research and destroying the embryo, research embryos are always created with the intention to destroy them (FitzPatrick, 2003). This is considered incommensurable with the limited moral value granted to embryos. Others have described the inappropriate attitude as the 'instrumentalization' of embryos (van Beers, 2009), whereby embryos are solely created and used as a means for our own interests (Murphy, 2012).

Opposing the view that intention grants a moral difference between using spare embryos and research embryos, bioethicist Katrien Devolder argues that if standard IVF practices are allowed, it would be no different to allow the creation of embryos for research (Devolder, 2005, 2013). In most countries where IVF is practiced, on average five to ten embryos are produced per

IVF cycle. One or two of them are transferred to the woman's womb in a single cycle to try to achieve a pregnancy. Even if several subsequent transfer cycles are tried, many embryos still end up in the freezers of fertility centers and will eventually be destroyed. The reason why more embryos are created than can be responsibly transferred in one cycle is to enhance the effectiveness of IVF. This is in the interest of women undergoing IVF, as the alternative would require more stimulation cycles and thus expose them to higher burdens and risks. For this reason, the present approach in which more embryos are created than will be needed may be called 'woman-friendly IVF' (Devolder, 2013). The majority of embryos created for woman-friendly IVF will thus not be used by the couple. As a result, these embryos will remain frozen, will be donated to other couples or for research purposes or will be destroyed. In practice, spare embryos are rarely used for reproduction purposes for other couples, which means that the majority of embryos will never result in a child. An alternative method would be to only create one or two embryos per cycle (which is the maximum that can be responsibly transferred to the womb in order to avoid the risks connected to multiple pregnancies). This may be called 'embryo-friendly IVF' (Devolder, 2013). Until its recent revision, this was required under the Italian embryos act: in order to protect embryos from destruction, it was not allowed in Italy to create more than three embryos per cycle, each of which had to be transferred to the womb (Setti et al., 2010). However, this increases health risks and discomfort for the woman and decreases her chances of having a child through IVF. Therefore, standard IVF practice in most countries involves woman-friendly IVF.

Devolder argues that since the gross majority of the early stage embryos in our standard way of performing IVF (woman-friendly IVF) will not be used for implantations into the womb of a woman, just like research embryos will not, there is no moral difference in creating spare embryos or research embryos. According to Devolder, "couples or individuals who create spare embryos apparently believe that the enhanced chance of a successful pregnancy and of fulfilling their wish for a child outweighs the moral value of each of the embryos" (Devolder, 2005, p. 181). The opponents of creating embryos for research, who base their argument on a distinction on intention, seem to consider early embryos as a group, arguing that as it is not known which embryo will eventually be chosen for transfer to the womb, it can still be said that the whole group of embryos is created with the intention of letting those embryos grown into a child (Devolder, 2005, p. 182). However, when considering each embryo separately, it is known

beforehand that the majority of embryos created for woman-friendly IVF will remain unused. Therefore, the embryos are created with the knowledge that most of them will never result in a child, just like embryos created for research are not. According to Devolder, to argue that each and every embryo created with woman-friendly IVF is created with the intention to let it grow into a child would thus be inconsistent, while so much would be needed to argue a difference between an intention to create embryos as ends in themselves (in IVF) versus creating them fully instrumentally as mere material (in research).

Furthermore, is has to be questioned whether in IVF the benefit of reducing harm to the woman due to potentially more hormone treatments and further egg retrievals is large enough to outweigh the morally challenging embryo deaths of spare embryos (Devolder, 2013, p. 535). According to Devolder, the principle of proportionality cannot be met in standard IVF and embryo research when the embryo is considered to be a person. Otherwise, it would mean that one thinks that the intentional creation and destruction of persons to reduce harm for another person or for research purposes would be acceptable. If one does think double effect can justify standard IVF, the moral status one accords to the embryo must be low. If it is that low, "how can it provide a decisive reason against sacrificing embryos for research that can potentially save and improve the quality of life of a very large number of people"? (Devolder, 2013, p. 536).

Another argument for allowing the creation of embryos for research states that neither the creation of an embryo, not its use and destruction, is bad or impermissible. Therefore, the combination of the three elements should not be morally problematic either (Brock, 2010). Medical ethicist Dan Brock argues that an embryo lacks sentience or consciousness, and therefore does not have interests or a good of its own. Therefore, it does not have any specific interest in remaining alive (Brock, 2010). "If they [embryos] cannot have an interest in becoming a person because they do not have any interest at all, then they cannot have a right to become a person and realize their potential" (Brock, 2010, p. 236). Following this line of argument, using and destroying already existing embryos does not harm them. Given the benefits of e.g. stem cell research, the use and destruction of embryos can be justified. Also the creation for the purpose of research is not intrinsically immoral, argues Brock. According to him, "no one believes that the creation of an embryo is in itself morally wrong and impermissible, and most do not believe that doing so by artificial means such as IVF is either" (Brock, 2010, p. 237). In the eyes of Brock,

combining the creation and the use and destruction of embryos should be just as justifiable as both elements separately.

Devolder and Brock thus both argue in favor of creating embryos for research. Devolder states that creating embryos for research is not any less ethically justifiable than creating spare embryos in standard IVF practices. If we allow standard IVF practices, we should also allow the creation of embryos for research (Devolder, 2005). Since spare embryos are created as an external means to a parental project, just like research embryos are created as an external means to the ends of scientific research, the element of intention does not draw a moral line between them. Also the principle of proportionality is used to argue in favor of creating embryos for research. If it would be proportional to sacrifice spare embryos for the benefit of women, it would also be proportional to sacrifice research embryos for the benefit of knowledge. Brock's reasoning follows a different path. Instead of focusing on the intention and proportionality of the creation embryos for research, he tears apart the element of creating embryos and using and destroying embryos for research. Since both elements separately are not intrinsically morally bad, the combination of them should not be morally bad either (Brock, 2010).

4.3. Ethical perspectives on obtaining donor egg cells

Another problem that rises with the creation of embryos for safety research is the demand for donor egg cells. Instead of arguing for a difference in intention in using spare embryos and creating embryos for research, this pathway problematizes the creation of embryos for research out of concern for the interests of women. To create embryos for research, egg cells and sperm cells are needed. Sperm cells are relatively easy to obtain, since these cells can be taken after normal ejaculation. Egg cells however, are much more difficult to obtain. Therefore, how to responsibly obtain egg cells forms a great part in the ethical debate on creating embryos for research.

4.3.1. Risks and benefits

In egg cell donation, women have to undergo several risks. First, these women have to take hormone medication to induce their ovulation and to increase their egg cell production. These medications have been associated with risks like ovarian hyper stimulation (Griesinger, Diedrich,

Tarlatzis, & Kolibianakis, 2006). Second, the egg retrieval procedure can lead to physical pain and injury. Last, the practice can bring about psychological and emotional stress (Baylis, 2000).

In IVF practice, the benefit for the woman undergoing these procedures is clear. The risks are accepted, because the treatment can help to pursue the reproductive goal of the woman. In donating for another woman the motive may be altruism: the wish to help an infertile couple to fulfill their child whish. In donating for research however, women undergo hormone stimulation therapy and invasive medical procedures, when there is no concrete benefit for the woman (Gerrand, 1993). The woman does not experience any direct or indirect health benefit. Also, in most cases, the women cannot choose the recipients benefiting from their egg cells for research or therapy. Last, it is very likely that the women will not benefit financially from collaborating in research (Baylis, 2000). If there are no benefits for women donating their egg cells, what then would be the motivation to participate?

4.3.2. Coercion and exploitation

The creation of embryos for the purpose of research can increase the risk of coercion for women (Baylis, 2000). The demand for donor egg cells can put vulnerable women under pressure. To give an example, the Korean researcher Hwang Woo-suk was accused of fraud in 2006. He claimed he succeeded to create embryos by cloning. It appeared that the data were fabricated and the research was misconducted (SNU, 2006). Although the research was not a success, he nevertheless needed many egg cells. It turned out that he gained the egg cells by pressuring his female employees from his laboratory (ZonMw, 2012, p. 30).

It has been argued that the creation of embryos might threaten women's autonomy (Gerrand, 1993). One aspect of being an autonomous agent is to be able to give informed consent to any procedure. Also choice and voluntary actions are aspects which play a role being an autonomous agent. Because the risks and long-term effects of hormone-stimulation are not fully understood yet, it is impossible for women to make a fully informed choice about egg donation (Gerrand, 1993). However, it has been argued that the risks of using hormone-stimulation medicines are negligible when responsibly using the medicines (Devroey, Polyzos, & Blockeel, 2011). Nevertheless, even if fully informed consent was possible, this does not mean that the risks of exploitation of women in vulnerable circumstances vanishes. For instance, the exploitation of women in a low financial environment would be still conceivable.

Moreover, several authors argued that ARTs cause several social concerns, including the possibility that women would be perceived as just being reproductive vessels (Arditti et al., 1984; Corea, 1985; Rowland, 1992). It is argued that if such a perception would result from using ARTs, this perception could certainly arise when women are used for harvesting eggs in order to create embryos for research, leading to the exploitation of women (Dickenson, 2002; Gerrand, 1993).

Altogether, the creation of embryos for research does not only bring ethical concerns for the embryos, but also for women. In egg cell donation, women are exposed to practical and social problems; practical, because of the hormone therapy and invasive IVF procedure without knowing the risks, and social, because of a potential exploitation of women by perceiving them as just being reproductive vessels. Both practical and social problems threaten women's autonomy in making informed and voluntary choices (Gerrand, 1993). By threatening the autonomy of women potentially participating in egg donation, without any physical, personal, or financial benefits, the risk of coercion and exploitation of women should be properly addressed in the discussion on research embryos (Baylis, 2000; Gerrand, 1993).

CHAPTER 5
CAN THE CREATION OF EMBRYOS FOR SAFETY RESEARCH ON SCD GAMETES BE JUSTIFIED?

For preclinically investigating the safety and effectiveness of SCD gametes in embryos, it is inevitable that specific research embryos are created. In the previous chapter I have mapped the ethical debate on the use and creation of embryos for research (pages 43-58). In this chapter, I will assess this debate and investigate if and under which conditions the creation of embryos for research can be justified in general, and specifically for research on SCD gametes.

The ethical assessment on the creation and use of embryos for research in this chapter will be performed by using wide reflective equilibrium (WRE). The first part of this chapter will give a brief introduction to procedural method of WRE. In the second part, I will assess the moral acceptability of using (spare) embryos and creating embryos for research in general, using the method of WRE. The third part will investigate the ethical justifiability of embryo research on SCD gametes as a case study. One question to study is: if the use and creation of embryos for research can be justified under specific circumstances, can it also be justified for research on SCD Gametes? I will argue that the creation of embryos for research on SCD Gametes can be justified, if the principles of subsidiarity and proportionality are met.

5.1. Wide reflective equilibrium (WRE)

In the first chapter of this thesis I argued why I chose for WRE to perform the ethical assessment in this thesis (pages 17-19). In this section, I will explain how I will use this approach.

In Rawls' theory there are three types of justification. The first is political justification, which only takes into account political values. The second is full justification, which only focuses on the own lives and comprehensive doctrines of citizens. In this thesis, I aim to reach the third type; public justification. This is a justification by political society in which citizens take into

account reasonable overlapping consensus (Rawls, 1993). The ground of justification is in this case the shared political conception. In such *overlapping consensus*, "people with divergent comprehensive doctrines can overlap in their acceptance of a conception of justice. They do not have to agree on everything but they do agree on principles of fairness" (Doorn, 2011, p. 68). This way, I aim to reach a ground of justification concerning the ethical justifiability of creating embryos for research in this ethically diverging debate.

Building further on the work of John Rawls (Rawls, 1971), philosopher Norman Daniels has given a structured description of the method of WRE (Daniels, 1979, 2011). According to Daniels, "The method of wide reflective equilibrium is an attempt to produce coherence in an ordered triplet of sets of beliefs held by a particular person" (Daniels, 1979, p. 258). In this method, a distinction is made between the following three levels of considerations:

(a) a set of considered moral judgments
(b) a set of moral principles, and
(c) a set of relevant descriptive and normative background theories.

To use the procedure of WRE, one starts with collecting initial moral judgements. These are considered 'intuitions' someone has about particular situations or cases (Daniels, 2011). Then, alternative sets of moral principles should be proposed that all "fit" with the moral judgements to various degrees. It is important not to choose the best fit right away, as this would provide only a 'narrow' equilibrium. One needs to use philosophical arguments to bring out the strengths and weaknesses of the alternative sets of principles. These arguments can come from relevant background theories. This means that the background theories should support the moral principles that are chosen over alternative principles, independent from the match of moral principles with one's moral judgements (Daniels, 1979). It is important to aim at coherence between the different levels (a, b and c) of considerations. This coherence can be reached by going back and forth between the different levels of considerations and revising the considerations, principles and theories that do not fit. This way, we arrive at a wide reflective equilibrium. It is called an 'equilibrium' if all levels of considerations cohere and are mutually supportive. We call it 'reflective' if the equilibrium is reached by going back and forth by between the different considerations. The reflective equilibrium is called 'wide' if coherence is

reached between all three levels of considerations and not only between one level (Doorn, 2011, p. 66).

In the next section, I will use WRE as a method to assess the consistency between moral judgments, sets of moral principles and background theories of different views on the justifiability of the use and specifically creation of embryos for research purposes.

5.2. Acceptability of the use and creation of embryos for research

Before turning to the case study of SCD Gametes, I will assess the arguments for and against the use of spare embryos and the creation of embryos for research in general using WRE. Based on my analysis, I will draw my own conclusion regarding the moral acceptability of using embryos for research.

In chapter four (pages 44-47) I have identified three different views considering the acceptability of using embryos for research. From these three views, three different sets of moral judgements and moral principles can be extracted. I begin this section with stating all considered moral judgements and towards the use of embryos for research, the moral principles that fit these considered moral judgements and all relevant background theories. I will show that each set of principles is related to the theories of personhood and potentiality.

After the paragraphs on the justifiability of using embryos for research, I will assess the acceptability of creating embryos for research, using the same method of WRE. I will compare the moral intuitions, principles and theories on the creation of embryos for research to the creation of spare embryos for women-friendly IVF.

5.2.1. A matter of moral status: personhood & potentiality

I have argued that three different positions regarding the acceptability of embryo research can be distinguished. I explained that supporters of the first position argue that embryos have the same moral status as born human individuals. Therefore, both should be protected to the same degree (Buckle, 1988; CDA, 1988). To use embryos solely for research purposes means to instrumentalize them, which cannot be justified considering their high moral status (CDA, 1988). The considered moral judgement resulting from these considerations is that embryo research cannot be justified. Furthermore, several moral principles can be identified in this view. First, embryos and born human individuals have an equal moral status. Second, embryos and born

human individuals should be protected because of their moral status. Last, to use embryos for research instrumentalizes them, which is not commensurable with their high moral status.

Following the second position, embryos have no moral status on account of which they should be protected. The considered moral judgement that can be identified here is that embryo research is just as acceptable as research with other body tissues. In this view, the moral principles consider moral status as well as in the first view. First, embryos have no moral status. Second, body tissue has no moral status and third, because embryos have no moral status they can be used under the same conditions as applying to research with any other body tissue.

The third view, holding the middle position, states that embryos have a limited worth of protection in comparison to born human individuals (Harman, 1999, 2003; Sandel, 2004; Steinbock, 2011). Because embryos have the potential to grow into a human being, or have a symbolic worth that connects them to humans, they do not have the same moral status as human beings, but a lower degree of moral status than born human individuals. In this view, the considered moral judgement thus states that embryos should be protected to a limited degree. This leaves the acceptability of using of embryos for research open. The first moral principle that is made here is that moral status comes in degrees. Furthermore, embryos have a lower moral status than born human individuals. Because of their lower moral status, they also have a lower worth of protection. Last, the principle is used that the potential that embryos have to grow into a human being or its symbolic worth grants them a degree of moral status.

What all positions have in common is that they (1) base their view about the worth of protection of the embryo on their view on the moral status of the embryo, (2) make a moral comparison between embryos and another entity (e.g. born human individuals or body tissues) and (3) imply that born human individuals have full worth of protection, whereas body tissues have none. Because all views base their position on the comparison of embryos to other entities (e.g. born human individuals with full moral status), it is essential to investigate why we give a moral status to specific beings and because of what qualities we grant them (full) moral status. Therefore, to perform an ethical assessment on the three sets of principles, I will give a brief introduction on the theories on which moral status is grounded; personhood and potentiality. Following the systematic approach of Daniels (Daniels, 1979), this leads to the following triplet of sets of considerations:

(a) Moral judgements of the three views: embryo research aimed to preclinically investigate the safety and effectiveness of specific technologies and methods can(not) be justified.
(b) Sets of moral principles of the three views: All consider the moral status and protection worth of embryos. The question all views answer is: "is the use of the embryo for research commensurable with its moral status?".
(c) Background theories: personhood and potentiality

The main reason we think grown human individuals deserve protection is because we consider them to be 'persons', having full moral status (DeGrazia, 1993; Warren, 1997). However, the view that being a person grants a being moral status and protection, the 'person view', does not automatically solve the issue of moral status though (Reinders, 1993). The question remains what the criteria are for being a person. What features make a being a person?

Several philosophers have answered the question on what criteria a being should meet to qualify as a person by returning to philosopher John Locke (Baker, 2000; Harris, 1985; Singer, 1980; Tooley, 1983). Following Locke, a being is a person when it has a specific mental capacity. A person should be able to imagine oneself in different times; past, present and future. This means that a person needs to be conscious of itself. Thus, according to Locke, a being without self-consciousness cannot be a person (Reinders, 1993). Although at several points departing from Locke, philosopher Lynne Rudder Baker agrees with him that the distinction between a person and a non-person lies in something mental. According to her, the possession of a first-person perspective is the essential feature of personhood (Baker, 2000). A first-person perspective must not be understood as a perspective from merely the biological body. According to Baker, personhood is not defined by being an organism; a person is not essentially biological. The essence of being a person is not to (only) have a body, but to have special mental properties to provide a first-person perspective. Baker gives the example of wondering how one is going to die or evaluating one's desires (Baker, 2000). This resembles the interpretation of personhood of philosopher Charles Taylor, calling persons self-interpreting animals (Taylor, 1985). Both authors describe a reflection on one's own life as an essential feature for personhood. However, Taylor and Baker want to go beyond Locke, who defines persons as only self-consciousness in the sense of distinguishing it from being a specific material or immaterial substance (Baker, 2000, p. 9; Moran, 2009). According to Taylor and Baker, being a person, a self-interpreting

animal, is more than that. Our experience is, as Taylor calls it, necessary that of an embodied agent (Taylor, 1995, p. 25). Baker emphasizes the necessity of embodiment as well: "a person is […] an embodied thinking substance with a first-person perspective (Baker, 2000, p. 77).

If a being is not capable of self-interpretation, does this mean that it has no moral status? Several authors have argued that properties for personhood can come in degrees (DeGrazia, 1997, 2008; Sumner, 1981). Philosopher David DeGrazia has argued that personhood can also be understood as a "cluster concept that serves as a summary placeholder for other concepts such as moral agency, autonomy, the capacity for intentional action, rationality, self-awareness, sociability, and linguistic ability" (DeGrazia, 1997). He argues that most of these properties can come in degrees, meaning that moral status might not be just a case of all-or-nothing. Even though a being is thus not considered a person with full moral status, it can have properties (e.g. moral agency, autonomy, self-awareness) of a certain degree that we connect to personhood. Having such properties to a certain degree can grant a being a proportional degree of moral status. DeGrazia argues that many of these properties, besides language and autonomy, can be found to a certain degree in many nonhuman animals (DeGrazia, 2008). Philosopher Leonard Sumner argued for a degree of properties that grant moral status to beings as well. According to him, the degree of moral status is connected with the degree of sentience (Sumner, 1981). Examples of beings having a different degree of sentience are persons, sentient animals and late fetuses. He argues that the degree of moral status is proportionate to the degree of sentience; "The animal kingdom presents us with a hierarchy of sentience. Non-sentient beings have no moral standing; among sentient beings the more developed have greater standing than the less developed, the upper limit being occupied by the paradigm of a normal adult human being" (Sumner, 1981, pp. 143-144).

Another ground for moral status, connected to the theory of personhood, is the potentiality theory. I have explained in chapter four (pages 44-45) that proponents of the first view, stating that embryos have the same moral status as born human individuals, grant full moral status to embryos, because embryos are already considered as human individuals. Proponents of the middle view argue that embryos can be viewed as beings actively developing their potential for personhood. They argue that the potentiality to grow into human beings grant embryos a limited moral status and proportionate worth of protection (Harman, 1999, 2003; Steinbock, 2011). In both positions, the view that an embryo has the potential to develop in a human being grants it a

degree of moral status. This means that the background theory of potentiality plays a role in determining the moral status of embryos in both views.

Potentiality is a concept first introduced by Aristotle. Aristotle makes a distinction between actuality and potentiality. Actuality is the current state of an entity. Potentiality is the ability to be in a different and more completed state. In the case of a wooden table, actuality is to potentiality as the wooden table to the wood. In the case of a human being, actuality is to potentiality as a human to an embryo. In Aristotle's teleological world view, potentiality is more than just 'possibility' in the sense of 'can become'. Rather, potentiality is what connects an entity to its end or completion ('telos') by defining what it is intrinsically determined to become. In this understanding, to say that an embryo has the potential to grow into a human being, is to say that it is intrinsically determined to realize its completion as a human being. The potentiality of an entity is its essence; an entity is essentially what it is meant to become (S. M. Cohen, 2016). This is quite different from how potentiality is understood in a modern scientific world view, in which the notion of an essence or an end generally cannot be understood as something apart from a physical entity. In this understanding, potentiality refers to a contingent relation of mere possibility: given the right circumstances, an embryo has the potential to become a human being.

I have shown that the theory of personhood supports the idea of moral status coming in degrees. The highest degree of moral status, full moral status, is granted to beings which we can consider persons. To call a being a person means that such a being has to have certain properties, such as the ability to reflect on one's life, embodiment and moral agency. If a being has these properties to a certain degree, we grant it a proportionate degree of moral status.

In the debate about the acceptability of embryo research, the theory of potentiality is highly connected to the theory of personhood, because the first and middle position contains principles based on potential personhood. The first positon uses the theory of potentiality to argue that embryos deserve the same respect as the human beings they can develop into. Supporters of this position consider embryos as already being human individuals. The third position, the middle view, uses the potentiality theory to argue for a limited worth of protection. Because an embryo has the potential to grow into a human being, but is not already one, it deserves a degree of respect. Having clarified the theories of personhood and potentiality, I will now continue assessing the three positions on the use of embryos for research by testing their coherency with these theories.

5.2.2. The Justifiability of Embryo research

When going back and forth between the theories of personhood and potentiality and the moral principles made in the first position, the views that embryos have the same moral status as born human individuals, or persons, is only coherent with the background theory of personhood if potentiality is understood as a teleological concept. Reasoning from an Aristotelian world view, the essential continuity between the embryo and the human being that it will become (if no external factors interfere with its completion) entails that embryos are to be considered as essentially persons and that as such they have a full moral status and must be treated accordingly (Eijk, 1997). Some proponents of this view specify that embryos deserve complete protection only from the point (after about fourteen days) when they can no longer split in two, as only after this stage it would be possible to ascribe a fixed individuality to each single embryo (Ford, 2002). However, others do not regard this a relevant criterion and hold that human embryos deserve complete protection already from the point of conception (Jochemsen, Garcia, Meir, & Harris, 2005; Vélez, 2004).

However, reasoning from a modern world view according to which potentiality refers to a contingent possibility rather than to an essential continuity, there are many differences between persons and early-stage embryos, which also grant a moral difference between them. As described in the previous paragraph, persons should have the ability to interpret their own lives in different times, which embryos in the early stages of development (fertilization stage, cleavage stage, blastocyst stage) cannot. Also the other properties for personhood, such as moral agency, autonomy and sentience or self-awareness cannot be identified in early-stage embryos. Therefore, on a modern understanding of potentiality, it is not coherent to state that embryos have the same moral status as born human individuals. This means that an early-stage embryo lacking these essential properties does not deserve the same level of protection as a grown human individual having these properties.

Moreover, saying that embryos are already persons essentially, is tantamount to saying that they are not so actually. As argued above, the properties which are necessary for personhood cannot be found in early-stage embryos. Insofar, the theory of personhood does not support the idea that embryos would already be persons. Unless understood in an Aristotelian manner, the

potentiality argument can thus not be used to argue that embryos are already persons, without departing from the theory of personhood.

Furthermore, the position that embryos have the same moral status as persons is difficult to combine with many accepted practices. Considering embryos as persons from the moment of conception, does not leave any room for practices such as abortion, intra-uterine devices that prohibit embryo implantation, and the creation of spare embryos in the context of IVF. These practices assume that embryos and fetuses have a different moral status than born human individuals. If we accept these practices, this cannot be coherent with the view that embryos have full moral status.

The second position is coherent with the theory on personhood, as well as with the theory of potentiality understood as referring to mere possibility. However, it does not accord moral relevance to the fact that this possibility, however contingent, makes embryos different from any ordinary human body tissue that cannot develop into a human being. Early-stage embryos have the potential to develop the properties of personhood. By denying that this has moral relevance, the second position is at odds with a widely held moral intuition.

The middle position, stating that embryos have a limited worth of protection, is also coherent with the theories of personhood and potentiality. Embryos at the blastocyst stage do not have the same properties as born human individuals, or persons, do. Since they cannot be identified as persons, they do not have full moral status and should not be protected to the same degree as persons. Using the potentiality argument, the potential of developing properties of personhood can give the embryo a worth of protection, yet not to the same degree of beings already possessing these properties. Also the argument of increasing worth (the more the embryo develops and the more it develops the structures necessary for later having the properties required for personhood, the more it should be protected) is in line with the theory that the properties of personhood can come in degrees, and that beings having these properties to a certain degree should be protected proportionate to the degree of owning these properties.

The second variant of the middle positon, using symbolic worth instead of potentiality, states that the embryo should not be protected because of its intrinsic moral value, but because of the community giving it meaning as a starting form of human life. Also this variant is coherent with the theories of personhood and potentiality. The value given to the embryo is in this case not because its being on its way to becoming a person would make it intrinsically valuable, but

because its connection to the human species as an early form of human life gives it a symbolic value. Still, it also acknowledges the potential the embryo has, because being a form of early human life, means having the potential to grow into a more developed form of human life; a person.

Altogether, both variants of the middle position are coherent with the theories of personhood and potentiality, while also acknowledging the moral intuition that human embryos have at least some (intrinsic of symbolic) value. Because early-stage embryos lack certain essential properties of personhood to grant them the same high moral status as born human individuals, they do not need to be protected to the same level as born human individuals. Yet, the fact that the embryo can potentially grow into a human being and the symbolic worth of the embryo grants it a limited degree of protection. Therefore, coherent with the theories of personhood and potentiality and the widely shared intuition that embryos are morally more special than just any body tissue, the moral value of an early-stage embryo is located between high and no moral value, which means they deserve a limited degree of protection.

5.2.3. A matter of double effect and instrumental value

In the previous section I have argued that the middle view and its set of moral principles are coherent with the background theories of personhood and potentiality, as well as with the widely shared intuition that embryos have a least some (intrinsic or symbolic) value. This means that within the framework of these theories, embryos have a limited worth of protection, which means that the use of embryos for specific research (e.g. stem cell research) can potentially be justified. Before I will move to the section investigating if the creation of embryos for the purpose of research can be justified, I will first identify the moral judgements, moral sets of principles and relevant background theories considering the creation of embryos for research.

I have argued in chapter four (pages 43-58) that the ethical difference between using spare embryos and creating embryos for research is centered around two main arguments. The first argument considers the intention of how these embryos are created. The second argument raises concern on the possible exploitation of women to donate their egg cells. I will first focus on the argument of intention.

Again, following WRE, I start with stating the considered moral judgements and matching moral principles. These can be identified in the different views on the (non) moral

difference between spare embryos and research embryos. A first view can be identified in van Beers' argument, which states that to create embryos with the intention to destroy them would instrumentalize them (van Beers, 2016). She argues that research embryos are only created for instrumental use, as against spare embryos that are created with a relational value; the reproduction process. Therefore, it is acceptable to create spare embryos and not acceptable to create embryos for research. The considered moral judgement in this view thus states that the creation of embryos for research is not acceptable. The moral principle that is made here is that the instrumentalization of embryos is wrong. She implies that an embryo that is created with a relational value is thus not instrumentalized. The moral principle of this view is based on the theory of instrumental value.

Murphy, as well as FitzPatrick, argue that the deaths of spare embryos in IVF are not intended, but only foreseen, as against the intended creation and destruction of research embryos (FitzPatrick, 2003; Murphy, 2012). In this view, the considered moral judgment is that the creation of research embryos cannot be justified. The second set of moral principles can be derived from their argument considering the acceptability of intentionally creating embryos for destruction. One moral principle is; intentionally creating embryos for destruction is morally wrong. A second moral principle states that it is permissible to create embryos that will be destroyed when the destruction is not the means for the end, but only a side effect. What these principles have in common is that they are both based on the theory of double effect.

A next alternative set of considerations can be identified in Devolder's view. Devolder argues against a moral difference between the intention of creating spare embryos and research embryos. In both cases, the embryos are created to serve a purpose other than their own. In the case of IVF, the creation of spare embryos reduces risks and enhances pregnancy chances for the woman (Devolder, 2005). In the case of research, the creation of embryos helps to investigate the effectiveness and safety of a technology or method. According to her, if we accept current IVF practices (effective and therefore woman-friendly IVF) we should also accept the creation of research embryos (Devolder, 2013). The considered moral judgment is thus that the creation of embryos for research is acceptable. The moral principle that is made here states that because embryos are justifiably instrumentalized in current IVF practices, instrumentalization of embryos for research should also be accepted. She argues that double effect cannot justify the creation of

spare embryos any more than research embryos. Here, the arguments are centered around the theory of double effect and instrumentality.

The last set of considerations considers the argument of Brock. He argues that the creation of embryos as well as the use and destruction of embryos is accepted, and that therefore the combination of these practices should also be accepted. Here again, the moral judgment that can be identified is that the creation of embryos for research is acceptable. The moral principle Brock states is that if one action is considered justifiable and another action is considered justifiable, the combination of them should also be considered justifiable. Since Brock implies that it does not matter with what intention an embryo is created, used or destroyed, his argument should be able to invalidate double effect reasoning. Therefore, also this set of principles is based on the theory of double effect.

In all different views the moral principles consider the moral difference (or non-difference) between the intention of creating spare embryos and research embryos. Furthermore, the intention arguments against and for the creation of embryos for research are centered around the theories of double effect and the instrumentalization of the embryo. This leads to the following triplet of sets of beliefs:

(a) Moral judgments of all views: The creation of embryos for research is (not) acceptable.
(b) Sets of moral principles: Intention grants a moral difference between creating spare embryos and research embryos versus there is no moral difference in intention between creating spare embryos and research embryos.
(c) Background theories: double effect and instrumental value

Before assessing the coherence of all sets of principles with the relevant background theories of double effect and instrumental value, I will first give an overview of these theories. The *principle of double effect* has already been explained briefly in chapter four (page 51), where I explained that the principle entails that causing harm can be justified when it is a foreseen but unintended side-effect of an action aimed at a good end (McIntyre, 2004). It thus aims to justify an effect that one normally finds impermissible, but that is a merely unforeseen side effect of a legitimate act. The principle of double effect can be first located in Thomas Aquinas' *Summa Theologiae*, in which he (e.g.) treats homicidal self-defense (Aquinas, 1981). Nowadays, the principle refers to a

set of ethical criteria, mostly but not exclusively used by Christian philosophers. To decide if an act is morally permissible, the next four ethical criteria of double effect should be met; (1) the *nature-of-the-act condition*, which states that the action itself should be good or at least indifferent in itself, (2) the *means-end condition;* the good effect and not the harmful effect should be intended, (3) the *right-intention condition* states that the harmful effect should not be a means to the good effect and according to (4) the *proportionality condition,* the harm should be proportionate to the good effect (Cavanaugh, 2007; Mangan, 1949).

The principle of double effect is used in several contexts, but often considers cases of pregnancy and abortion (Bennett, 1966; Donagan, 1979; Foot, 1967; McIntyre, 2004). Imagine a doctor who thinks that abortion is morally impermissible, even as a means to save the mother's life. However, the same doctor could believe it is permissible to perform a hysterectomy on a pregnant woman with ovarian cancer (McIntyre, 2004). In performing the hysterectomy, the doctor aims to save the life of the woman. He foresees the death of the fetus, but does not intend to kill it. In performing an abortion, on the contrary, the killing of the fetus is a means to save the mother. In this case the killing of the fetus is not foreseen, but intended. Thus, following the principle of double effect, the killing of the embryo can only be justified in performing a hysterectomy, in which the killing of the fetus is not intended, but only foreseen.

The concept that an entity can be 'instrumentalized' is based on the second background theory; the theory of instrumental value. In philosophy, a distinction is made between intrinsic and extrinsic, or instrumental, value. Intrinsic value is the value something has "in itself, or "for its own sake" (Zimmerman, 2014). To give an example, a singer could say that she loves to sing. If she loves to sing because of the singing itself, and not because she could get famous or earns her money with it, singing has an intrinsic value to her. The opposite of intrinsic value is extrinsic value. Extrinsic value is given to things not because they have value in itself, but because they can lead to something else to which they are related in some way (Zimmerman, 2014). To use the same example again, if the singer loved singing because she can pay her house and fancy car with it, she grants an extrinsic value to singing. It has been argued that the relation between the end and the extrinsic means to get to that end is an instrumental relation (Korsgaard, 1983). Going back to the example, in the second case, the singer makes instrumental use of singing, to reach her goal; a house and a fancy car. If we apply this on the creation of embryos, we could say that if we use embryos to reach a goal, we are using the embryos instrumentally. If someone says that a

specific action "instrumentalizes" embryos, he thus means that we use an embryo to reach a goal, other than in the interest of the embryo. By using the embryo instrumentally, we give an instrumental value to it.

5.2.4. The justifiability of creating embryos for research

Having clarified the theories of double effect and instrumental value, I will now assess the coherence of the moral judgments, sets of moral principles and these theories. I will show that double effect and instrumental value cannot provide a moral distinction between the creation of embryos in standard IVF procedures and the creation of embryos for research.

The first set of moral principles I discuss is the set identified from the argument of van Beers (van Beers, 2016). She argued that spare embryos in IVF have a relational value (a parental plan), and research embryos only have an instrumental value. The moral principle that can be identified states that it is morally wrong to instumentalize embryos. However, the argument of van Beers is not coherent with the theory of instrumental value, because this theory applies to research embryos as well as to spare embryos. In creating spare embryos for woman-friendly IVF, the majority of embryos also serves as a means to reach a goal; to increase the chances of a successful pregnancy and to decrease risk of the harms for the woman. This means that in standard IVF practices, embryos are instrumentalized in order to perform a successful IVF procedure.

Van Beers could reply that there is still a difference, because of the relational value of spare embryos, since they are considered to be part of a parental plan. However, with this response she would only confirm the fact that spare embryos are just as much instrumentalized as research embryos. Following the theory of instrumental value, something has instrumental value when it is (also) used to serve a purpose other than its own. To say that spare embryos have a relational value because they are part of a parental plan, is to say that we use embryos instrumentally to benefit this parental plan. Additionally, in the use of research embryos to investigate the effectiveness and safety of ARTs, it can be argued that these embryos also have a relational value. The goal of creating these embryos is to responsibly introduce ARTs into clinical practice. These ARTs can be used to help several couples with their parental plans. The argument of instrumental use and relational value can thus not be used to defend a moral difference between spare embryos and research embryos.

The following set of moral principles I discuss is the one from Murphy and FitzPatrick (FitzPatrick, 2003; Murphy, 2012). According to this set of principles, intentionally creating embryos for destruction is morally wrong. Furthermore, it is only permissible to create embryos for destruction when the destruction is not a means to the end, but only a side effect. Murphy and FitzPatrick argue that, using the principle of double effect, the destruction of embryos in standard IVF is only foreseen, as against the intentional destruction of research embryos. However, does double effect really justify standard IVF procedures? The creation of spare embryos in woman-friendly IVF cannot be understood as merely foreseen, because one could very well limit the creation of embryos to the amount (one or two) that can be responsibly transferred to the womb in one IVF-cycle (embryo-friendly IVF). The majority however accepts current IVF practices and sticks with woman-friendly IVF. This means that in a society that accepts woman-friendly IVF to be the standard IVF practice, it is incoherent to say that creating embryos for research instrumentalizes embryos and that creating more embryos than that will be used (spare embryos) does not instrumentalize embryos. To make the choice to perform woman-friendly IVF, necessarily means to intentionally create spare embryos that will be destroyed (or remain frozen) and will thus not result in a child. Therefore, it is incoherent to argue that the creation of research embryos not resulting in children is intended and the creation of spare embryos not resulting in children is merely foreseen.

As to the intentional destruction of embryos, in performing woman-friendly IVF, the procedure necessarily involves creating spare embryos. The gross majority of these spare embryos will never be used for reproductive purposes (including by another couple). Even if (in several subsequent cycles) all embryos created for woman-friendly IVF would be placed inside the womb of the woman, it is indubitably known that the majority of embryos will not result in a child and will thus die. Because standard woman-friendly IVF practices are intentionally chosen over embryo-friendly IVF practices, double effect cannot justify embryo deaths in standard IVF procedures and can therefore not be an argument for a moral difference between spare embryos and research embryos.

FitzPatrick's adds the argument of constitutive relation to the argument of double effect discussed above (FitzPatrick, 2003). According to FitzPatrick, creating embryos for research is morally different from creating embryos for IVF, because creating embryos for research and the destruction of embryos is a constitutive relation. To create embryos for research, means thus to

create embryos for destruction. However, it is incoherent to argue that the creation of spare embryos is not intentionally in a constitutive relation with destroying them. Because choosing woman-friendly over embryo-friendly IVF is so closely connected to creating spare embryos, it cannot be argued that the creation of spare embryos is a merely foreseen and not intended element of standard IVF. Therefore, using the argument on constitutive relation of FitzPatrick, performing the standard IVF procedure and creating spare embryos are also in a constitutive relation. Knowing that the majority of spare embryos will not be used for another couple's reproductive purposes, creating spare embryos automatically means that they will remain frozen or be used for research and/or be destroyed. FitzPatrick's argument stating a difference in intention and foreseeability between spare embryos and research embryos is thus incoherent. In standard IVF practices, embryos are created and destroyed (or at best remain frozen) in the same constitutive relation as in creating embryos for research, only for a different purpose; decreasing risks and increasing pregnancy chances for the woman. Therefore, double effect cannot be used to argue for a moral difference in performing standard IVF practices leading to spare embryos and creating embryos for research purposes.

How coherent is the set of moral principles identified in Devolder's argument? According to her, if we allow standard IVF practices, we should also allow the creation of embryos for research (Devolder, 2005, 2013). This can be interpreted as an argument of *overlapping consensus*, because the ground of justification is in this case the general acceptance of standard IVF practices. In my view, she rightly argues that double effect cannot justify the creation of spare embryos any more than research embryos, as I have shown this in the previous paragraphs. According to Devolder, proponents of a moral distinction between the creation of spare embryos and research embryos grant moral value to the whole group of early-stage embryos in the IVF procedure (Devolder, 2005). This is precisely what happens when proponents of the moral distinction argue that in IVF the instrumentalization of embryos is not hundred percent, as against the hundred percent instrumentalization of research embryos. Indeed, one of the created embryos for IVF will result in a child and might therefore be not instrumentally used. When you perceive all the embryos as a group and the IVF cycle yields ten embryos, ninety percent of the embryos is instrumentalized when one embryo results in a child. In a case of creating embryos solely for research, one hundred percent of all embryos are instrumentalized. This is however incoherent when you do not perceive early-stage embryos a group, but separately. An argument one could

imagine is to say that one does not know beforehand which embryo will result in a child and which embryos will end up being spare embryos in IVF. This way, all embryos at IVF have at least a chance to become a child. However, this does not make any sense when we consider our standard IVF practices. The fact that you do not know beforehand which one of the embryos is going to result in a child does not mean that you then should ignore the fact that they are separate entities, each of which has a similar chance of not being chosen for transfer to the women. In playing Russian Roulette, the person who gets the bullet is not only instrumentalized for 16,67 percent (one out of six) to save the other players. The fact is, as Devolder correctly explains (Devolder, 2005), the embryos that remain unused after IVF, are fully instrumentalized individual entities. Moreover, the fact that some embryos will be chosen for transfer, does not detract from the fact that they were not created with the intention that these specific embryos would indeed be allowed to grow into a child. Even the embryo resulting in a child could be perceived as instrumentalized. The fact that it is not known beforehand which embryo will result in a child, means that every embryo is instrumentally used to provide the ability to choose one out of them. I conclude that the creation of embryos in standard IVF is no less instrumentalizing than the creation of embryos for research.

The instrumentalization of embryos in standard IVF practices as well as of embryos created for research can thus be considered equal. However, how strong is Devolder's argument that because embryos are instrumentalized in standard IVF, it should also be accepted to instrumentalize embryos by creating them for research? In the light of health risks for the woman and success rates of pregnancy, woman-friendly IVF is the current standard procedure in IVF. This means that by performing woman-friendly IVF instead of embryo-friendly IVF, we imply that the creation of spare embryos is proportionate to the benefits for the woman. To say that a certain action is morally right because it is proportionate to the benefits means that this action meets the proportionality principle. I will explain this principle more extensive in the last part of this section. As for now, I will leave it to the explanation I just gave.

Devolder, rightly argues that in woman-friendly IVF, the proportionality principle can only be met when the value of the embryo is considered rather low (Devolder, 2013). To accept the creation and destruction of spare embryos in order to benefit the health of the woman, means that the embryo cannot be considered to have full moral status. Otherwise, the health benefit for the woman would not be proportionate to the deaths of the embryos. I have already argued above

that the middle view, granting a limited moral value to embryos, is coherent with the background theories of personhood and potentiality. The rather low value of the embryo described by Devolder is thus coherent with the overall principles and theories. According to Devolder, because the creation and instrumentalization of spare embryos is justified in IVF because of the benefits for the woman, the creation and instrumentalization of embryos for research can also be justified because of the benefits regarding safety and effectiveness of important ARTs (Devolder, 2005). In other words; if the moral value of the embryo is considered rather low in IVF procedures, its low moral value should not stand in the way in performing important research. Although Devolder succeeds to invalidate a difference in instrumentalization between spare embryos and research embryos, she seems to overlook another difference in intention that can be made by opponents of creating embryos for research. Devolder has shown that creating and instrumentalizing spare embryos for standard IVF is accepted because of the rather low moral status of embryos. However, is there not a difference in using embryos to benefit a reproductive purpose against using embryos to benefit research purposes? Before I will turn to this question, I will first discuss the last set of principles.

The last set of moral principles I assess is extracted from the argument of Brock. His argument states that neither the creation of an embryo, not its use and destruction, is bad or impermissible and therefore, the combination of the three elements should not be morally problematic either (Brock, 2010). The moral principle that can be extracted from this reasoning (if one action is considered justifiable and another action is considered justifiable, the combination of them should also be considered justifiable) does not succeed in invalidating double effect reasoning, because Brock's argument completely overlooks the intention argument. In his argument, he implies that the intention of an action does not matter, while the intention is exactly the combining factor between creating embryos and using and destroying embryos. The act of creating embryos solely for the use and destruction in research is argued to be morally impermissible because opponents argue that it is wrong to create embryos with the intention of destroying them. They argue for a difference in intention between creating spare embryos and research embryos using double effect. By ignoring the fact that the intention of creating research embryos is the reason why the combination of the three elements (creation, use and destruction) is perceived as morally problematic, Brock does not overcome double effect reasoning.

Thus far I have shown that it is incoherent to argue for a difference in instrumentalization between spare embryos and research embryos. I have also shown that double effect is as incapable of justifying the creation of spare embryos in women-friendly IVF as it is with regard to the creation of embryos for research. In the creation of spare embryos and the creation of research embryos, the embryo deaths are intended and not merely foreseen. Does this mean that the intention argument is made invalid?

An argument I have not yet discussed, is the argument that the instrumental use of embryos for reproductive purposes is different than the instrumental use for research purposes. Creating embryos to benefit a reproductive purpose, might still be connected to the 'natural', original purpose of embryos, whereas the creation of embryos to benefit research purposes lacks this connection. However, as already been argued in the paragraph assessing the coherency of van Beers' argument, creating embryos for research on ARTs also benefits reproductive purposes. This means that the embryos created for research are still connected to a 'natural purpose' to a certain degree. Nevertheless, it must be admitted that this connection is more indirect than in the case of standard IVF. Furthermore, this only counts for the creation of embryos for ARTs.

The argument considering a so-called 'natural' purpose also leads to another possible argument against the creation and instrumentalization of embryos for research; the *slippery-slope argument*. If we allow the creation and instrumentalization of embryos for research, this might lead to a slippery slope towards possibly dangerous and dehumanizing (unnatural) practices. Examples of such practices could be the use of fetuses for spare parts, cloning babies or the creation of designer babies.

The slippery-slope argument raises legitimate concerns, but the possibility that the creation of embryos for research will lead to dangerous and dehumanizing practices is very unlikely. Several dehumanizing practices, such as the creation of embryos for body parts, can be prevented by a simple ban on reproductive cloning and other relevant regulations that are already in force in many countries (Sandel, 2004). For instance, in the Netherlands, it is already included in the law that when the ban on the creation of embryos for research would end, article 9 and 11 of the embryo law, stating that cloning and other dehumanizing purposes will not be allowed, will come into force (CBO, 2003). Moreover, the criteria of proportionality and subsidiarity (laid down in the treaty on European Union) have to be met in every case where embryos would be

created for research purposes (de Wert & Dondorp, 2008). With the proper regulation, it is thus very unlikely that allowing the creation of embryos for research will lead to a slippery slope of dangerous dehumanizing practices with embryos.

5.2.5. The ethics of obtaining egg cells to create embryos for research

The second argument against the ethical justifiability of creating embryos for research concerns the oocyte donors. To assess these arguments, I include practice-based intuitions supported by different researches. Although the concerns should be taken very seriously in the debate on research embryos, it has been argued that the risks for egg cell donors are not as big as often is suggested (Olsthoorn-Heim et al., 2006). Considering the practical risks for egg cell donors, ovarian hyper stimulation syndrome (the biggest risk of hormone stimulation) has been associated with the emergence of a pregnancy (Devroey et al., 2011; Mertes & Pennings, 2011). This means that women who donate their egg cells outside a reproductive procedure are less likely to being at risk. As to the social risks, several legal conditions for egg cell donation prevent the possible exploitation of women. An example of such condition is that women are not allowed to be paid for their donated egg cells (Olsthoorn-Heim et al., 2006). If egg cell donation would have financial benefits, it is not unthinkable that this could lead to the exploitation of women in a precarious financial situation (Baylis, 2000; Rao, 2006). In such a case, women of a lower economic status could be persuaded to collaborate in egg cell donation, because they might be in desperate need of money. These women would then be more vulnerable for exploitation than women with a higher income. This does not only lead to inequality between more and less wealthy people, but it also threatens these women's autonomy.

Although the medical and social risks are not as big as often suggested, this does not mean that we should not pay attention to them. It stays important to include the risk of coercion and exploitation of women in the debate of creating embryos for research. To assume that a situation so closely connected to potential violation of the rights of women does not need constant check-up would be naïve and ignorant. The creation of embryos for research can thus only be justified when taking the potential risks for egg cell donors into constant consideration. This means that to allow the creation of embryos for research, there should be proper regulation regarding the responsible obtainment of egg cells.

One suggestion to responsibly obtain a sufficient amount of egg cells for research is the initiative of egg sharing (Ahuja, Simons, & Edwards, 1999; Blyth, 2002). Egg sharing is "an arrangement in which a woman is offered free or reduced-cost assisted conception treatment in return for 'donating' oocytes for the treatment of another woman or for research, the cost of her treatment being subsidized by the recipient of her oocytes" (Blyth, 2002). Instead of paying women for their donation, the donor receives free or reduced-cost reproductive treatment, such as IVF. During the reproductive treatment, already several mature egg cells will be produced in standard IVF. In egg sharing, a couple of these egg cells will be donated. This initiative may still come with increased medical risks for women, since the arrangement to donate some of the woman's oocytes may entail that more often a further stimulation cycle is necessary than would be the case if the woman could use all oocytes obtained in one cycle to create embryos for herself. Moreover, egg sharing can still lead to exploitation since it is thinkable that only women of a lower income will participate because of the high treatment costs in countries or settings where IVF Is not reimbursed. However, egg sharing rules out the possibility to sell gametes to earn money. Furthermore, research has shown that women participating in egg sharing acknowledge the demand of egg cells can be exploitive, but emphasize that they make an own decision to volunteer for egg sharing (Haimes, Taylor, & Turkmendag, 2012). These women argue that they have the ability to act autonomously in their decision to volunteer. Nonetheless, as these women still make a decision under (financial) circumstances not necessarily of their choosing, egg sharing can only diminish, but not rule out all risks for women. Therefore, it is key to make sure the risks of obtaining egg cells are always proportionate to its benefits.

5.2.6. Subsidiarity and proportionality

I have argued that if we accept the use of embryos for the purpose of maximizing success and safety for woman during IVF, we could also accept the creation of embryos for important research purposes. This does not mean that we can freely create embryos for research without any constraint. How to decide in which cases it can be justified to create embryos for research? To constantly reflect on the possible risks for egg cell donors is one example of a condition we have to meet. Moreover, focusing on the limited moral value of the early-stage embryos and the risks towards egg cell donors, one can identify two conditions which have to be met to justify the creation of embryos for research.

The first condition is to meet the subsidiarity principle, which states that the creation of embryos for research is only permissible when the research cannot be performed in an alternative (suitable) way to reach the same goal (Isasi & Knoppers, 2006). To give an example, the creation of embryos for the purpose of research can only be justified when the same research cannot be performed with spare embryos or without any kind of embryos. It could be the case that there are no spare embryos available, that the research in question can only be performed with specially created embryos, or that research with e.g. animal models cannot give the same important information. In all cases, there is no adequate alternative research methodology to perform the needed research, which means the creation of embryos for research can be justified according the subsidiarity principle.

Second, research embryos should not be created for every arbitrary purpose. Creating and destroying embryos for research on e.g. cosmetics would not commensurate to the specific respect they deserve. However, if the destruction of embryos serves a morally important purpose, their social respect and limited moral status are not violated (Brock, 2010). To decide which research is 'important enough' to be balanced against the costs of creating end destructing embryos, research has to meet the so called 'proportionality principle'. In the case of embryo research, the proportionality principle refers to "constraining embryo research to practices that serve important and worthwhile goals and purposes" (Isasi & Knoppers, 2006). This means that the study using research embryos should be likely to yield important scientific or clinical data (ASRM, 2014), such as research results concerning the treatment and prevention of serious human disease and suffering (Brock, 2010). Also considering proportionality, the creation of research embryos should be performed with the minimum required gametes or embryos for adequate research and minimal risks for gamete donors (ASRM, 2014).

5.3. The case study: SCD Gametes

I have argued that the creation of embryos for research can be justified under certain circumstances. I have identified two conditions for justifying the creation of embryos for research. Clearly, the creation of embryos cannot be justified for every arbitrary goal and in any arbitrary study plan. To illustrate how to decide if the creation of embryos for a certain study can be justified, I will perform a case study on embryo research on the safety and effectiveness of using SCD gametes. Thus; can the creation of embryos for research be justified for research

aimed to preclinically investigate the safety and effectiveness of reproduction using SCD Gametes?

5.3.1. Subsidiarity

The first principle that has to be met is the principle of subsidiarity. I argue that there are two approaches of subsidiarity.

The first approach questions if the research can be performed in an alternative effective way. I have already explained that embryo research on SCD gametes cannot be performed with spare embryos. The embryos to be investigated need to be created using both naturally derived and either SCD sperm or oocytes. There is thus no alternative for performing embryo research into the safety and effectiveness of SCD gametes than by creating embryos. It can also be questioned if there are possibilities to do sufficient safety research on artificial gametes without performing embryo research. Animal research and preclinical studies can also provide information on the effectiveness and safety of SCD Gametes. However, as I already have argued in chapter two and three (pages 21-42), embryo research forms an important step between using the technique on animals and using it on born human individuals, by giving essential information on the development of the embryo created by this technique (Brison et al., 2013; Dondorp & de Wert, 2007, 2011; Hinxton, 2008). This means that there is no adequate alternative to perform the same important research in another way.

The second approach questions if the goal of the SCD gametes can be reached in an alternative way. Are there other options to help couples with reproduction? Adoption or the use of donor gametes can also help couples that face infertility problems to get a child. However, the difference between adoption or the use of donor gametes and using SCD gametes is the fact that the future child can only be genetically related to both parents in the latter case. Currently, there is no alternative for couples facing infertility problems to create a genetically related child. This means that it should be investigated if the benefit of creating a genetically related child can be balanced against the cost of creating embryos for research. This will be discussed in the section beneath, considering proportionality.

Since there are no alternative adequate research methodologies to perform research on SCD Gametes or to get a biologically related child with other reproductive options, the creation of embryos for research on SCD gametes can be justified following the principle of subsidiarity.

5.3.2. Proportionality

The second principle questions if the benefits of SCD gametes and embryo research on SCD gametes are big enough to justify the creation of research embryos? I argue that there are also two approaches of proportionality.

The first approach questions if the importance of SCD gametes is proportionate to the creation of research embryos. As I already explained above, the difference between the use of SCD gametes and other reproductive alternatives is the possibility to have a genetic link between parents and child. The fact that there are no alternative ways for infertile couples to get a biologically related child is enough to meet the subsidiarity principle. To meet the proportionality principle however, it has to be shown that the importance of the genetic link is proportionate to harms of the creation of embryos. This means that to justify the creation of embryos for research on SCD gametes, it is key to investigate the importance of the genetic link.

Although the importance of the genetic link needs further scrutiny and several researches have suggested that there are no significant differences considering psychological well-being between biologically and socially related parents and children (Golombok et al., 2004; Golombok et al., 2006; Lansford, Ceballo, Abbey, & Stewart, 2001), it appears in reality that parents as well as children consider the genetic link to be very important (Mertes & Pennings, 2010). The importance of the genetic link for parents appears in the fact that couples cooperate in invasive ART treatments like IVF and ICSI, when they could also choose for alternatives such as the adoption of a child. To give an example, ICSI holds a "statistically significantly higher risk of malformations for the offspring than natural conception. Still the overwhelming majority of patients opt for this technique" (Mertes & Pennings, 2010, p. 270). Furthermore, the decision to choose for donor conception is also often made after a long process of failed ART treatments. This implies that the treatments offering a genetic link between parents and child are generally favored in comparison to options without a genetic link. As to the child, it is very common that a child created with a donor gamete, or a child that has been adopted, wants to meet his or her biological parent(s). This means that the child apparently sees value in the biological link between him or her and the biological parents. The importance of the genetic link can thus not be found in studies regarding psychological well-being of genetically related parents and children, but in the fact that many parents and children consider this link to be valuable. The question is

then; is the desire of parents to have a genetically related child important enough to justify the creation of embryos for safety research?

Furthermore, after the safety and effectiveness of SCD gametes are established, SCD gametes can be used to decrease the need of oocyte donors. Using the technique to develop SCD gametes makes it possible to derive gametes out of stem cells. This way, there can be created egg cells and sperm cells in the amount we need for research or therapy, which means that the pressure on gamete donors would decrease remarkably. Additionally, the method can improve the safety of current IVF practices, by making hormone stimulation redundant.

As to the second approach, is the importance of embryo research on SCD gametes proportionate to the creation of research embryos? As already explained under the principle of subsidiarity, embryo research is considered an important contribution to the research process. The question then remains; is the extra safety proportionate to the creation and destruction of embryos? I have already argued that embryos have a limited worth of value, and that if they are used in IVF to maximize pregnancy chances and lowering risks for women, the moral value of the embryo is also proportionate to use it in important research. If embryo research would be left out of the research process, this means that the use of SCD gametes would be tested from animal models directly to humans in clinical trials. Considering the full moral status of born human individuals as against the limited moral status of early-stage embryos, the use of embryos for research to prevent exposing the unknown risks to born human individuals can be perceived as proportionate.

Aditionally, it has been argued that SCD gametes can help in fundamental research to understand the development of sperm- and egg cells and of early embryos (Hinxton, 2008; ZonMw, 2012). Therefore, the embryo research is not only benefitical towards a responsible safe introduction of SCD gametes, but also benefits fundamental research.

In the light of the assumption that the genetic link is of moral importance and the benefits considering oocyte donors, the improvement of IVF and safety, the creation of embryo for research on SCD gametes meets the proportionality principle. To perform the creation and research of embryos in a responsible, respectful and proportionate way, I want to emphasize that it is important to use a minimal amount of embryos and donor gametes to perform adequate research. In conclusion, by meeting the subsidiarity principle as well as the proportionality

principle, the creation of embryos for safety research concerning the responsible introduction of SCD gametes into clinical practice can be justified.

CHAPTER 6
CONCLUSION

In this thesis, I investigated if the creation of embryos for safety research can be ethically justified, in particular on safety research concerning the responsible introduction of SCD gametes into clinical practice, and under what conditions.

6.1. Results

I have argued that many ARTs are introduced into clinical practice without sufficient safety research. Several authors have pointed out that all too often, the introduction of new ARTs has in the past taken place on a trial and error basis (Brison et al., 2013; Dondorp & de Wert, 2011; Harper et al., 2012; Pennings et al., 2007; Provoost et al., 2014). I have shown that IVF as well as ICSI lacked sufficient safety and effectiveness research and were merely introduced on a trial-and-error basis (Dondorp & de Wert, 2011). The introduction of ARTs into clinical practice without proper research is not only a matter of the past. The fact that there was no to little preclinical testing before introducing the mitochondrial supplementation treatment 'Augment' into clinical practice is a recent illustration of the point.

In the light of the health interests of children conceived through these technologies, as well as of the health interests of the parents, current safety research should be improved (Dondorp & de Wert, 2011; Harper et al., 2012; Pennings et al., 2007). The Task Force on Ethics and Law of the European Society of Human Reproduction and Embryology (ESHRE) argued that sufficient safety research should be performed to serve both the welfare of the child and public health, and to inform potential parents (Pennings et al., 2007). ESHRE recommends formal research divided into four steps; a) animal studies, b) preclinical embryo research, c) clinical trials and d) follow-up studies (Pennings et al., 2007). The American College of Obstetricians and Gynecologists (ACOG) supports the necessity for safety and effectiveness research. According to them, the risks of ARTs should be properly investigated because of the right on informed consent for the patients and adequate information for clinicians (ACOG, 2006a). The American Society

for Reproductive Medicine (ASRM) adds with regard to embryo- and gamete research that such research always has to meet certain conditions, such as the importance of the goal of the study and the necessity for approval by an ethics committee (ASRM, 2014).

Although there are several good recommendations on how to safely introduce new ARTs (ACOG, 2006a; ASRM, 2014; Pennings et al., 2007), these are often not followed in practice. As seen in the introduction of *Augment* treatment, new technologies are despite of all the recommendations still introduced into clinical practice without sufficient evidence of safety and effectiveness. This means that introducing new ARTs in clinical practice with the current way of safety research procedures would be irresponsible. Therefore, current research practice should be improved. This concerns also the safety research for the responsible introduction for SCD gametes in specific.

Thereafter, I have shown that the creation of SCD gametes is an emerging development in the field of ART. Although the development is still at a research stage, current research suggests medically assisted reproduction using SCD-gametes is a possible scenario (particularly for couples currently dependent on donor gametes for reproduction) in the near to midterm future (Hinxton, 2008; Marques-Mari et al., 2009).

As a new technique in ART, SCD gametes can have many applications. One can think of SCD Gametes as a fertility treatment for infertile or subfertile couples or post-menopausal women, but they could also potentially help transsexuals, intersexual persons and gay couples with reproduction. Furthermore, in addition to reproductive goals, SCD gametes can be useful in research. It has been argued that SCD gametes can help in fundamental research to understand the development of sperm- and egg cells and of early embryos (Hinxton, 2008; ZonMw, 2012). Moreover, the possibility to create gametes out of stem cells decreases the need for gamete donors for research and therapy and can also make hormone stimulation redundant in IVF treatment.

In an environment where ARTs are often introduced without sufficient safety research, the possible introduction of SCD gametes in medically assisted reproduction raises the question how this should be safely performed. A process of animal research, preclinical embryo research, clinical trial and follow-up studies is recommended to investigate the safety and effectiveness ARTs, and specifically of SCD gametes (Brison et al., 2013; Dondorp & de Wert, 2007, 2011; Hinxton, 2008). Embryo research is a very important step in the process, because it can provide

essential information on the development of the embryo created using a certain ART (Brison et al., 2013). In most cases of research on ARTs, spare embryos left over from IVF can be used for preclinical embryo research. However, research on the safety of SCD gametes needs to be performed with specially created research embryos. The use of specifically created embryos for research is however regarded as morally problematic, because of concerns on the moral status or value of embryos and/or to the risk that women will be pressured into donating oocytes against their best interest.

In chapter four, I mapped the ethical debate, identified in the selected literature, concerning the use and creation of embryos for research. I argued that this debate can be structured around three main ethical issues. First, there is the question if embryos can be used for research in general. This is closely connected to the moral status we describe to the embryo. I have argued that there can be distinguished three different views on this. Proponents of the first view considers embryos to have the same moral value as grown human individuals. According to this view, it cannot be ethically justified to use embryos for research. Proponents of the second view consider embryos to have the same value as any other body tissue. They are not opposed to the use of embryos for research any more than to the use of any other body tissue for research. The third view, inhabiting the middle position, states that embryos have a limited worth of protection. They grant limited moral value to the embryo because it can potentially grow into a human being or because of its symbolic connection with mankind. Their moral value is not as high as it is for grown human individuals, but also not as low as for any body tissue. People supporting this view grant a moral value to the embryo which increases the more the embryo develops. Following this view, the use of embryos for research can be justified when the research is commensurable to the limited value of the embryo.

Supporters of the first view clearly forbid the creation of embryos for research and supporters of the second view clearly would not mind creating embryos for research. The middle ground, which is supported by the majority, leaves room for discussion. Opponents of the creation of embryos for research argue that such practices instrumentalize embryos because of a difference in intention between creating spare embryos and research embryos (van Beers, 2016). Using double effect reasoning, the opponents argue that in IVF, spare embryos are created as a foreseen side effect of the procedure, whereas research embryos are intentionally created for research and thus for their destruction (FitzPatrick, 2003; Murphy, 2012). Proponents of the

creation of embryos for research argue that double effect reasoning cannot offer a moral distinction between the creation of spare embryos and research embryos, because in current IVF practices, spare embryos are created with the same instrumentalization as research embryos (Devolder, 2005). In accepting current IVF practices leading to spare embryos, the moral status of the embryo must be considered that low that it should also be accepted to create embryos for research (Devolder, 2013). It has also been argued that the creation as well as the use and destruction of embryos is separately justified, which means that the combination of the three elements should also be justifiable (Brock, 2010).

Another problem that rises with the creation of embryos for safety research is the demand for donor egg cells. In IVF practices, the benefit for the women undergoing these procedures is clear. The risks are accepted, because the treatment can help to pursue the reproductive goal of the women. In donating for research however, women undergo hormone stimulation therapy and invasive medical procedures, when there is no concrete benefit for the woman (Baylis, 2000; Gerrand, 1993). In egg cell donation, women are exposed to medical and social problems; practical, because of the hormone therapy and invasive IVF procedure without knowing the risks, and social, because of a potential exploitation of women. Both medical and social problems threaten women's autonomy in making informed and voluntary choices (Gerrand, 1993). By threatening the autonomy of women potentially participating in egg donation, without any physical, personal, or financial benefits, the risk of coercion and exploitation of women should be properly addressed in the discussion on research embryos (Baylis, 2000; Gerrand, 1993).

In chapter five, I first assessed the moral acceptability of using (spare) embryos and creating embryos for research in general, using the method of WRE. I identified three sets of principles considering the use of embryos for research and identified four different sets of principles considering the creation of embryos for research, based on the arguments of several authors. I argued that the middle position, granting a limited moral value and limited degree of protection to embryos, is coherent with the background theories of personhood and potentiality as well as with the widely held intuition that embryos have some (intrinsic or symbolic) value. Because early-stage embryos cannot be considered persons, they do not deserve full moral status. Yet, to respect their potentiality to grow into human beings and their social connection to the human species, they deserve more protection than any other body tissue. This means that their

moral status is located between full and no moral status, and thus deserve a limited degree of protection.

Thereafter, I have shown that the moral sets of principles found in the arguments of several authors are incoherent with the background theories of double effect and instrumental value (Brock, 2010; FitzPatrick, 2003; Murphy, 2012; van Beers, 2016). Both theories cannot serve as a foundation for a moral distinction between spare embryos and research embryos. The moral set of principles identified in the argument of Devolder (Devolder, 2005, 2013) fit best to the background theories, but still fails to convince that creating embryos to benefit research purposes is morally similar to creating embryos to benefit reproductive purposes. I explained one could argue that to create embryos for reproductive purposes is commensurable to the 'natural' aim of creating embryos, but the creation for research purposes can be perceived as indirectly supporting reproductive purposes as well. Last, the idea that creating embryos for research leads to a slippery slope of dangerous and dehumanizing practices is very unlikely, because of governmental regulation.

Additionally, although the concern that the creation of embryos for research leads to the exploitation of women should be taken very seriously, the risk of exploitation can be diminished by proper regulation as well. An example I have given of a possibility of a practice in which oocytes can be obtained against acceptable risks for egg cell donors is the egg sharing initiative (Blyth, 2002; Haimes et al., 2012).

Thereafter, I have argued that to decide if specific research can be balanced against the harm of creating and destructing embryos and the risks for egg cell donors, research should meet the principles of subsidiarity and proportionality. In the case study on SCD Gametes, I studied the ethical justifiability of embryo research on SCD gametes. The question I posed was; if the use and creation of embryos for research can be justified under specific circumstances, can it also be justified for research on SCD Gametes? I argued that research concerning the responsible introduction of SCD gametes into clinical practice does meet the principles of subsidiarity and proportionality. Since there are no alternative adequate research methodologies to perform research on SCD Gametes or to get a biologically related child with other reproductive options, the creation of embryos for research on SCD gametes can be justified following the principle of subsidiarity. Furthermore, I have shown that as to research and therapeutic purposes, the research on SCD gametes meets the proportionality principle. Could SCD gametes be introduced into

clinical practice after proper research, egg cells could be easily created so that enough egg cells are available for research and therapy. This means that the demand for egg cell donors will increase significantly. Additionally, the creation of SCD gametes makes the use of hormone stimulation in reproductive treatments like IVF redundant. As to the reproductive purposes of SCD Gametes, to meet the proportionality principle, it is important to further investigate whether the importance of the genetic link is proportionate to the harms of the creation of embryos and risks to egg cell donors.

6.2. Strengths and limitations

A strength of this thesis is that it provides an ethical framework to assess the acceptability of the creation of embryos for research in the broad field of ARTs. This makes this thesis relevant to questions that consider the justification of embryo research on contemporary, but also on future emerging ARTs. Furthermore, the ethical assessment on the creation of embryos for research provides insights not only applicable on ARTs, but also on other bioethical issues, such as stem cell research. Additionally, the case study on SCD gametes provides an example of how the principles of subsidiarity and proportionality can be used as criteria for justification on the creation embryos for specific research purposes.

A limitation of the thesis is that the discussed ethical debate mainly focuses on a practical ethics approach. This means that other approaches that can also give insights in the justifiability of the creation of embryos for research, such as virtue ethics, feminism or mediation theory have not been taken into account. Although this thesis can give insights in the niche of practical biomedical ethics, I do not claim to cover all possible approaches to the ethical issues presented in this thesis.

The strength of using WRE in this thesis is that it enabled me to identify relevant background theories behind moral intuitions and principles. In this case, I discovered that the different views on the moral status of the embryo were based on the theories of personhood and potentiality. Also the arguments considering the moral difference between spare embryos and research embryos were based on background theories; double effect and instrumental value. These theories formed a moral framework, in which the moral principles could be assessed. Within the moral framework of relevant background theories and current moral intuitions and principles, I have shown that the creation of embryos can be justified.

A limitation of WRE is that it can only provide justification within a specific framework. Although WRE can shed light on where it is that opposing moral judgements and principles conflict, it cannot provide an absolute justification. In the case of embryo research, WRE showed that the third view, stating that embryos have a limited degree of value, is coherent with the theories of personhood and potentiality. However, it is possible that other alternative parties disagree on the current content of these theories. The Catholic Church for instance, disagrees at many points with the current concept of personhood. WRE thus illustrates where the problem of two views collapsing lies (in this case in the concept of personhood), but still does not enable me to say that one moral position is true and another is not. WRE thus only provides justification within a certain framework, but cannot give conclusions concerning truth.

6.3. Recommendations

In the case study of this thesis, I investigated if the creation of embryos for research on SCD Gametes can be justified under the principles of subsidiarity and proportionality. To meet both principles, it is important to have relevant literature. In performing the assessment, there appeared a gap in the literature considering the reproductive benefits of SCD gametes and considering embryo research on SCD gametes specifically. Therefore, it is important to expand current literature.

Although SCD Gametes can provide benefits in research and therapy and improve other reproductive technologies such as IVF, the specific benefit for clinical application for reproductive purposes remains unclear. One specific gap in the literature is research on the moral importance of the genetic link between parents and children. Although research has provided intuitive arguments on the importance of the genetic link (Mertes & Pennings, 2010), the topic needs further scrutiny. Therefore, I recommend further research on the topic of the importance of the genetic link between parents and child. If the genetic link would appear as important as suggested, it would enable a stronger position in meeting the principle of proportionality.

One approach to justify the creation of embryos for research on SCD gametes is to argue from a reproductive autonomy perspective. Instead of arguing for an objective moral importance of the genetic link, this approach argues for subjective autonomy. If the genetic link cannot be proven objectively morally important, is not the reason that some parents strongly prefer a genetic link enough to meet the proportionality principle? Since more research on the benefits of

SCD gametes against other reproductive technologies is needed, I recommend to investigate the argument of reproductive autonomy concerning the importance of a genetic link.

As a last recommendation, research specifically on the effectiveness of embryo research on SCD gametes is lacking. Although many researchers have argued that embryo research improves research on ARTs (Brison et al., 2013; Dondorp & de Wert, 2011; Pennings et al., 2007), research on the effectiveness of preclinical embryo research on SCD gametes is too limited. This has probably to do with the fact that the creation of SCD gametes is still at a highly experimental stage. However, since preclinical embryo research can only be justified under the condition that it can provide additional safety information that would reduce the gap between animal studies and clinical application, the effectiveness of preclinical embryo research on SCD gametes should be further investigated.

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