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BUILDING THE BRIDGE FROM BENCH TO BEDSIDE:

ETHICAL ISSUES IN TRANSLATIONAL STEM CELL RESEARCH

To my parents

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ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. Hug K, Hermerén G. Do we still need human embryonic stem cells for stem cell-based therapies? Epistemic and ethical aspects. *Stem Cell Reviews and Reports* 2011; Volume 7 (4): 761–774.
- II. Hug K, Hermerén G. When can we start first-in-human trials and what patient groups should be asked to participate in such trials? The cases of Parkinson's and Huntington's diseases: Ethical and epistemic considerations. *Journal of Clinical Ethics* (accepted for publication).
- III. Hug K, Hermerén G. Differences Between Parkinson's and Huntington's Diseases and Their Role for Prioritization of Stem Cell-Based Treatments. *Current Molecular Medicine* (accepted for publication).
- IV. Hug K, Hermerén G, Johansson M. Withdrawal from biobank research: Considerations and the way forward. *Stem Cell Reviews and Reports* (submitted).

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INTRODUCTION

“If we knew what it was we were doing, it would not be called research, would it?”, said Albert Einstein. This phrase seems to summarise one of the reasons why research, especially very innovative one, such as stem cell research, often raises a number of ethical concerns. In the area of stem cell research, these concerns differ depending on, e.g. the type of research conducted or the type of stem cells used for it. Stem cells, which are unique in that they have no specialized physiological properties, such as carrying oxygen through the blood stream or producing movement, are found in the pre-implantation stage embryo, the foetus, placenta, umbilical cord, in many different tissues of the body and have also been engineered from somatic cells. Research on stem cells coming from these different sources has raised different ethical concerns. The types of research conducted using stem cells can also differ. Stem cells can be used to study normal development of an organism, genetic and molecular controls of abnormal cell division and differentiation thus investigating how diseases such as cancer and birth defects arise, to model disease processes in the laboratory for better understanding of disease development, or to test safety of new medications on specialized cells generated in large numbers from stem cell lines. These applications of stem cells have not been the subject of much ethical debate, except when cells from certain sources, such as human embryos, were used in them.

As stem cells have the ability to produce both copies of themselves (the so-called *self-renewal*) and other more specialized cell types (the so-called *differentiation*) every time they divide, they have the ability to replace damaged cells and treat disease. Stem cells are already used in treatment of extensive burns, and to restore the blood system in patients suffering from, e.g. leukaemia. Stem cell research is also conducted to enable the use of these cells to replace cells lost in many other diseases for which no efficacious cures or only symptomatic treatments are available. If stem cells can be directed to differentiate into specific cell types, they could be used for treatment of Parkinson’s disease, stroke, heart disease, diabetes, spinal injuries, Alzheimer’s disease, Huntington’s disease and a number of other diseases and conditions. The use of stem cells in this type of research has raised a number of ethical concerns.

Unknown or insufficiently known risks, possibilities of applications, rates of efficacy and other similar aspects related to this research raises a lot of questions, the answers to which are not ethically neutral. This seems to be especially true in the case of stem cell research which aims to pave the way for clinical applications, the so-called *translational stem cell research* thus translating the results of basic stem cell research into diagnostic and

therapeutic applications. Translational stem cell research can consist of a number of different stages, as I will show later.

In this research area there is still much that scientists know that they do not know: e.g. the probability that certain known harm will occur, the magnitude of this harm, or both. Likely, there is also much that scientists do not know that they do not know: e.g. they may not be aware of certain harm that may result to patients from the application of certain experimental stem cell-based intervention. This state of knowledge with many known and unknown unknowns contributes to raising a number of questions, which need to be answered to advance from one stage of translational stem cell research to another. The answers to these questions will depend on which values we want to protect or promote, and this will depend on what we want to achieve and why. Knowledge premises – what we know and do not know – however, play an important role in choosing the ways how to protect or promote these values. Consider that safety of patients is a value which should be protected. One may choose different ways to achieve this value depending on the available knowledge premises. One may choose to conduct more research on animals before trying the first experimental therapeutic applications on patients. Or one may use such applications in clinical trials to provide desperate patients with a possibility to receive such therapies in a regulated environment instead of trying their luck in so-called “stem cell clinics” and putting their safety at risk by receiving scientifically unproven “treatments”.

Another one of the reasons why stem cell research has been surrounded by heated debates could be summarised in the words of Isaac Asimov: “The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom”. However, as this quote may imply, this problem is not unique to translational stem cell research but often is a rather common problem with emerging technologies. Although translational stem cell research is still marked by insufficient state of knowledge, it is the area of science which advances very quickly, thus raising ethical concerns which have not yet been discussed previously or discussed in a different context. Moreover, these concerns often have to be addressed on the basis of previously raised ethical questions which have not yet been answered. For example, the discovery of the possibility to turn any cell of the body into a pluripotent (able to make any cell type of the body) stem cell, called human induced pluripotent stem (hiPS) cell, has raised concerns about the possible applications of such cells, considering the potential of such cells to start a new life. Meanwhile, the debates about how much the early human life, such as pre-implantation embryo, should be protected have not been settled.

A common concern in scientific meetings involving scientists, ethicists, lawyers, and patients is that many of the existing national and international legal regulations, and some of the ethical guidelines, are not adapted to meet the challenges raised by clinical translation of stem cell research results. Why is that the case? Is translational stem cell research in a special category, raising challenges that have not already been addressed?

An important difference exists between clinical translation of stem cell research and clinical translation in other lines of research such as pharmaceutical research: in clinical translation of stem cells research results, it is notoriously difficult to weigh harms and benefits, because of the knowledge gaps both with harms and benefits. Results obtained from pre-clinical research may not successfully transfer to clinical application in humans. These uncertainties complicate the process of obtaining free and informed consent from prospective research participants and avoiding therapeutic misconceptions. To further complicate matters, translational stem cell research is accompanied by an almost omnipresent risk of hype, due largely to fierce competition among scientists to be the first to offer clinical applications of stem-cell-based therapies and often biased coverage of research by the media. Of course, these risks are not unique to translational stem cell research. Consider the question why this research raises challenges unaddressed in legal and ethical documents. The difficulty is not just that the research *is* translational, but also that so many knowledge gaps exist.

Different stages of translational stem cell research raise a number of different ethical questions. Some of them have been discussed extensively for quite a few years, like the questions concerning the acceptability of using human pre-implantation embryos for stem cell research or the intellectual property rights in the context of stem cell research. Others have been less discussed in this context and the debate concerning these questions could therefore benefit from an ethical analysis using specific examples or a discussion drawing attention to issues which seem to have not been sufficiently acknowledged in the ongoing debate. In this thesis, I discuss ethical questions arising at different stages of stem cell research. Considering the limitation of ethical questions that can be discussed in a thesis, I have chosen four different ethical questions that I was most interested in.

Before this choice can be explained in greater detail, however, we need to address some conceptual issues as well as cover the background and the context in which these ethical questions arise.

SOME CONCEPTUAL ISSUES

The term “translational research” is not exclusive to research on stem cells: pharmaceutical research, gene therapy research, or research in synthetic biology can also be translational. Translational research has been characterized in the literature as “translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease” (Fontanarosa & DeAngelis, 2002). In the case of stem cell research, translational research links pre-clinical research on the one hand and therapeutic applications in patients – based on knowledge obtained from pre-clinical and clinical research results – on the other. The goal is to transform the knowledge obtained from pre-clinical research to knowledge needed for routine administration of new therapeutic applications.

However, this is not the only view on what translational stem cell research should involve. Some would say that translational stem cell research should rather be seen as a “two-way flow of knowledge between bench and bedside, not from bench to bedside, as is the usual mantra” (Webster, 2010), or that partnership between pre-clinical researchers and clinicians “should proceed along with basic research”: the rationale being that waiting to “understand everything” about stem cells “may delay the potential they have for therapeutic use” (Davison, 2010). Clinical studies, conducted after the proof of principle has been achieved in basic research and certain conditions met, should, in their turn, inform basic researchers of questions to clarify with subsequent pre-clinical research.

More specifically, the term “translational research” can be used to refer to stages of research linking laboratory and clinic. These stages usually raise different challenges (Kon, 2008; Westfall *et al.*, 2007). Discussing ethical questions in translational research without specifying which stages are referred to can lead to misleading generalizations. Unfortunately, the same term – “translational research” – *is* used to refer to different stages and means different things to different people (Woolf, 2008).

As Woolf has argued, the most common description of translational research is probably the “bench-to-bedside” enterprise of “harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients” that can be used clinically or commercialized. Meanwhile, for those conducting research in health services and public health and focusing on healthcare as the primary outcome, “translational research” means translating research into practice, ensuring that “new treatments and research knowledge actually reach the patients or populations for whom they are intended and are implemented correctly”. For these researchers, the production of a new

drug, device, or therapy – an end point for “bench-to-bedside” translational research – is only the starting point (Woolf, 2008).

How many translation stages can one name? In clinical research, some authors distinguish two major stages (Woolf, 2008; Sung *et al.*, 2003). According to Sung *et al.*, the first, referred to as T₁, is “the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans”. The second, T₂, is “the translation of results from clinical studies into everyday clinical practice and health decision making” (Sung *et al.*, 2003). T₁ seems to attract more funding than T₂ (Woolf, 2008).

Other authors describe translational research in terms of five stages, starting at the pre-clinical level (Kon, 2008; Westfall *et al.*, 2007). First, basic or pre-clinical data must be translated into animal models: e.g., starting with non-primate mammals and continuing to non-human primates (Westfall *et al.*, 2007). Such pre-human experiments can represent many sub-layers of translation, collectively called T₀ (Westfall *et al.*, 2007). The first clinical stage, T₁, involves the translation of basic research to humans (Kon, 2008): e.g., in pharmaceutical research, researchers normally assess clinical applications under limited clinical conditions through controlled, early-phase clinical trials (Westfall *et al.*, 2007). The second clinical stage, T₂, transforms knowledge from T₁ to patients (Kon, 2008). In drug trials, these studies take the form of Phase 3 trials (Westfall *et al.*, 2007). The third clinical stage, T₃, transforms knowledge from T₂ into routine clinical practice and daily care of patients (Kon, 2008). The final stage, T₄, moves scientific knowledge into the public sector, changing the everyday lives of people by improving public health and decreasing medical costs (Westfall *et al.*, 2007). There is no guarantee, of course, that all research ends up as routine applications in the public sector. If one looks at examples from other areas of research – such as the development of a new chemotherapeutic agent to treat a particular cancer – the probability that the agent will go from Phase I to Phase III trials is “probably a bit higher than 20% if the agent is a ‘me too’ drug” and less if it is “the first intervention using that particular type of mechanism” (Magnus, 2010).

Practice-based research – often necessary before “distilled knowledge” can be implemented (Westfall *et al.*, 2007) – can also belong to T₄. Mapping the five-stage system onto the two-stage one, T₁, T₂ and T₃ in the five-stage system correspond to T₁ in the two-stage one, while T₄ corresponds to T₂.

I will apply the five-stage system in this thesis. The two-stage system is not sufficiently fine-tuned to capture all the differences between different stages for some areas of research – certainly in the case of translational stem cell research. One should note some important differences between some of the five stages in this research and analogous stages in e.g. pharmaceutical research: e.g., T₁ will not involve healthy volunteers as often happens in pharmaceutical research, because of the risks. A similar rationale is applied in some other areas of medical research: e.g., research into anti-cancer drugs or gene therapy treatments.

Some terminological issues need to be clarified about T_1 before any further discussion. It has been argued (e.g., Magnus, 2010) that the literature – even the regulations – are often confusing when terms such as “first in human”, “first in class”, and “first in kind” are used. For Magnus, a *first in human* clinical trial refers to the “first time an intervention under investigation is used in a human clinical trial” and can “include an intervention that is very similar to other interventions”: e.g., a new statin to treat high cholesterol; whereas a *first in class* clinical trial “would involve a trial that is not merely first in human, but also the first intervention using the particular type of mechanism”: e.g., the first statin. Finally, research leading to discovery of a new kind of intervention is *first in kind* or *frontier research*, involving clinical trials that are “sufficiently different from other kinds of approved interventions in clinical use, meaning that there exists insufficient evidence for any kind of claims about the probability (or even possibility) of going from Phase I through Phase III”. Magnus offers as examples of such research the first attempts at organ transplantation or gene transfer. If one applies Magnus’ nomenclature, not all kinds of stem-cell-based interventions qualify as frontier research: e.g., “hematopoietic stem cell trials” (Magnus, 2010). Since the term “first in human” seems to be the most commonly used – both in the literature and in scientific meetings – I employ this term in the *kappa* as well as in the following articles. That said, I use this term with roughly the same meaning as Magnus’ “frontier research”.

In stem cell research, the transition from T_1 to T_2 would imply increasing numbers of patients. Whether this transition would also imply decreased risk to research participants is debatable. The uncertainty is likely to decrease with the advancement from T_1 to T_2 , but it is not certain that risk would decrease. Consider e.g. that sham comparators may be used in Phase II clinical trials and that the doses of administered experimental and potentially harmful therapies are likely to be increased.

In translational stem cell research there would be no sharp differences between T_1 and T_2 as one finds in pharmaceutical research: e.g., ethical questions relating to therapeutic misconceptions, quality of informed consent, and harm-benefit balancing are relevant for both T_1 and T_2 , even though these questions are likely to be more acute in first-in-human studies at T_1 .

This thesis analyzes ethical questions arising at T_0 , T_1 , T_2 , and T_3 (for summary of descriptions of each, see Table 1).

Table 1. Stages of translational stem cell research

| Stage of translation | Description |
|----------------------|--|
| T ₀ | Preclinical research, including translation of preclinical research results into animal models |
| T ₁ | Translation of preclinical research results into first clinical application on small numbers of human participants (“frontier research”) |
| T ₂ | Translation of “frontier research” results into subsequent clinical applications of larger numbers of patients |
| T ₃ | Translation of knowledge obtained at T ₂ into clinical practice and daily care of patients |

I deliberately leave out analysis of ethical questions at T₄ for three reasons. First, the scope of research conducted at T₄ remains unclear, with no consensus forthcoming (Woolf, 2008). Potential research areas at T₄ are numerous: “dissemination, health services, knowledge translation/transfer, implementation, or quality improvement research” (the latter including studies into “improving access, reorganizing and coordinating systems of care, helping clinicians and patients to change behaviors and make more informed choices” and “strengthening the patient-clinician relationship”) (Woolf, 2008). Second, facing the limitation of the number of ethical questions that can be analysed in this thesis, the analysis of questions raised at this level of translation in the case of stem cell research would be too hypothetical, considering the current state of knowledge in the previous levels of translation. The ethical questions at T₄ could arguably be addressed in the case of somatic stem cell-based therapeutic applications that are already widely used, such as bone marrow transplants or transplants of stem cells from umbilical cord blood. Non-experimental stem cell-based therapeutic applications are, however, outside the scope of this thesis.

Finally, besides translational pre-clinical and clinical research, other types of research – e.g., trials that test the application of scientific evidence in areas like health habits, environmental policy, injury prevention, parenting, workplace safety, and school programs – and other interventions outside the clinic can be just as important for health promotion as T₄ work in clinical settings (Woolf, 2008). At the same time, labeling this type of research as “translational” will likely contribute to even greater terminological confusion. Moreover, it is unlikely that scientific evidence obtained from stem cell research *could* be applied in anything other than clinical settings.

BACKGROUND

In many cases the ethical questions raised by translational stem cell research are similar to those raised by other types of biomedical research, such as pharmaceutical or surgical research, or research involving human donated biological material. In the context of translational stem cell research, however, discussion of ethical questions concerning, e.g. informed consent, first-in-human clinical trials or priority-setting require special attention to the risks and uncertainties related to stem cell-based interventions. According to the International Society for Stem Cell Research (ISSCR) Guidelines for the Clinical Translation of Stem Cells, stem cells and their direct derivatives, due to their relative novelty in science, could behave more unpredictably when delivered to patients than, e.g. drugs used off-label or modified surgical techniques (ISSCR, 2008).

The ethical debate over human stem cell research in general has been ongoing for more than a decade. With each new scientific achievement, new ethical questions appear, while existing questions may become either more acute or less important. Some ethical questions are debated heatedly in some countries, but have nearly lost the interest of the general public in others. Of course, public opinion is not the only indicator of a question's importance; but it does influence which ethical questions can or should be discussed openly. Meanwhile, some questions are raised by the scientists themselves. As a member of more than one research project funded by the EU under the Sixth and the Seventh Framework programmes, I have had opportunity to observe the change in ethical debate in Western Europe over human stem cell research, and to participate in these debates.

Ethical debates over research on human stem cells

Many ethical questions concerning stem cell research interrelate, so that discussion of one often requires consideration of others, even if they are not of primary importance in a given country or culture. Before considering the ethical questions discussed in the four articles constituting this thesis, it is important to be aware of the general debate concerning research on human stem cells. This debate has, to a greater or lesser degree, influenced the research questions asked in each of the four articles in this thesis.

I wish briefly to present the way that the ethical debates over research on human stem cells have developed, without claiming completeness, maintaining any strict chronological order, or observing particular geographical distinctions. I have already presented a historical overview, albeit covering a shorter period of time (2002–2007),

elsewhere (Hug, 2009a), and will now focus on the ethical debates that have been most relevant to the research questions discussed in this thesis.

The moral status of the human embryo

One ethical problem that has been in focus since the beginning concerns the moral status of the human embryo at the blastocyst stage: the stage at which stem cells are usually isolated. This ethical problem has been important for the research question posed in Paper I of this thesis, discussing the ethical acceptability of human embryonic stem (hES) cell research after the discovery of hiPS cells.

Research on human blastocysts has caused legal and social controversy since the first successful laboratory-based culturing of hES cells in 1998 (Robertson, 2010), hindering hES cell research in the EU (Hoppe & Denoon, 2011). As Hoppe and Denoon have pointed out, a diverse number of arguments have been used to object to use of hES cells; but they generally fall “in one of two main categories: either an opposition to the mode of derivation of the cells or a fundamental objection to using human embryos at all”. The latter objection is usually tied to the view that destroying human life is morally wrong. The question then becomes “when life has developed certain attributes” where there ought to be a moral “threshold that prevents interference or destruction” (Hoppe & Denoon, 2011).

Different positions on the moral status of the human embryo before implantation are still hotly debated (Brock, 2010; Doerflinger, 2010; Robertson, 2010; Andersson, 2011). They will likely continue to be important, especially given other ethical debates, such as those concerning intellectual property rights. That said, the issue – on its own – appears no longer to be the major obstacle for research that it has been (Robertson, 2010) – at least in some countries: so e.g. comparative study of nine European countries found a plurality of perceptions on embryo research, which ranged from the view that human embryos have the same status as live human beings, as in Austria and Germany, to the view that human embryos in their earliest stages are not yet sufficiently developed to constitute individual human entities, as in Denmark and the U.K. (Pardo & Calvo, 2008). Some (Caulfield *et al.*, 2009; Robertson, 2010) think that this moral “divide” is unlikely ever to be removed completely.

According to the original technique, derivation of stem cells from human blastocysts inevitably results in the destruction of these blastocysts. Such destruction becomes morally problematic if a human blastocyst is attributed the status of either person or potential person. On one position, a human blastocyst has full moral status immediately upon fertilization of the egg (for a survey of positions, see, e.g. Hug, 2006; Brock, 2010).

A more intermediate position states that human blastocysts have a moral status that begins with deserving some level of protection which increases as the embryo becomes more human-like. The diversity of opinion on when protection should begin is huge,

reflecting the quite different points in development they reference: e.g., implantation, the formation of the so-called “primitive streak”, gastrulation, start of heartbeat, or viability outside the womb. According to various legislations, the point at which protection begins is the fourteenth day after fertilization: the time when implantation is most likely to occur, and the beginning of the central neural system and thus sentience. Implantation has been seen as significant for several reasons. It signifies individualization of the embryo: after implantation, twinning normally does not occur and it becomes more likely that the embryo will be able to develop and be born than not, whereas the opposite is more likely before implantation (Bellamy, 2010).

The intermediate position seems to imply that, depending on which point of the development of the embryo is considered morally relevant, failure to protect the embryo after this point amounts to “wrongdoing”. An approach, proposed by Espinoza and Peterson (2012) would allow for a more nuanced and less polarised way to deal with the ethical debate over hES cell research in general. These authors suggest “[i]ntroducing a non-binary notion of moral rightness and wrongness” and instead of “trying to convince people of opposing ethical opinions to drastically change their views [...] to consider the possibility that one’s opponent is [...] somewhat right and somewhat wrong” (Espinoza & Peterson, 2012).

Derivation of stem cells from human blastocysts can be morally problematic if the moral status of the blastocysts remains unresolved. Some would argue that no such entity should be destroyed if there is *any* uncertainty whether it is even a potential person – just as a hunter should not shoot unless he is certain that the object moving in front of him is the animal he hunts, not another hunter (Gomez-Lobo, 2004). Of course, others, e.g. Brock, argue that “intermediate moral status requiring special respect” is compatible with “the use and deliberate destruction of embryos in research”. According to this commentator, one can compare hES cell research to research on species such as monkeys or dogs, to which many persons assign intermediate moral status. If these animals, which “are not mere things to be used for human purposes in any way we wish” are “used and sometimes killed or destroyed in the course of biomedical research aimed at understanding and treating serious human disease”, then human embryos “could be shown the special respect that intermediate moral status requires by limiting their use to comparably important human purposes”, not using them for “relatively trivial human purpose such as developing cosmetics” (Brock, 2010).

Finally, on the least restrictive position (for support, see Hug, 2006), the fertilized human egg has no moral status at all. It should be regarded as organic material with a status no different from other body parts. The arguments for and against these positions lie outside the scope of this thesis.

On any but the final position, human embryonic stem cell research poses a moral problem, bringing into tension two fundamental moral principles that people highly value: the duty to prevent or alleviate suffering, and the duty to respect the value of human life. The harvesting of human embryonic stem cells violates the second duty: it results in the destruction of a potential human life. In the case of embryonic stem cell research, it is impossible to respect both principles simultaneously. The moral question then is: which principle ought to be given precedence?

The destruction of human blastocysts can be seen as morally problematic for different reasons: e.g., either because no living human entity should be used solely as a means to achieve somebody's ends, no matter how good those ends – what some authors have identified as the *Kantian objection* (Hoppe & Denoon, 2011); or because “bad consequences will happen if we do not respect human life at the earliest preimplantation stages” – what Robertson (2010) identifies as the *consequentialist objection*. Examples of such “bad consequences” could be the decreased respect for human life also at its subsequent stages, after the implantation and even after birth, such as in the case of persons in permanent vegetative state.

Both objections can be criticized. For Kantian objectors (e.g., Doerflinger, 2010; Suaudeau, 2011), the use of human blastocysts for derivation of embryonic stem cell lines – potentially leading to treatment of incurable diseases – can be compared to reproductive cloning of human beings for organ supplies to save the lives of patients who need organ transplants. According to Brock, the Kantian “injunction against using ‘rational humanity’ solely as means for the benefit of others... applies to rational beings because they are agents who have ends and purposes of their own that cannot be justly disregarded in their treatment”. The question must then be answered whether an embryo at the blastocyst stage is “the kind of entity that has purposes, interests, or rights that would be violated by its use solely as means” (Brock, 2010). Besides Brock, other critics include (Goldstein, 2010).

However, there is also another question that should be answered. Namely, are all ways of using “rational humanity” solely as means for the benefit of others equally wrong, if we accept the above-mentioned Kantian injunction and if we agree that human blastocysts have purposes, interests and rights? Conducting studies by simply observing living human embryos is also a way of using them for the benefit of science, but such use of living human embryos as means does not seem to raise objection even among those who claim that the human embryo at the blastocyst stage has purposes, interests and rights. Then it is not only the fact of using human blastocysts as means, but also the way of using them that seems to be important for those objecting to the use of human blastocysts in hES cell research.

The consequentialist objection is likewise open to criticism: several decades of experience with abortion and removing life-sustaining treatments for patients in permanent vegetative state does not support the claim about bad consequences (Robertson, 2010). This debate, however, needs clarification of what exactly is meant by “bad consequences”. Those objecting to destruction of any form of human life are likely to object to abortion or removing of life-sustaining treatments for patients in permanent vegetative state, and may consider these acts as “bad consequences” of the lack of respect for the human life at its earliest forms. However, the relation between e.g. allowing destruction of human blastocysts and allowing removal of life-sustaining treatments is not clear. This ethical debate is unlikely to advance without first clarifying these questions.

The ethical questions concerning the moral status of the pre-implantation embryo relate directly to clinical translation of stem cells. In some countries, arguments over these questions limit what kinds of research are permitted. The claim of protecting human dignity is a “conversation stopper” that risks eliminating from debate – or diminishing the importance of – other important ethical questions. In countries where questions concerning the moral status of the human embryo dominate the debate over human stem cell research, other ethical questions have a smaller chance to reach the public consciousness, even if they are discussed in narrower circles of e.g. scientists, ethicists, or philosophers.

Condemnation of hES cell research is often *not* shared by patients and patient organizations, who could potentially benefit from clinical translation of stem cells (EFNA, 2005), leading some (EFNA, 2005; EuroStemCell, 2006) to advocate their involvement in the decision-making process over use of hES cells. No such call for involvement is to be found with respect to reproductive cloning, in the process of which numerous embryos would be destroyed; or – to take a generally less controversial example – *in vitro* fertilization (IVF). No one here is arguing that moral questions should be decided by majority vote or the influence of the most active groups, or e.g. that patients’ organisations should determine when clinical trials of stem-cell-based therapies should begin – only that the patients should play a role in framing the debate: offering insights and allowing their needs to be better understood. There is a danger, however, that having a great interest in advancement of the creation of stem cell-based therapies, patients’ organisations may be less critical concerning the risks, efficacy and clinical competitiveness of such therapies.

Acceptability of sources of human embryonic and embryonic-like stem cells

Moral acceptability of various sources of hES cells is another issue that has been discussed since the beginning. Ethical questions concerning such acceptability are closely related to the ethical problem concerning the moral status of the human embryo and have also been of importance for the ethical discussion in Paper I of this thesis. What precisely

those sources are has changed over time, given new scientific discoveries. It is commonly known that the main sources of hES cells have been e.g. already existing embryonic stem cell lines; embryos left unused after IVF procedures (so-called “spare” embryos); or embryos created by means of the somatic cell nuclear transfer (SCNT) technique (the same technique used to create Dolly the sheep). In addition, embryonic germ cells, similar to embryonic stem cells in their pluripotency, have been derived from primordial germ cells obtained from the so-called *gonadal ridge* of late-stage embryos – a part that normally develops into the testes or the ovaries.

The extensive discussion for and against some of these sources, presented in (Hug, 2005), lies outside the scope of this background section; but I will mention some arguments to illustrate the debate.

Yet another – so far only theoretical – possibility for creating human embryos is from hiPS cells. That said, the ability of iPS cells to form organisms capable of developing into live animals has been proven only in mice (Zhao *et al.*, 2009).

Different sources of human embryonic stem cells raise different ethical concerns (Hug, 2005): e.g., experimenting on unused embryos created for IVF raises the question whether using “spare” embryos for research implies a lack of respect for the beginning of human life; while SCNT raises the question whether creating embryos is morally worse than experimenting on already created but unused embryos (for support, see Hug, 2005). Although pre-existing embryonic stem cell lines seem the least controversial source of hES cells, questions have been raised whether use of these lines does not encourage the destruction of human embryos for production of stem cell lines, and thus whether one can justify the product while condemning the source (Neri, 2011).

Answers to these questions depend on the values one wants to protect and the goals one wants to achieve. In shaping policy, different countries have answered these questions in different ways. In some cases, wishing to avoid the destruction of human embryos, alternatives to research on viable human embryos were sought with the hope that they would be equally suitable for research (Hug, 2005; Suaudeau, 2011; Nichogiannopoulou, 2011). The ethics and practicalities of these alternatives lie outside the scope of the present work. Examples of such alternatives are research on non-viable human embryos or human-animal entities, such as various kinds of chimeras or hybrids, e.g. where the cytoplasm is of animal origin and the nucleus of human origin. Choosing these alternatives instead of research on “ordinary” human embryos may affect the quality of research and thus the safety and efficacy of experimental stem cell-based interventions.

Creation of human embryos from hiPS cells – if possible – would raise numerous ethical questions (Sugarman & Mathews, 2009; Hug & Hermerén, 2011): e.g., so far only some somatic cells can be reprogrammed into iPS cells; does this affect the “natural” potentiality of iPS cells to generate an organism intrinsically capable of developing into a

foetus, and thus the moral value attached to these cells and the embryos created from them?

It remains unclear whether there are ethically relevant differences between the method of creation of human embryos by means of SCNT and the so-far-hypothetical hiPS technique. Some have argued that – unlike gamete-fusion or cloned embryos – iPS cells cannot be ascribed moral status, because iPS cells on their own are unable to generate a full-grown organism; they require provision of a surrogate trophoblast by tetraploid helper cells to do so (Condic, Lee & George, 2009). This difference between hiPS cells and human embryos, if proven, is likely to be considered ethically relevant from the perspective of those who condemn the destruction of early human embryos as entities with a moral status. For those, who do not share this view, however, this difference would not be ethically relevant, and they would likely advocate the use of the type of cells which prove to be the best – e.g. in terms of safety and efficacy – and the most suitable for the treatment of the disease in question.

Others argue that if iPS cells *are* shown to demonstrate totipotency – required for the generation of new human life – they would essentially *be* human embryos (Baylis, 2008). Robertson (2010) thinks that the ability to derive human gametes from hiPS cells, if proven, could “lead to easy production of the eggs” needed to perform at least some hES cell research and to “tailoring the stem cell line sought to a particular genotype”, thus “lessen[ing] the need for female donors and the controversy over paying women to produce eggs for research”.

Despite these problems, researchers such as Suaudeau (2011) argue that hiPS cells “not only present the same characteristics and same biological and therapeutic potentialities as hES cells, but also offer advantages over the latter in that they are free of all ethical problems”. Clearly, Suaudeau fails to acknowledge a number of ethical questions that hiPS cell research could raise as well as the existing biological differences between hiPS cells and hES cells. Recent findings suggest that hiPS cells differ from hES cells (Dolgin, 2011); but how these differences affect pluripotency – the ability to develop into the body’s many different cell types – remains unclear (Ledford, 2011).

Unsurprisingly, numerous commentators disagree, pointing out that some of the potential ethical questions in hiPS cell research would be similar to those associated with hES cell research, whereas other ethical challenges resemble those in genetics, because hiPS cells contain the genetic information of the donor and can thus raise privacy and consent issues, including withdrawal from research (Caulfield *et al.*, 2010). For example, the need to guarantee the donor’s confidentiality and to prevent unauthorised third parties from accessing the donor’s genetic information, the need to ensure that the donor has understood the risks associated to donation, or the challenge of determining the scope and the limits of withdrawal of consent to participate in research.

The pluripotent nature of hiPS cells raises issues of the possible use of hiPS cells to create gametes (Mathews *et al.*, 2009; Caulfield *et al.*, 2010). Although the methods used to create hiPS cells may not be as ethically problematic or controversial as those used in hES research, some of the uses of hiPS cells, once they have been created, almost certainly are (Zarzewny *et al.*, 2009; Caulfield *et al.*, 2010; Robertson, 2010).

Concerns have been raised that either male or female gametes provided by one's partner or using both sets of gametes derived from hiPS cells could be used for *in vitro* reproduction (Zarzewny *et al.*, 2009). Such application of hiPS cells could raise kinship and family issues, especially in cases where somatic cell donors are the genetic father and mother of the child (Zarzewny *et al.*, 2009; Robertson, 2010; Hermerén, 2010).

The potential applications of hiPS cells in experimental stem cell-based therapeutic interventions raise ethical concerns about the safety of patients, especially considering the epigenetic changes acquired during the hiPS cell derivation process (Zarzewny *et al.*, 2009). Nonetheless, if proven safe, hiPS cells could be “a tremendous resource for drug development”. A collection of hiPS cell lines, representing a variety of genetic and ethnic backgrounds, could be “differentiated into a panel of human primary somatic cell types that would, at least partially, encompass the range of genetic variation in humans” (Porteus, 2011). Sugarman and Mathews (2009) argue though that the therapeutic value of hiPS cells depends a lot on the derivation method employed.

The answer to the question whether there are ethically relevant differences between hES cells and hiPS cells, discussed in Paper I of this thesis, can affect policy-making regarding basic research on these types of cells and thus influence translating the results of this research into clinical applications. However, making such policy decisions today favouring research on one or another type of cells seems premature. Numerous commentators have stressed that more research is needed in order to determine the similarities and differences between these two types of cells (Trounson, 2009; Hei, 2010; Hovatta *et al.*, 2010; Fung & Kerridge, 2011). At this stage continued research on all types of stem cells, either derived from embryos or foetal or adult tissues, is necessary as it is “too early to predict their value in a specific field” and also because the knowledge derived from research on different types of cells, including hiPS cells, is complementary (Hovatta *et al.*, 2010).

Besides their influence on policy-making, the questions raised above can affect the choices of patients whether to accept stem-cell-based therapies: e.g., some patients may prefer to reject hES-based therapies in favour of hiPS-based ones. This example highlights the need to ensure that patients are well-informed about the sources of cells used as a basis for the experimental intervention in question. Issues of safety, efficacy, and accessibility of therapies based on hES versus hiPS cells also need to be considered. Together, these issues are the subject of Paper I.

Creation of human-animal entities for translational stem cell research

To avoid some of the ethical questions related to research on viable human embryos as well as to diminish the demand for human ova, some scientists have made experiments using ova from cows or rabbits for translational research (Taupitz, 2008). Different kinds of human–animal entities have been created for different research purposes, such as studying human diseases on animal models, thus raising a number of new ethical questions: e.g., which features of such human-animal entities should be considered morally relevant for their moral status. Should it be their capacity to feel pleasure and pain, their possible rationality, their interests and needs, their potential to develop into a self-conscious person, their appearance, or their membership in the biological species *homo sapiens*?

That last point raises two further questions. Is crossing species boundaries wrong and, if so, when? Does the creation of human-animal entities at the level of stem cell “chimeras” represent an actual instance of such crossing? (Hyun *et al.*, 2007). The line between the acceptable and the unacceptable becomes even less clear at the level of genes, cells, or metabolites (Hyun *et al.*, 2007; Badura-Lotter & Düwell, 2011).

Arguments for and against the various positions can be found in e.g. (Hug, 2009b). What is important here is that concerns have been raised regarding the probability of success for such research: namely, that research on human-animal entities is “unlikely to be effective due to the efficiency of the process being too low... or due to such differences between human and animal eggs that anything resulting would not be biologically informative” (UK Human Fertilisation and Embryology Authority, 2007). Experiments on human-animal entities may only be scientifically relevant in light of *certain* therapeutic options (Taupitz & Weschka, 2009). It is therefore important to be explicit about efficacy and relevance of such experiments, since the quality of the results of preclinical research is crucial for their successful translation into clinical applications.

The scientific relevance of experiments on human-animal entities can be of importance to the safety and efficacy of therapeutic applications based on the knowledge obtained from such experiments. Although research on human-animal entities is not discussed in this thesis, safety and efficacy of stem cell-based therapeutic applications play a very important role in the search for the answers to the ethical questions, related to the beginning of first-in-human clinical studies and the prioritization of stem cell-based therapies, discussed in Paper II and Paper III of this thesis.

Donation of human eggs and embryos for stem cell research

Research on human stem cells is very much dependent on the availability of human biological material, such as human eggs and embryos for hES cell research or different kinds of human tissue for adult stem cell or hiPS cell research. Disclosure of the possible harm to the donors related to such donation is essential for the donors’ decision to participate in or decision to withdraw from such research. The ethical debate concerning

the donation of human eggs and embryos for stem cell research is therefore of relevance to the ethical question tackled in Paper IV of this thesis discussing the scope and limits of withdrawal from research involving donated human biological material.

Research with hES cells – using “spare” embryos from IVF treatments or SCNT-created ones – depends on the donation of eggs and embryos. Several ethical problems arise. The risks of oocyte donation – both medical and psychological – are hotly debated (Klitzman & Sauer, 2009), with some (Ellison & Meliker, 2011) arguing that the risk in oocyte donation for SCNT research is outweighed by the research potential and others (Bamford, 2011; Baylis & McLeod, 2007) expressing concerns about potential exploitation such as women being pressured to deliver eggs. The means of obtaining informed consent becomes an important issue. Reducing risk of psychological harm to donors is likewise important (Baylis & McLeod, 2007).

If consent is to be freely given, information must be provided in a way that does not influence people’s choices. At the same time, motivating people to donate their left-over embryos for research could be enormously beneficial. There are ways to increase motivation without trespassing on freedom of consent. Numerous ethical studies identify, among the factors contributing to willingness to donate, knowledge of the purpose of research: in particular, the potential benefits of stem-cell research for regenerative medicine (for evidence of such studies see Hug, 2008). The findings of these studies suggest that more research is needed into the motives behind the decision of couples or women receiving assisted reproduction treatment whether or not to donate their surplus embryos. Such studies would become especially important if comparative research with hES and hiPS cells showed advantages for using hES cells in stem-cell-based therapies.

That said, scientists do not need to “constantly go back for the blastocysts from which they derive hES cells” when “banked stem cell lines, suitable for that particular research project, are available” (Coffey, 2010). The possibility of accessing banked stem cell lines for research may reduce the need for oocyte and embryo donation.

Stem cell banking

Therapeutic cloning is thought to be a costly and unlikely way to achieve clinical progress on a large scale. This means that stem cell banks are becoming an increasingly important resource (UK Biobank Ethics and Governance Council Review, 2009). Together with repositories and registries of stem cell lines, they are likely to become even important in future – if and when stem-cell-based therapies exist. Given that cell lines “can behave very differently from one another”, a centralized source for distributing cells is needed; without it, there may be problems with the timing for cell receipt and “potentially even the quality of the cells that are distributed”; needless to say, “cell quality can have a huge impact on research quality and subsequently clinical success” (Hei, 2010).

Stem cell banks raise a number of ethical questions: e.g., processing of already collected human tissues and cells, necessary safety testing, and standardization of procedures all raise questions regarding access to the stored biological material: who should have access to the samples and information collected on what conditions, and who is going to decide; while procurement of new tissues and cells raises aforementioned questions regarding informed consent. What exactly should the donors be told and in how much detail? Is presumed consent sufficient or is explicit consent required? In the context of biobank research, should consent be specific or should it rather be broad? If specific, how specific should that consent be?

In the context of research projects involving donated human biological material and aiming at subsequent clinical applications of stem cell-based therapies, withdrawal of consent raises special ethical questions, which are addressed in Paper IV of this thesis. What exactly does withdrawal of consent in such a context mean in terms of action? What precisely should be done when a donor claims that he/she withdraws his/her consent? Whereas the questions concerning the access to information and informed consent have already been much discussed (see, e.g. Hansson *et al.*, 2006; Da Rocha & Seoane, 2008; Caulfield & Kaye, 2009; Broström & Johansson, 2011), there is still much disagreement concerning the forms and limits of withdrawal in basic research and there is therefore the need to address the questions about whether, under what conditions, and to what extent withdrawal should be allowed in biobank research. These ethical questions have inspired the topic of Paper IV of this thesis.

Different options concerning consent withdrawal need to be clarified, as a first step toward any clinical translation of stem cells; while operation of stem cell banks is complicated by heterogeneous laws, guidelines, and ethical standards from one country to the next (Hug, 2009c) – which can only be harmonized by, among other things, evaluating options, scope and limits for consent withdrawal.

The way from bench to bedside

The traditional path “from bench to bedside” involves a number of steps, each of which raises the question: what must be demonstrated in order to proceed to the next step? How much should one know, with how much certainty, about the safety and efficacy of stem-cell-based therapies before they are applied to humans (for quality considerations, non-clinical and clinical considerations, see ISSCR, 2008; EMA, 2011)? How should potential risks and benefits be assessed? When is it appropriate to move from animal to human testing? What – again – are the appropriate procedures for obtaining informed consent? If and when first-in-human studies of experimental stem cell-based therapies begin, what should be the procedure of reporting the adverse events and how to distinguish correctly between negative effects caused by the experimental therapy and harm caused by the process of the disease?

The answers to these questions are of utmost importance to the ethical question discussed in Paper II of this thesis, tackling the problem of which patient groups should be asked to participate in first-in-human clinical studies involving stem cell-based interventions. One must accept that, in many cases, knowledge gaps will persist, and existing knowledge will prove insufficient when stem cell-based therapies are applied to human patients for the first time. The question discussed in Paper II arises in view of the possibility of unknown risks with unknown magnitude and the irreversibility of stem cell-based therapies.

In as much as they affect safety and efficacy of stem cell-based therapeutic applications, if and when they become available, the answers to these questions are also important to the ethical question discussed in Paper III of this thesis, addressing the problem of prioritisation of stem cell-based therapies of certain diseases over such therapies of other diseases.

Although the challenges at each step of translation of basic research results into clinical applications arise “whenever genuinely new medical advances are translated from bench to bedside”, these challenges are particularly important in cell replacement therapy “due to the unique risks which are involved, the relative unreliability of available animal models, the vulnerability of the target patient group, and the intense public scrutiny that surrounds stem cell research” (Fung & Kerridge, 2011). Clinical research with stem cells poses “additional safety challenges than those raised by small molecule drugs produced by pharmaceutical companies” (Robertson, 2010) – challenges that arise from such factors as (a) cellular products being more difficult to manufacture and purify than small molecule drugs, (b) cells often growing in culture for some time before their differentiation, (c) use of animal models for many diseases sought to be treated with hES cells presenting important limitations, (d) the predictive utility of animal models for human diseases being often unknown – even when risks such as tumorigenicity and the need for immunosuppression *can* be evaluated in animal models (Robertson, 2010), or (e) difficulty to withdraw cell materials once they are administered in many experimental therapeutic applications (NeuroStemcell, 2011).

Results concerning safety and efficacy cannot always be transposed from animals to humans given important differences in biology. That a therapeutic application has proven safe and efficacious in pre-clinical trials does not mean it will be safe and efficacious applied on humans. Research on animals cannot offer even tentative answers to some questions: e.g., mice cannot be used to test the efficacy of speech reconstitution after stem-cell-based therapy for Parkinson’s disease. Where it can, those answers may not be very accurate (Fung & Kerridge, 2011) and even when stem cell-based therapies appear to be validated, the mechanisms are not always clear (Dunnett & Rosser, 2011).

Data on differentiation and targeting, obtained from animal testing, “may differ for humans due to species-specific parameters such as cell signalling pathways, hormone and cytokine effects and response to other biochemical signals”. Such inconsistencies between

e.g. animal and human models of Parkinson's disease make it particularly difficult to accurately predict both the risks and the efficacy of first-in-human trials (Fung & Kerridge, 2011). In spite of rapid progress in research on stem cell-based therapies in brain diseases, the conditions for reliable, well tolerated and effective cell-based therapies in e.g. Parkinson's and Huntington's diseases are not yet fully established (Dunnett & Rosser, 2011).

In parallel to the first stage of translational stem cell research on humans, stem-cell-based medical interventions may be applied to individual patients. It must be stressed that although such interventions do not constitute research (and thus fall outside the scope of this thesis) – their main goal is to improve the patient's condition – they still contribute to the accumulation of medical knowledge by recording the interventions applied and the results observed. Such interventions involve many uncertainties including e.g. irreversibility of cellular interventions, mis-differentiation, and mis-targeting of introduced cells. For effective translational stem cell research it is very important that medical innovations do not become “short-cuts” to avoid formal first-in-human clinical trials. Otherwise medical innovation using stem cell therapies “may exploit desperate patients, undermine public trust in stem cell research, and unnecessarily delay better designed clinical trials” (ISSCR, 2008).

Context of translational stem cell research

Context can be influential for what research questions are posed and how they are answered. The context is usually shaped by different factors, and some of these factors can be more influential than others to research questions asked. Five factors seem to be particularly important for filling the gaps and shaping the questions in the translational stem cell research: communication disruptions among groups of stakeholders, increasing demand for clinical translation, regulatory context, economic context, and surrounding hype.

Communication disruptions among different groups of “players” and stakeholders

The success of stem cell clinical translation depends not only on scientists but is conditioned by a joint effort also involving clinicians, lawyers, ethicists, politicians, journalists, and patients. Each group of such “players” can contribute to successful translation of knowledge of stem cell science into everyday clinical applications. In many cases, however, these contributions can only bring results if they are made by “players” working together rather than in isolation. Communication between e.g. basic scientists and clinicians is very important (Murdoch, 2009).

In some cases the state of knowledge can only be improved by one specific group of stakeholders, such as basic scientists or clinicians. Whether this is the case will depend on

what knowledge gaps we have in mind. There are questions, such as those concerning cell differentiation that only basic scientists can answer. In many cases, however, the state of knowledge cannot be improved without interaction among the various stakeholders, other “players” or groups affected by translational stem cell research.

As identified in NeuroStemcell Report (2011), the impact of experimental interventions on patients’ quality of life can only be measured if researchers know what is important to the patients. The main reason for developing stem cell transplantation is to achieve something that patients will find beneficial; so clinicians and scientists need to understand what makes any new treatment better than those already available. In the case of neurodegenerative diseases, different symptoms will be affected depending on where in the brain that stem cell treatments are applied; so it is important to know which symptoms bother patients most. Patients’ preferences are likely to be different in different phases of the disease: depending e.g. on how advanced the disease is or which symptoms they currently are or not suffering from (Neurostemcell, 2011).

Communication among different groups of “players” can influence the research questions asked. For patients suffering from Parkinson’s or Huntington’s disease, e.g., the safety and efficacy of stem-cell-based therapies may not be the only measures of value; the patients’ ability to participate in social life should also be measured. Communication with patients is vital to get this information (Neurostemcell, 2011).

Consider the problem of defining the quality-control requirements of large-scale cell culturing before securing clinical grade lines: this will require dialogue between regulators, stem cell banks, clinical research laboratories, and private companies (Webster, 2010). These examples illustrate that the way the questions regarding safety and efficacy of stem cell-based therapies are asked can depend on the presence or absence of communication between e.g. basic scientists, clinicians and patients. Safety and efficacy are of great importance for the ethical discussion in Paper I, Paper II and Paper III of this thesis.

A few years after research into human embryonic stem cells began, concerns appeared in the literature regarding the lack of connection between the social worlds of medicine and biomedical science (Wainwright *et al.*, 2006) – apparently due to the different roles of researchers and clinicians: scientists were seen as “oriented towards the horizon of scientific knowledge”; clinicians as affected by the “immediate presence of patients and the demands of clinical relationships”, inclined “to look for what might be experimentally applicable today” (Cribb *et al.*, 2008). Such different outlooks result in a lack of interaction between the two groups and thus the lack of exchange of expectations, needs, aims, and concerns. Already in 2003, warnings came that failure to communicate across the divide might result in failure to develop new therapies: robust interaction of laboratory research and clinical results is needed (Duyk, 2003), instead of a research model based on decentralized, independent researchers each pursuing her own line of work, where much becomes “lost in translation” (Maienschein *et al.*, 2008).

Research into the opinions of scientists concerning this issue found that the scientists thought clinicians who were also doing “bench” research were very important, because “they have got hands in both camps” (Wainwright *et al.*, 2006). That said, wearing two hats is not the only way to promote interaction between “camps”; basic communication helps as well, taking stock of each group’s concerns and challenges.

Communication between scientists and other groups of “players”, such as ethicists and lawyers is also very important to ensure successful translation of basic research results to clinical applications. Translational stem cell research needs legal regulation to ensure its transparency and to reduce the likelihood of scientific fraud. International research efforts become difficult if countries involved in common research projects have significantly different legal regulation. Harmonization of legislation in different countries is therefore important for the advancement of international research efforts, and harmonization cannot be achieved without the help of lawyers. This research raises numerous ethical questions, and the help of ethicists is important in addressing them.

The EuroStemCell Project – the European Consortium for Stem Cell Research Integrated Project, funded under the EU’s Sixth Framework Programme – is an instructive example of groups of “players”, including ethicists and lawyers, working together. The project concluded on 31 January 2008. During EuroStemcell’s four years, more than one hundred researchers from 27 of Europe’s best stem cell laboratories tackled the basic, applied, clinical, and ethical issues needed to build the foundations for regenerative medicine. The exchange of knowledge and experience between scientists and ethicists has been very enlightening for both groups and enabling to see issues that may have gone unnoticed without this interaction.

The importance of interaction with other groups of stakeholders, such as the patients, or other groups of “players”, such as the media, has been increasingly acknowledged over time. The role of patients in shaping the research agenda was acknowledged early on and continues to be stressed (Sipp, 2011). In December 2005 in Brussels, a conference entitled Stem Cell Research in Europe: The Patient’s View – organized by the European Federation of Neurological Associations (EFNA) – brought together representatives of various patients’ organizations. Of almost five hundred attendees, approximately 60% were patients or patient representatives, coming from all 32 countries in the European Research Area, and beyond. The aim of the conference was to stimulate informed debate; to allow patients, in particular, to learn more about all aspects of the issue; and to promote patients as an important group of stakeholders in translational stem cell research.

“In recent years, most debates on stem cell research have taken place in isolation from one another, with scientists talking to scientists, politicians to politicians, ethicists to ethicists, etc. So far, the patients – the people for whom these matters hold most importance – have not been involved. This means that decisions have already been taken by researchers and policymakers across Europe, without any real knowledge of the views of the very large section of the public which would be most affected by potential stem cell therapies” (EFNA, 2005).

The NeuroStemcell Project – the European Consortium for Stem Cell Therapy in Neurodegenerative Diseases, a four-year project funded by the EU under the Seventh Framework Programme – provides another instructive example of bringing different groups of “players” together. NeuroStemcell includes both basic and clinical scientists, from six European countries. It was formed to create a world-leading consortium on stem-cell-based therapies for diseases like Parkinson’s and Huntington’s. As part of this project, patients have been invited to share their opinions on such issues as informed consent, harm-benefit calculations, sham surgery, and setting research goals.

According to the NeuroStemcell Report, patients can be brought more into the decision-making process in various ways. In adapting new informed-consent procedures, researchers need to know what information patients consider most helpful. They should consult patients who are in need of therapies as well as those who have some past experience of them, focusing on what the patients would like to know when making decisions about therapy. Of course, patients are likely to have different needs and desires for information, as grounded in their own experiences: influenced by culture, age, education, and so on. One should therefore be careful when “tailoring” patient information papers according to the information received from surveying patients’ opinions, although such information may indeed be valuable when indicating gaps in provided information (NeuroStemcell, 2011).

Patients may find it difficult to talk in the company of highly educated professionals. They need to be encouraged to share, knowing that they will be listened to. At the same time, they will be likely to focus on their own, immediate needs and not necessarily be aware of how long-term research works (NeuroStemCell, 2011).

Successful translational stem cell research requires *international collaboration* among groups of scientists and *harmonization* of relevant laws. Research cannot advance far without the support of politicians, whose trust must be curried by making research transparent and being willing to talk, openly and honestly, about the present state of knowledge – including what is presently unknown.

The media is no less important. It can reach a vast audience in a very short time. The information it presents has a potential to influence public opinion. In the words of gene

therapy researcher James Wilson, who directed a clinical trial involving gene therapy that led to the death of 18-year-old Jesse Gelsinger in 1999, the “hyperaccelerated translation to the clinic that occurred in the field of gene therapy in the 1990s was driven by multiple factors”, including: “unbridled enthusiasm of some scientists in the field, fueled by uncritical media coverage” (Wilson, 2009). The media oversold gene therapy because it was exciting and sellable (Hayden, 2009).

If mistakes are made in the rush to bring bench to bedside – resulting in injury or death – the media might well attribute this to corporate sponsorship and scientists’ consequent conflicts of interests (Marks, 2008), or to the overall safety or efficacy of the research. The media might as well be right in doing so, depending on whether the media report is accurate and unbiased. An inaccurate or a biased reporting of such events may indeed give the whole research area a bad name. Mistakes made in the rush to bring bench science to the bedside could have very negative consequences not only because human lives are put at danger, but also because both patients and the general public may come to question the transparency of science and lose their trust in it – which may mean difficulties recruiting patients for future clinical trials. Meanwhile, lack of trust from sponsors may result in unwillingness to fund further research. Underestimation of the probability of favourable translational outcomes leads to undermining health care systems by impeding clinical translation; overestimation potentially exposes research participants to unjustified burdens which may be considerable in first-in-human studies involving unproven interventions (Kimmelman & London, 2011).

The general public – as taxpayers and as decision-makers via elections – is another important stakeholder. The freedom of choice of the general public, as Duprat has pointed out, must be reinforced by (in essence fully neutral) scientific knowledge meaning that personal views should be informed by scientific reality. Outreach programs are essential – especially in fields that are not unanimously supported – as are imaginative ways of communicating research to the public and creating conditions for constructive dialogue (Duprat, 2011).

Increasing demand for translation

Pressure for translation derives from increasing faith in translational research (Burke *et al.*, 2008). Translational demands affect the way scientific inquiries are organized (Schwab & Satin, 2008) and thus the priority with which knowledge gaps are filled. A growing pragmatism in hES cell research encourages researchers to “produce what are seen as productive results”, thus shifting “from a search for ‘essential’ to ‘functional’ attributes” of hES cells, focusing “on ‘how’ rather than ‘why’ lines do what they do” (Webster, 2010).

At the same time, it is unclear how translational demands affect any *particular* area of research. Moreover, effects can be both positive and negative. Where it is unclear how

inquiries should be organized, effects are as likely to clarify matters as to distort (Schwab & Satin, 2008).

Stem cell research is developing at the same time as demand for results. Some have expressed concern that this simultaneous development may affect “pure” research: i.e., the pressure to ask particular questions may undercut the possibilities to address others not, perhaps, directly related to stem cell therapies (Maienschein *et al.*, 2008). There are, of course, scientists conducting basic stem cell research concerning scientific questions which are not necessarily related to stem cell-based therapies, but the proportion between basic and applied research can always be a question for debate.

The increasing demand for translation can affect the way research questions regarding safety and efficacy of hES cell- as well as hiPS cell-based therapies will be answered or in which order. Safety and efficacy play an important role in the ethical discussions in Paper I, Paper II and Paper III of this thesis.

Porteus (2011) writes that “the public and private excitement surrounding the development of iPS cells for regenerative medicine can lead to a potentially troublesome bias”; given the “incentives for all stakeholders in the field—including researchers, journals, funding organizations, biotechnology companies, and patient groups – there is a natural urge to focus on the positive, headline-grabbing advances” and “an understandable desire to avoid doing experiments that might undermine the field”. Meanwhile, “experiments that elucidate the risks and barriers to translation are exactly those that should be undertaken first because they will identify the problems that need to be solved before the technology can be applied to improve treatment for patients”.

Translational demands can, however, inject important guiding principles into the research endeavor (Schwab & Satin, 2008). After all, translational research is about the way basic research is integrated with the development of applications and clinical trials and not the determination of research priorities (Chapman, 2008).

Meanwhile, the push towards translation can be dangerous if it encourages uncautious clinical applications. Both scientists and clinicians are skeptical of the rush to experimental treatment in some areas of stem cell research (Cribb *et al.*, 2008), “translating from sadly incomplete benchside and bedside source languages”, languages with “unknown grammar, unknown syntax, and few if any native speakers” (Maienschein *et al.*, 2008).

Another danger lurks in lumping all translational demands together (Schwab & Satin, 2008). What may be distorting or clarifying at one stage (e.g., T₁) may not be at another (e.g., T₃).

The regulatory context

Regulatory context – including funding and commercialization policy, patent policy, and policy on the use of monetary payments for donation of human reproductive materials – inevitably shapes the conduct of stem cell research: e.g. steps like procurement, derivation, banking, distribution, and use of stem cell lines; variability in regulatory context has the potential to introduce inefficiencies regarding sharing of information and production of research (Caulfield *et al.*, 2009). These steps are important for ensuring safety of stem cell-based therapeutic applications, and the quality of knowledge available about this safety is important in ethical discussions in Papers I, II and III in this thesis.

Variability in regulations may introduce inefficiencies related to the sharing of materials and data and to the production of research (Caulfield *et al.*, 2009), inhibit collaboration, both nationally and internationally, restricting the flow of research and researchers (Winickoff *et al.*, 2009), and is likely to have an impact on clinical translation (Caulfield *et al.*, 2009).

The regulatory context can also be influential to how the questions about the ethical controversy concerning hES cell- and hiPS cell-based therapies, discussed in Paper I of this thesis, are answered. European countries may be classified into three groups, based on their positions on research using human embryonic stem cells: a) restrictive (Iceland, Lithuania, Denmark, Slovenia, Germany, Ireland, Austria, Italy, Norway, and Poland), b) liberal (Sweden, Belgium, United Kingdom, and Spain), or c) intermediate (Latvia, Estonia, Finland, France, Greece, Hungary, Switzerland, the Netherlands, Bulgaria, Cyprus, Portugal, Turkey, Ukraine, Georgia, Moldavia, Romania, and Slovakia) (Liras, 2010).

Regulation of stem-cell-based interventions may vary depending on how they are classified: e.g., as drugs, medical devices, or biological products (*biologics*). Requirements for proof of safety and efficacy – before and during first-in-human applications – may vary as well. The result is that ensuring a consistent level of patient protection internationally for those receiving first-in-human stem-cell-based interventions can be very challenging (von Tigerstrom, 2009).

The movement of researchers across national borders raises issues of ethics education – or, as Caulfield has labelled it, *reorientation of migrant scientists* (Caulfield *et al.*, 2009). Such education or reorientation – though needing to be culturally sensitive, and potentially resource intensive – may stimulate cross-cultural alignment of norms.

That said, “as stem cell research is a controversial area that engages various ethical, religious, intellectual, social and cultural beliefs, some degree of variation in policy and perspective” is inevitable, even healthy: plurality invites innovative approaches, new perspectives, and a balance between extremes (Caulfield *et al.*, 2009).

Economic context

Translational stem cell research is expensive. Public funds are sometimes insufficient or restricted by legislation. The funding for stem cell research and the room for commercialization varies by jurisdiction. In Singapore and the US state of California, stem cell research is part of a special, state-sponsored, strategic initiative. In the UK and Canada, it is primarily supported through government funding and private foundations (Caulfield *et al.*, 2009).

First, the source of funding – public or private – may influence the goals of research: the goals of scientific discovery can be different in academic and corporate settings (Yim, 2005). According to one study, more than 20% of mid-career US scientists receiving NIH funding admitted that they had changed the design, methodology, or results of a study under pressure from a funding source (Martinson *et al.*, 2005). If this is true, such actions could affect the safety or efficacy of stem cell-based therapies. However, further empirical work is required to explore precisely why each of these different kinds of change is being made (Marks, 2008).

Second, the role of private companies – especially pharmaceutical companies – raises concerns about intellectual property rights (Yim, 2005). The pharmaceutical companies are well aware that effective stem cell therapies could have a huge impact on their market share for diseases such as diabetes (Wainwright *et al.*, 2008). This could affect the prioritization decisions regarding treatments of which diseases should be prioritized – the ethical question discussed in Paper III of this thesis.

Third, commercialization of research may introduce competition and inhibit collaboration and sharing of resources; patients may be attracted away from academic institutions and toward private trials offering greater accessibility and faster results (Yim, 2005). However, at present it is unlikely that publicly funded clinical trials will lack participants; in the absence of such trials, many patients are travelling to stem cell clinics where they receive treatments that are both expensive and risky.

Fourth, stem cell research raises questions about the appropriate allocation of governmental and private resources, in at least two ways: setting of research priorities and the relative status of research versus healthcare (Dresser, 2010).

Private companies may invest where they see the greatest potential for financial return (Dresser, 2010); they are unlikely e.g. to research stem-cell-based therapies for rare diseases (Persson *et al.*, 2007). Justice – one of the fundamental principles in research ethics – appears to be violated.

Economic pressures may encourage fraudulent or unethical research: e.g., private funding may allow researchers to conduct research under less strict reporting requirements and ethical review (Yim, 2005). Privately funded research may not be impartial (Chadwick & Privitera, 2006; Johnston & Vohra, 2006; Twombly, 2007), whereas academic research is meant to be (Yim, 2005). That said, the picture is hardly so black and white. It is in

private industry's best interests to avoid scandals and negative publicity; while the idea of academic research as a "disinterested search for truth and knowledge" is naively idealized (Chapman, 2008). Academics are not insulated from the influence of political, social, cultural, moral, economic, or personal factors – such as advancing a career (Resnick, 2007).

Economic pressure is not the only factor that can contribute to distortion of science. Other factors have been mentioned in the literature, e.g. that "the small proportion of results chosen for publication are unrepresentative of scientists' repeated samplings of the real world", and that the "self-correcting mechanism in science is retarded by the extreme imbalance between the abundance of supply (the output of basic science laboratories and clinical investigations) and the increasingly limited venues for publication (journals with sufficiently high impact)" (Young *et al.*, 2008).

Private funding of translational stem cell research can also have a positive impact on communication between groups of stakeholders. Collaboration between academia and private industry need not be a bad thing. The outcomes depend on how the collaboration is organized.

An example of beneficial collaboration is the ESTOOLS Project, funded under the European Union's Sixth Framework Programme to investigate the biology of human embryonic stem cells and their differentiation into specialized cell types. At the time, ESTOOLS was the largest ever grouping of human-embryonic stem cell researchers in Europe, drawing on researchers from ten countries and 21 academic and commercial research teams.

Another example is the Life & Brain Research Center a campus-based biotechnology company located at Bonn Medical School in Bonn, Germany. Their core message is that the relationship between universities and private industry must change. The intention is that the academic side of the centre incubates bright ideas from the university's academics, while the company side lends both technical and business support to those ideas, resulting in a revolving door between academia and industry: giving academics the freedom to follow their ideas into commercialization and back again (Stafford, 2006). Others have acknowledged the "need to make universities and other public research bodies more aware of the importance of transferring the technology they produce to the private sector" (Ulloa, 2010).

Transparency of relations between the academic and commercial teams and transparency of research are prerequisites for positive results. Transparency is also crucial to maintaining trust of research subjects, patients, and society at large.

Private industry is unlikely to invest money if intellectual property rights are not protected, raising questions about e.g. patents. Ulloa (2010) writes that "one of the biggest obstacles faced by stem cell researchers is the insecurity when it comes to determining whether the result of their research is or is not patentable". How stem cell

research is affected “will be determined in part by the scope of the patents granted as well as how scientists, biotech companies, and investors handle the barriers presented by IPR [intellectual property rights]” (McCormic & Huso, 2010).

In March 2011, the Court of Justice of the European Community ruled that, even if techniques involving human embryonic stem cell lines do *not* involve the direct destruction of embryos, they are not patentable, as that would constitute industrial use

“...contrary to ethics and public policy” (Abbott, 2011). Some scientists fear that the ruling could prompt some countries to tighten their legislation on such research or ban it altogether (Abbott, 2011). Concerns have been raised that the current European Patent Office approach to patenting hES cells “requires a revision to adapt to the fast development” of stem cell technologies (Hovatta *et al.*, 2010).

Meanwhile, in the US, embryonic stem cell lines *are* patentable. The impact that differing patent policies will have on research remains uncertain (Caulfield *et al.*, 2009). Patenting of “inventions” based on human stem cells raises both legal and ethical issues, starting from the so-called morality clause in the European Patent Convention (Hermerén, 2011a). Current regulations force “...jurists to determine the imprecise line of what is ethical and what is not” (Ulloa, 2010). Lawyers and patent examiners should not be left on their own in tackling these questions.

Hype

Experimental stem-cell-based interventions, being “sufficiently different from other kinds of approved interventions in clinical use”, represent “hope for fundamentally new avenues of treatment, and new scientific breakthroughs” (Magnus, 2010) – indeed, “high hope for cures and treatments for debilitating disease on the part of individuals and families affected by disease and much hype for quick and definitive success in finding these cures and treatments on the part of disease advocacy groups, stem cell research supporters, and scientists” (McCormic & Huso, 2010). Besides desperate patients hoping for a magic treatment, public, media and researchers themselves all contribute to the tendency to hype (Magnus, 2010). Controversy surrounding hES cell research has only contributed to “making advancements with any type of stem cell in the context of disease of newsworthy interest” (McCormic & Huso, 2010), the media adding to the hype “by providing overenthusiastic and promising reports on scientific findings” (Wilson, 2009).

Although this situation is hardly unique to stem cell research (McCormic & Huso, 2010), there does seem to be “greater public enthusiasm for many of these frontier interventions compared to standard avenues of research” (Magnus, 2010); the “excitement over stem cell research is unprecedented”, which “creates fertile ground for exaggeration” (Dresser, 2010).

Hype can have an influence on what knowledge gaps are filled and in which order. Generation of new knowledge relates not just to what research is done but also what is

said regarding expectations for the research (Cribb *et al.*, 2008). Blame for exaggeration or misrepresentation of results often falls on the media. Research shows that physicians have particular concerns about managing the expectations of patients, given the role the media can play in raising unrealistic expectations (Cribb *et al.*, 2008). The media may bias perception of the chances for successful treatment (Silani & Cova, 2008) and affect public confidence in the research process (Yim, 2005).

Responsibility for all the hype cannot be laid on the media alone. Hype often originates in the competitive arenas in which stem cell research is conducted, especially concerning competition for resources; facing such competition, scientists can find it difficult to strike the right balance between avoiding hype and keeping research in the public eye (Cribb *et al.*, 2008). Scientists may feel “torn” between promoting collaboration on the one hand, and not over-selling the prospects of translational research on the other hand (Wainwright *et al.*, 2006). It can thus happen that some scientists also contribute to promoting the hype.

Hype can have damaging effects on patients’ health: e.g., patients may request interventions before the efficacy and safety of those therapies have been demonstrated in clinical trials (Yim, 2005; Silani & Cova, 2008; Jacobson & Parmet, 2007; Lo *et al.*, 2008).

Once again, the distinction is not black and white. Therapeutic misconceptions among patients may lead them to lobby patients’ organizations and patients’ organizations to lobby the government for more translational stem cell research. The lobbying may lead to hype, which, in turn, may generate further therapeutic misconceptions.

The definition of therapeutic misconception, since its first articulation by Appelbaum *et al.* in 1982, has in the last decade been debated by numerous authors (see, e.g. Hochhauser, 2002; Miller & Joffe, 2006; Appelbaum & Lidz, 2006; Kimmelman, 2007; Appelbaum *et al.*, 2008; Kim *et al.*, 2009). According to the original formulation by Appelbaum *et al.*, to maintain a therapeutic misconception is “to deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself” (Appelbaum *et al.*, 1987). Kimmelman points out that this formulation “centered on the failure of subjects to appreciate that research imposes practices on investigators that conflict with conventional ways of practicing medicine”, but many later uses of the term *therapeutic misconception* have “strayed to a definition along the following lines: the mistaken belief held by many research subjects that research projects will directly benefit them” (Kimmelman, 2007).

Some authors have distinguished the *therapeutic misconception* from a *therapeutic misestimation*, meaning that therapeutic misconception occurs when one confuses the context of experimental clinical research with the context of therapeutic medicine, as in Appelbaum’s original formulation, whereas the therapeutic misestimation occurs when research subjects underestimate the risks of their participation in a clinical trial,

overestimate the benefits, or both (Horng & Grady, 2003). The term *therapeutic error* has also been used and applies to a situation “when a research participant falsely believes that participation in a clinical trial is in her best medical interests, *and* this false belief leads her either to enroll in the trial or continue to participate in the trial after she has enrolled” (Jansen, 2006).

Without claiming completeness of all definitions of *therapeutic misconception* and debates about using this term, the above examples illustrate that there seems to be no consensus about what exactly should not be misconceived, under- or overestimated. Kimmelman also points to the consequences of misconception and the need to clarify what ethical concerns should be raised regarding therapeutic misconception: exploitation and validity of informed consent, as in Appelbaum’s original articulation, or also other ethical concerns, e.g. “diminished study value (because the misconception inhibits compliance with research activities)” and “validity (because the misconception produces a large placebo effect or interferes with the use of procedures like placebo controls)” (Kimmelman, 2007).

If therapeutic misconception is understood as the mistaken belief of research participants that research projects will directly benefit them, to avoid it, the goals and methodology of research should be properly understood. Phase I trials are often referred to as *safety studies*, where primary goal is to determine whether an intervention is safe, not whether it works. To claim a potential benefit from a Phase I trial, “there must be a reasonable possibility that the intervention under investigation will successfully make it through Phase III”; but, in experimental stem cell research, “not much can be known or said about the likelihood that the intervention will go through Phase III” to clinical use (Magnus, 2010).

That said, and “despite the low prospect of direct therapeutic benefit, it *is* possible that research subjects may obtain other kinds of personal benefit (psychological or otherwise) from participating in first-in-human trials, e.g. from the knowledge that they are contributing to the expansion of medical knowledge and from the close contact with researchers and clinicians throughout the research study” (Dresser, 2009). Distinction, however, should be made between moral benefit, as in the examples above, and health-related benefit. The research participant may experience moral benefit while he/she has been expecting health-related benefit. Unless it is clear which type of benefit the research subject has been expecting, it should not be claimed, as Magnus has done, that believing that patients may benefit from participating would not constitute therapeutic misconception (Magnus, 2010). The design of the first-in-human trial – e.g. aiming to assess safety and tolerability of the intervention or designed to assess safety and efficacy simultaneously – is also relevant to whether and what kind of benefit for research participants can be expected.

Therapeutic misconceptions can arise even when patients “fully comprehend that no therapeutic benefit may be achieved and in fact, potential harm is a very real risk”; they may wish to participate “simply be doing something, if not directly for themselves, then at least others in the future”, but “this does not remove the probability that there is an

underlying hope that the direct benefit will be gained” (McCormic & Huso, 2010). One may understand the design of a double-blind, randomized, placebo-controlled trial, but one may still hope to be allotted to the active intervention group.

Inflated promises can harm vulnerable people urgently seeking treatment, participating in clinical trials that may not meet safety and ethical standards. They can harm the research endeavour: e.g. by diminishing public support when the public realises how much work remains (Hyun *et al.*, 2008; Dresser, 2010). Hype can threaten basic scientific integrity “when stem cell research becomes the basis for exaggerated claims by interest group lobbyists” (Dresser, 2010).

The problems

In the beginning of human stem cell research, questions about the moral status of the fertilized human egg and the ethical acceptability of human embryonic stem cell research, at least in some countries, did not leave much space for other emerging ethical questions and at the same time sometimes influenced them, such as the question of patentability of human embryonic stem cells or the ethics of research on human-animal entities. Proof of principle in animal models, showing the potential of stem-cell-based therapies to help treat so-far incurable diseases, gave early promise to the translation of knowledge to clinical applications. Beyond all the issues mentioned so far, stem cell research raises issues of social justice (who gets treated and who does not?) and prioritization of scarce resources.

I have chosen to analyze the types of problems emerging at different stages of translational stem cell research. I have chosen problems that either have not yet received much attention in the literature (papers I and IV), or could benefit from ethical analysis of specific examples (papers II and III).

THE THESIS

Why this topic?

Translational stem cell research raises many interesting ethical questions, which have, to a greater or lesser degree, been debated at an international as well as at an interdisciplinary level. Despite of that, there is still no international consensus regarding how a number of ethical questions related to this research should be answered. Moreover, many of these ethical questions create a real challenge to translation of basic research results into clinical applications, e.g. the questions regarding providing informed consent, withdrawal of consent in different research scenarios, or choice of patient groups most suitable to be asked to participate in FIH clinical studies. Translational stem cell research is an area where multidisciplinary efforts to answer these ethical questions are very much needed.

My interest in translational stem cell research was increased in December 2005 when I had a possibility to participate in the conference “*Stem Cell Research in Europe – The Patient’s View*” organised by the European Federation of Neurological Associations (EFNA), dedicated to stimulate informed debate on stem cell research in Europe, its ethical, religious and political aspects. Although this particular conference was not my first contact with the ethical questions in stem cell research, as I was already contributing to research projects tackling some of these ethical questions, the conference was an eye-opener in terms of the possibility to experience the multifaceted nature and possible effects of such research on different groups of stakeholders. Better understanding of the perspectives of different stakeholders, including the patients, has encouraged the interest in ethical questions raised by translational stem cell research. Since then I have written a number of review articles dealing with various ethical questions related to stem cell research. This has acquainted me better with ethical problems and questions in this area of research and has helped to understand that my principal research interest was related to translational stem cell research.

The thesis discusses a number of ethical questions related to stem cell research and arising at different stages of translation of the results of basic laboratory research to clinical applications, the so-called translation “from bench to bedside”. Some ethical questions analysed in this thesis have been inspired by the research projects to which I was contributing at the time of writing the corresponding articles (Papers I, II and III). The last topic of this thesis, discussed in Paper IV was initially my own choice, having observed the need to contribute to the on-going debate in the area.

Aims, methods, results: In brief

The overall aim of the thesis is to analyze some of the major ethical questions arising at different levels of translation of knowledge generated by preclinical and clinical stem cell research. Among other things, this will include suggesting ways to address the same problems in clinical translation of stem cells, involving other variables, such as different diseases (Papers II and III) or to suggesting ways to address certain types of ethical questions arising in translational stem cell research as well as in some other areas of biomedical research (Papers I and IV). For example, the discussion in Paper IV is relevant to biobank research in general, and the approach applied in Paper I can be used in other research contexts where ethical relevance of similarities and differences between certain variables needs to be distinguished.

This thesis does not attempt to provide solutions to the problems analyzed, but rather to suggest how these problems can best be approached. Solutions cannot be offered until the state of knowledge has been improved and until certain fundamental moral questions have been tackled; otherwise, the final balancing of interests and concerns will not be well founded as the results of all four studies indicate. For now it is better to take a cautious approach.

The thesis explores:

- (a) whether there are ethically justified reasons to regulate basic research on human embryonic cells (hES) and human-induced pluripotent stem cells (hiPS) differently: a very immediate issue at T_0 (Paper I);
- (b) which groups of patients should be asked to participate in first-in-human clinical studies of stem-cell-based therapies, on what grounds: a very immediate issue at T_1 (Paper II);
- (c) how to prioritize stem-cell-based therapies if and when they become routine, in the face of limited resources: a highly likely T_3 issue (Paper III);
- (d) whether, under what conditions, and to what extent withdrawal of consent from research involving donated human biological samples should be allowed: an immediate issue at T_0 (Paper IV).

This thesis is a theoretical work, and the methods used are theoretical approaches. In Paper II and Paper III the concept of stakeholder is important, since the perspectives of different stakeholders play an important role in the analysis conducted in these papers. In both papers the current state of knowledge and knowledge gaps are identified on the basis of the available scientific literature. The possible courses of action are outlined, the stakeholders concerned by the alternative courses of action identified. Their interests are then described and evaluated in the light of certain value premises, e.g. values endorsed by major different types of ethical theories (such as utilitarianism, virtue ethics, as well as

human dignity and human rights-based theories) or values enshrined in European and international guidelines, declarations, directives or conventions. These values are applied to the alternatives. Arguments are provided concerning what should be done in the light of the knowledge we have and in the light of value premises. In Paper I and Paper IV the discussion of different arguments expressed in the literature play an important role. These arguments are presented and their ethical relevance is discussed in the light of different types of ethical theories, as in Paper I, or attention is drawn to a number of areas that need to receive greater attention in order for the debate to make progress, as in Paper IV. The results of this thesis, as they are reported in each paper, are summarized below.

The problem of regulation of basic research on different types of stem cells (Paper I)

Human embryonic stem cell (hES) research has raised heated debate over the ethics of conducting such research and applying the results therapeutically. Research on hES cells has been forbidden or restricted in a number of countries, with research on adult stem cells promoted instead. With the discovery of human-induced pluripotent stem (hiPS) cells, policy-makers in these countries have embraced hiPS cell research as a replacement. However, the scientific community is far from certain that such replacement is possible or scientifically justifiable (Robertson, 2010; Hovatta *et al.*, 2010). One of the EU-funded projects conducting research on hES cells – ESTOOLS – has requested that I carry out an ethical analysis whether hES cells are still needed. That analysis became Paper I.

The question whether hES cells are still needed can be answered at least three possible ways: *yes*, *no*, and *too early to tell*. If one refers to present circumstances, the answer is *yes*. In particular, differences have recently been discovered between disease models based on hES cells and hiPS cells. If one refers to the future, the answer is *too early to tell*, given the infancy of the field, and existing uncertainties and knowledge gaps. The scientific picture is likely to change.

If the scientific picture changes and this change influences the scientific and other arguments actual at present, the moral relevance of scientific and other differences between hES cells and hiPS cells must be re-assessed. Paper I thus illustrates that the answers to the question whether we still need hES cells for stem cell-based therapies after the discovery of iPS cells are relative to (1) the scientific state of the art, where there are still considerable disagreements among scientists and many uncertainties, as well as (2) the normative starting points, where there are considerable disagreements among many ethicists and many uncertainties.

The question analysed in paper I is one of the ethical questions arising at T_0 – already in preclinical stage of stem cell research and is directly related to legal regulation of basic research on different types of stem cells. Considering the current state of knowledge on hES and hiPS cells and their relative utility for clinical applications, should research on them be regulated differently? Of course the cells are different, but are there *ethically* relevant differences between hES cell- and hiPS cell-based therapeutic applications?

Paper I analyses such differences concerning patient safety, treatment efficacy, accessibility of stem cell-based treatments to large numbers of patients and concerning the ethical controversy attached to the use of these types of cells, and discusses whether the known differences can justify the difference in regulation of research on these two types of cells. Paper I shows that we cannot make a decision today about which type of cells is going to lead to safer, more efficacious, more accessible and less ethically controversial therapies. More research on both types of cells is needed in order to answer this question. The knowledge gaps and uncertainties should be openly acknowledged, since they influence the risk assessment and risk management. The dilemma is that the research field must be regulated *today*, even though it is too early to tell whether research on hES cells and hiPS cells requires different regulation.

The problem of choosing patient groups to participate in first-in-human trials of stem cell-based therapies (Paper II)

The question at the heart of Paper II is one of the major ethical questions arising at T_1 : when can first-in-human trials start, and what patient groups should be asked to participate: those in advanced stages of disease, those in less advanced stages, or those who have no treatment alternatives? In other research areas where healthy volunteers are not an appropriate population for Phase I safety studies, the usual standard has been to use the sickest patients, because they are not as likely to be harmed, and because they “may not be as appropriate for Phase II studies”, which might lead to the “false conclusion that the intervention provides no benefit when it might work in healthier patients” (Robertson, 2010).

The likelihood of being harmed is, however, a matter of discussion. If the same amount and type of harm is inflicted upon a patient in the advanced stage of disease and a patient in a less advanced stage of disease, it is not evident which patient will be harmed more in terms of e.g. amount of suffering, pain or reduction of quality of life. The result of such comparison depends on how that inflicted harm is defined as well as on the values of the patient that will be undermined by the inflicted harm. It does not mean that if the sickest patients are not suitable candidates for Phase II studies, they will be for Phase I studies.

The suggested standard for stem-cell-based interventions has been to reserve the early trials for “patients for whom existing treatments are not an option”; the “less serious the

condition, the less justification there is for the research” if the harm-benefit ratio for participants is relatively poor (Magnus, 2010).

A particular disease requires a particular treatment with particular goals. In the case of neurodegenerative diseases, the goal of stem-cell-based therapies is to restore a network that is no longer functioning as it should, where the success of the restoration may depend on the stage of the disease. While “the general principles for ethical translational research are known, the specifics can be resolved only in specific clinical contexts, which include the underlying disease, alternative therapies for it, the site where stem cells are injected, the amount and purity of cells, and the intended function of the transplanted cells”; the “resolution of these issues for Parkinson’s disease will differ from other neurologic conditions, which will differ in turn from treatments for macular degeneration, diabetes, heart disease, and the many other conditions for which stem cell interventions may be tried” (Robertson, 2010).

To address the question of which patient groups to use, Paper II uses the examples of Parkinson’s disease and Huntington’s disease, between which there are important medical and societal differences. Paper II shows that several dimensions are relevant for decision-making and that the answer to which groups of patients should be asked to participate in first-in-human studies is disease- and treatment-dependent.

Paper II shows that many knowledge gaps need to be filled before one can decide in a non-arbitrary way which patient groups should be asked to participate in first-in-human trials of Parkinson’s or Huntington’s. Ethical starting points need to be explicit, including what one wants to achieve and avoid with the trials.

Paper II argues that the answer to the question to which patient groups should be asked to participate in first-in-human trials will depend on what values are promoted or protected as well as how they are ranked in importance relevant to each other. Similarities and differences between Parkinson’s and Huntington’s are of varying importance depending on the normative point of reference. Analyzing medical and societal differences between Parkinson’s and Huntington’s in light of different types of ethical theories could shed light on decision-making about similar problems raised by other diseases exhibiting the same types of differences.

At the present time, it cannot be determined whether patients in earlier or later stages of Parkinson’s or Huntington’s would make the best candidates for first-in-human trials. The most important knowledge gaps relate to, first, how one measures treatment safety, treatment efficacy, health, quality-of-life, and economic consequences of the disease, both for the patient and the patient’s family; and, second, how one applies these definitions and the results of measurements to the diseases compared. The state of knowledge also needs to be improved regarding how one defines and measures the impact of treatment safety or treatment efficacy on patient’s health, quality of life,

economic situation, life expectancy or loss or reacquisition of autonomy and how one chooses the method of measurement and interprets the results.

It is not only the stage of disease that should be considered when deciding which patient groups to use, but also the availability of alternative therapies, as in the case of Parkinson's; or alternative methods of alleviating symptoms, as in the case of Huntington's. The relative efficacy of stem-cell-based therapy is one of the decisive factors. From a normative point of view, however, a precise definition of efficacy is often crucial in order to evaluate its importance in this decision-making.

Just because stem cell therapy has proven efficacious in animal models does not mean that it will in humans. First-in-human studies are necessary to enable later tests of such efficacy.

The priority setting problem (Paper III)

At T_3 – when knowledge from T_2 translational studies is transformed into actual clinical practice and daily care of patients – the problem arises of choosing which diseases to treat first. At least in the beginning, stem-cell-based therapies are likely to be expensive and require a developed infrastructure, as well as physicians familiar with the therapies. Should one focus limited resources on diseases with the highest prevalence, ones with the highest mortality rate, ones for which stem-cell-based therapies are likely to be most efficacious, ones that cause the greatest suffering, ones that cost most for the patients and their families, or ones that cost most for society? Which of these problems should be addressed in the first place and on what grounds?

In the case of stem cell research, priority setting has not received much attention so far. Paper III again uses the examples of Parkinson's Disease and Huntington's Disease. Other diseases exhibiting important societal and medical differences could also have been used as examples, such as juvenile diabetes and Alzheimer's Disease.

Priority setting of treatments based on new and emergent technologies raises special problems, related to the uncertainties and knowledge gaps. Decision-making when knowledge is incomplete is difficult and should be approached very carefully. Not only do stem-cell-based therapies present unknown and uncertain long-term effects, the treatments are not reversible. Prioritization decisions are therefore complicated by inability, at least today, to predict the known and unknown consequences of stem cell-based therapies and thus the inability to evaluate the consequences of prioritization.

Improving the state of knowledge will not necessarily make priority setting easier. Even when one is equipped with reliable knowledge, one would not necessarily become better decision-maker: one's behavior is emotionally influenced; decision makers are inevitably short-sighted and "prone to serious errors of refraction" (Sahlin *et al.*, 2011). The risk picture may also be complicated by new knowledge. There can be other, today yet

unknown facts that could be relevant for priority setting given different sets of values. It may turn out that the only relevant differences between diseases competing for treatments relate to values that differ between societies. Despite of this, improvements of the current state of knowledge is necessary to enable rational priority setting.

Priority setting depends on the particular disease (e.g. its seriousness and prevalence), the particular treatment (e.g. its safety, efficacy, long-term effects), and the context of the existing healthcare system, available resources, and e.g. health-insurance coverage. The safety and efficacy of established therapies is known; this is not and cannot be the case for new and experimental therapies.

Knowledge about the availability and quality of alternative therapies is needed since evaluation of the efficacy of stem cell-based interventions can be dependent on these factors. Stem-cell-based interventions must not only be efficacious, but also clinically competitive (NeuroStemcell, 2011), meaning that they are as good or better than already existing therapies, if any. Knowledge gaps regarding the costs of diseases in question also need to be filled, since this information can be relevant for decision-making given certain normative positions, which influence what goals we aim to achieve and what consequences we aim to avoid.

It is crucial to be precise about what is meant by the terms used. Different interpretations of what consequences of diseases and their treatments are “health related” affect the tenability of the underlying arguments. It is crucial as well to be clear about one’s underlying normative point of reference, be it deontological, utilitarian, or virtue ethics-based. Depending on the normative position considered, priority setting may vary together with the definition of consequences.

Differences between diseases therapies of which are competing for prioritization will also play a role for setting priorities. The diseases need to be compared in terms of health related and non-health related consequences of these diseases for patients, their relatives and third parties, as well as in terms of social justice-related consequences of stem cell-based therapies. For rational priority setting, the ethical relevance of such differences must be analyzed. How ethically relevant such differences are will depend on the values supported and the variables considered, such as safety of therapy, its efficacy, its costs and the like.

Such steps of analysis could be helpful when setting priorities among treatments of other diseases with similar differences as those between Parkinson’s and Huntington’s, if clarity and transparency are desired.

Enabling the way forward in the debate about allowing withdrawal from biobank research (Paper IV)

The right to withdraw one's consent at any time after having agreed to participate in research without providing rationale for this decision is a fundamental principle in contemporary research ethics. Biobank research has posed new challenges to this fundamental principle recognized in international legal documents and ethical guidelines concerning biomedical research on human subjects. Different concerns have been expressed about allowing withdrawal from biobank research, including numerous arguments in favor and against. It has been questioned whether this right should apply to research conducted on donated biological samples and whether the ethical requirements for withdrawal from research on human biological specimens should differ from those usually applied in research involving human participants.

The questions about whether, under what conditions, and to what extent withdrawal should be allowed in biobank research are important at T_0 . The lack of agreement about the forms and limits of withdrawal in basic research may complicate international cooperation among laboratories in different countries. This problem is relevant to all types of research involving human biological specimens, including research conducted on products derived from donated human tissues and cells, such as cell lines as well as on data originating from research on both donated samples and their biological derivatives. The problem has been raised not only in the academic literature, but also in international meetings of scientists – e.g. in one of such meetings under the EU-funded project NeuroStemcell. The perception of the great need to address this problem has dictated the topic for Paper IV of this thesis.

Paper IV argues that the debate concerning the questions about whether, under what conditions, and to what extent withdrawal should be allowed in biobank research is unlikely to make significant progress unless more attention is paid to a number of things. Paper IV brings attention to distinctions that need to be made, and to assumptions that still need to be argued for, in order to settle the issue. The paper briefly presents a number of different considerations that have been, or that reasonably could be, put forward in favor or against allowing donors to withdraw from biobank research and suggests a number of areas that need to receive greater attention in order for the debate to make progress and before any conclusions can be drawn as to whether donors should be given the right to withdraw, or under what circumstances withdrawal should be allowed. These areas include considerations about autonomy, harm to donors, duty to participate in (good) research, possible economical and non-economic costs related to allowing withdrawal, and withdrawal and trust in science.

Moreover, Paper IV argues that there are important reasons for adopting a cautious approach when deciding whether withdrawal from biobank research should be allowed,

under what conditions and to what extent. The cautious approach would consider what inferences from inconclusive empirical evidence are safest for policy to depend on, if at the end of the day it turns out that empirical evidence was wrong. Is it better, e.g. to assume that denying people the right to withdrawal will negatively affect their trust in science when in fact it does not than to assume that it does not have such impact when in fact it does?

Firstly, if arguments based on factual information, such as the ones concerning benefits, harms or costs, are going to be used, there is a need to first fill the currently existing knowledge gaps with robust knowledge, from, e.g. empirical research. Numerous concerns raised in this paper are grounded on considerations based on facts, such as economical and non-economical costs of allowing withdrawal. The lack of reliable knowledge regarding empirical questions precludes decision-making in a non-arbitrary way.

Secondly, given that some empirical issues will remain unsettled, the discussion would also profit from explicitly raising the issue of caution, allowing policy to be informed by considerations regarding what empirical mistakes might be easiest to live with.

Thirdly, empirical data do not alone decide the questions of whether, under what conditions, and to what extent withdrawal from biobank research should be allowed. The answers to these questions depend on the goals we want to achieve, and the values we want to promote or protect. Certain fundamental moral questions need to be tackled in spite of their complexity, in order for the final balancing of interests and concerns to be as well-founded as possible.

Paper IV also makes the point that tenability and relevance of arguments in favor and against allowing withdrawal from biobank research cannot be evaluated unless one is specific about which forms of withdrawal these arguments relate to. The tenability and relevance of these arguments will depend on the form of withdrawal, and thus distinctions between various ways of withdrawing need to be kept in mind. Taking into account most of the possibilities touched upon in the literature, the paper presents a number of options of withdrawal, ranging from the ones requiring little to the ones requiring much effort from researchers to satisfy the research subject's wish to withdraw.

Paper IV also argues that the distinction between having a right to withdraw and being allowed to withdraw without much friction also needs to be kept in mind. Although much of the debate concerns whether there should be a right to withdraw, many of the concerns raised by those who oppose this right could be given credit without committing us to the rather radical position that research participants should not have any such right. An intermediate position is possible between having and not having the right to withdraw from biobank research – namely, this right could be a conditional right (e.g. upon good enough reasons being offered for withdrawing) or be associated with some difficulty at least in some circumstances.

Concluding discussion

What is the final lesson of these papers? Each paper addresses different ethical problems – either presently actual or likely future – relating to different levels of translational stem cell research except T₄, which is not discussed in this thesis. A line linking all the papers is the problem of knowledge gaps and uncertainties.

All emphasize that it is crucial to fill the knowledge gaps with more knowledge, to enable rational decision-making concerning regulation of research, choice of patients for first-in-human studies, or setting of priorities. Uncertainties and knowledge gaps hinder evaluation of harms and benefits and thus risk analysis at different levels of translational research involving stem cells.

Improving the state of knowledge is not enough. Even in possession of reliable knowledge, “we generate too few, and too narrow, hypotheses” so that “once we have a pet hypothesis, we look for confirmatory evidence, neglecting countervailing evidence”; one should “think at least twice about our state of knowledge”, in particular when making a serious risk assessment. Meanwhile, “the fact of irrationality, when unnoticed, can make us far more certain than we should be” (Sahlin *et al.*, 2011).

It is important to be precise, however, how many knowledge gaps are “too many” and thus an obstacle for ethically justifiable decision-making. It is also important to bear in mind that what is considered “too many” will depend on values that we want to protect or promote.

It is necessary to identify uncertainties and knowledge gaps that hinder rational decision making and spell them out openly. One should “honestly portray our present state of epistemic uncertainty” and “not pretend that our knowledge and information is more precise or better than it is” (Sahlin *et al.*, 2011). For translational stem cell research to advance, public support is indispensable. Public support is not possible without society’s trust in scientists and their research. Trust is not possible without transparency of research. Honest identification and communication of uncertainties and knowledge gaps is necessary for transparency.

Identifying knowledge gaps and uncertainties is important for another reason: protecting prospective participants in clinical trials. Patients participating in such studies should be as informed as possible, including what is presently known concerning particular stem cell therapies as well as what is not known or believed with some uncertainty.

Perception of harm and its magnitude is at least partly dependent on individual values. Thus, the state of knowledge concerning harm cannot be filled by knowledge obtained through empirical studies alone, since the values of surveyed persons may be different from the value-judgment of the concerned person. However, risk analysis of harms and benefits could nevertheless inform the decision-making of patients suffering from the

same condition or disease, although their perception of harm and its magnitude may differ.

As mentioned before, there are many kinds of knowledge gaps when it comes to stem cell research: the safety of stem-cell-based therapies, their efficacy, their chances of success, their accessibility, their costs, along with the health-related effects of the diseases they aim to treat, the impact of those diseases on the quality of life of patients and families, and the effects of untreated disease on society. There are uncertainties about the underlying scientific foundations: e.g., the ability of hiPS cells to generate an organism capable of developing into a foetus. There are uncertainties about withdrawal from research and its consequences.

Some of these uncertainties cross several levels of translation; others are typical to one particular level. All have ethical implications. Improvement of the present state of knowledge regarding the above-mentioned aspects would enable us to make decisions that can be better justified from an ethical point of view.

Knowledge gaps and uncertainties discussed in this thesis relate to the following types of information at T_0 - T_3 :

Safety of hES cell-based and hiPS cell-based therapies

Patients' safety is endorsed, to varying degree, by different ethical theories; protected by European and international guidelines, declarations, conventions, and directives. At T_0 , knowledge about the relative safety for therapeutic applications of hES versus hiPS cells is critical to how research should be regulated. At T_1 , it is difficult to decide what patients should be asked to participate in first-in-human clinical studies if the safety of such therapies remains undefined. This knowledge is needed at T_3 to set priorities e.g. of which diseases to treat first. Even when knowledge gaps are filled, new questions concerning safety arise at each level of translation, with the advancement of research.

An important point from Paper I is that safety is almost never black and white. Safety comes in degrees and depends in part on the types of patients receiving treatment. Given the present state of knowledge, treatments based on hES versus hiPS cells can be considered *either safer or riskier*, depending on what is considered and how much weight we attribute to e.g. risks of harm such as graft-versus-host disease or malignant tumours, or unpredictable long-term effects. It is obviously very difficult to evaluate risks in a non-arbitrary way when the harm is unknown or its probability and/or magnitude is unknown.

At T_1 , substantial improvement of patients' health and quality of life is necessary to justify taking risks. "Complete understanding of the biological mechanisms at work after stem cell transplantation in a preclinical model" is obviously not a prerequisite to first-in-human trials; proof of principle concerning safety and efficacy, using animal models, is (ISSCR, 2008).

Without doubt, long-term follow-up of patients who have received stem-cell-based interventions is necessary for estimating the safety of such interventions (NeuroStemcell, 2011). Such follow-up cannot be done without the patients' cooperation. Despite "the need for acquiring long-term data regarding efficacy and safety of cell-based interventions, it is not necessarily clear that patients who agree to participate in early trials will be willing to undergo long-term follow-up with potentially invasive monitoring, such as tissue biopsies"; gathering this data "must be balanced against the willingness of patients to provide them" (Sugarman, 2010).

Another challenge is the requirement coming from e.g. the US Food and Drug Administration (FDA) for substantial non-human primate data to establish the safety of particular products and interventions for humans; use of primates is "both expensive and potentially ethically troubling, and can become a major source of debate" (Magnus, 2010). At the same time animal models that most closely recapitulate the human disease are generally the most desirable (Kimmelman, 2010), but this may be ethically problematic as it becomes more difficult to draw clear differences between the animal model and the human target population (Fung & Kerridge, 2011).

Another challenge, not specific to translational stem cell research, is the difficulty of publishing negative results; scientific journals prefer to report positive results. Many researchers have stressed the importance of publishing negative results so that e.g. other patients are neither harmed nor exposed to ineffective interventions in further trials (Lo *et al.*, 2008; Sugarman, 2010).

It can be difficult to strike the right balance between being overly cautious and not being prudent enough. How much proof of safety is sufficient? An "overly cautious approach may delay or prevent the development of promising treatments, but the risks of moving too quickly to clinical trials are very serious – both to individual research subjects and to the development of the field" (von Tigerstrom, 2009). These risks always exist when new products are tested, for the first time, in humans; but they are aggravated in the case of stem-cell-based therapies where the predictive value of preclinical studies is notably limited (ISSCR, 2008; von Tigerstrom, 2009).

There is the question of how to estimate safety: what to include in the estimations. The "fact that iPS cell therapy targets the central nervous system when administered to patients with neurological disease" raises the possibility that such intervention may affect not only one's physical capacities, but also one's cognition, emotion, and personality – given that the brain is "central to the construction, maintenance and manifestation of identity and of the 'self'" (Fung & Kerridge, 2011). Finally, how should the need to ensure the safety of first-in-human research participants be weighed against the potential benefits of expedited access for the broader patient community?

The question has been raised whether, in the case of certain stem-cell-based interventions, all first-in-human trials should be blocked until adequate safeguards have

been developed, even if this would significantly delay the bench-to-bedside translation (Fung & Kerridge, 2011). Given that safety trials may need a long time of follow-up to provide reliable data about safety of stem cell implants, patients may “head off to unregulated territories for expensive, uncertain, and potentially risky treatments abroad” (Sinden, 2010).

Efficacy of hES- and hiPS-cell-based therapies

As long as the knowledge gap exists at T_0 , it is not possible to say whether direct reprogramming of hiPS cells could generate sufficient numbers of patient-specific pluripotent stem cells (provided other necessary conditions for stem-cell-based treatment are fulfilled). At T_1 , uncertainties regarding the efficacy of stem-cell-based therapies make it hard to determine what categories of patients should best participate in first-in-human trials; while at T_3 , they make it impossible to prioritize one therapy over another.

When “research teams underestimate the probability of favourable clinical or translational outcomes, they undermine health care systems by impeding clinical translation”; but when they “overestimate the probability of favourable outcomes, they potentially expose individuals to unjustified burdens” (Kimmelman & London, 2011). In both cases, mis-estimation threatens scientific integrity and frustrates prudent allocation of resources (London *et al.*, 2010).

Lack of obvious success in clinical trials need not mean that these trials are not worthwhile (Magnus, 2010; NeuroStemcell, 2011). A failed trial may mean a failed strategy rather than a failed therapy.

When gaps in knowledge can be considered filled depends on what the regulators require as proof of efficacy: e.g., clinical endpoints in non-human animal data, such as symptom relief in spinal-cord-injured rats; or surrogate (non-clinical) endpoints, such as tumor shrinkage (Magnus, 2010). There is a danger that regulations can slow down progress; to avoid that, regulations should be sensitive to the “dynamics of the stem cell field” (Hyun, 2010).

Possibility of hES cells and hiPS cells to develop into a human embryo

Difference in the theoretical capacity to develop into embryos is, for some, a morally significant difference between hES and hiPS cells, justifying different regulations: most directly at T_0 , although it may be important even at T_1 - T_3 if patients receiving stem cell therapies are concerned about the capacity of the cells used in their therapies to generate an organism intrinsically capable of developing into a foetus. In the case of hES cell research, there is evidence that concerns about hES cell research could stop some individuals from benefiting from hES cell research results or allowing family members to benefit (EFNA, 2005). In the case of hiPS cells, to date it is not proven that these pluripotent stem cells could directly produce an entire embryo.

On the other hand, for someone like Demetrio Neri (2011), hES- and hiPS-based therapies are equally problematic for those who extend protection of human dignity to human pre-implantation embryos.

Similar need not mean interchangeable: hESC and iPSC may well be similar but not interchangeable, or *vice versa*: as Sahlin *et al.* put it, it is not similarity of these cells that is important but “how the induced cells function, that they do the job they are supposed to do and nothing else” (Sahlin *et al.*, 2011). Further, when talking about similarity or difference, it is important to say similarity or different *with respect to what factors*.

Of course, ethically justifiable decision making can and often must be undertaken even where knowledge remains incomplete. Consider the following examples from T₁–T₃.

Likelihood of intervention success

At T₁, decisions must be made concerning which patient groups should be asked to participate in first-in-human studies. If there is reason to believe that stem-cell-based therapies will be more efficacious on some patients than others, then it would be ethically unjustifiable not to favour the one group. At T₃, if it is not possible to evaluate positive and negative effects of therapies, then priority-setting decisions should be postponed. In evaluating chances of intervention success, the criteria for “success” and “improvement” are crucial, allowing the same intervention to be deemed successful or not.

Patients’ quality of life

In this thesis, I have discussed quality of life mainly in the context of T₃: as information necessary for setting priorities for established treatments. However, quality-of-life uncertainties can be important at T₁ as well – helping determine selection for first-in-human therapies, where the worst off (in medical terms and in terms of quality of life) may be the best candidates.

It is important not to consider safety and efficacy of stem-cell-based therapy in isolation from quality of life: e.g., the patient’s ability to participate in social life. Patients’ quality of life can hardly be evaluated without consulting the patients themselves. The perception of researchers or of society can be quite different. It is necessary to ask patients what therapy-induced changes they would consider most important for their quality of life, while noting that patients’ priorities can change as the disease advances: patients adapt to new circumstances, and these adaptations can change what they value (Sahlin *et al.*, 2011). There are paraplegic patients who have “gone on to become physicians, painters, scientists, and athletes” with “long, high-quality lives”; although their self-assessment of quality of life may initially be quite poor, “their... assessment of their quality of life is likely to change” (Magnus, 2010). Newly disabled persons “may overestimate the long-term emotional impact of a recent injury (Scott, 2008). Geron’s first-in-human embryonic stem cell research on spinal-cord injured patients has been criticized on precisely these grounds (Bretzner *et al.*, 2011).

By considering safety and efficacy of a stem cell-based therapy in isolation from the issue of quality of life, researchers may overlook the general effect of this therapy on patient's ability to participate in social life. Participation in social life can largely affect the patient's quality of life. Such empirical studies, consulting patients on quality-of-life issues, can reveal new knowledge gaps. Improving the state of knowledge is a long and complicated process.

Not only must scientists and clinicians translate scientific findings into caring for patients and informing the everyday lives of the public; they must translate the concerns of the public into scientific inquiry. In this particular sense, translational research can and should be a "two-way street" (Westfall *et al.*, 2007). In terms of testing safety or efficacy of stem cell-based interventions the "two-way street" should not be acceptable: it would be too risky for research participants if they are used e.g. to generate hypothesis which then need to be tested preclinically.

Economic consequences of disease and treatment

Economic consequences include both the costs of experimental treatments and the costs of non-treatment – for the patient, the patient's family, and society. This is important at T_1 for deciding whether patients in earlier or later stages of disease would be better candidates for first-in-human studies; it is important at T_3 for setting treatment priorities. Different ethical theories will factor costs differently. For utilitarians, all costs – health-related and non-health-related – should weigh equally; whereas for deontologists, only those costs of non-intervention that amount to infringement of the patient's human rights – such as right to life and not being subjected to inhumane treatment – should be relevant.

Global accessibility and fair access to stem-cell-based treatment

At the present time, stem-cell-therapy production costs are high, mainly because drug products are prepared on an almost individual scale. A course of treatment may cost more than \$40,000 USD, involving – besides the drug costs – multiple surgical procedures, strict aseptic conditions, training of technical staff, technical support, specialized facilities, and marketing strategies (Liras, 2010). These costs are likely to decrease in future due to e.g. availability of cryo-preserved cell banks.

The question arises "whether these costs will be compatible with at least partial funding by governments, medical insurance companies, and public and private health institutions, and with current and future demographic movements" (Liras, 2010). Will stem-cell-based therapies be available to patients of all backgrounds and means (Robertson, 2010, Hermerén, 2011b)?

Questions of social justice become even more urgent when considered in an international context: to date, stem cell research is "concentrated in wealthy nations and much of this research targets conditions arising later in life" (Dresser, 2010). Justice may require that

prosperous nations devote more of their research funds to conditions that cause premature death in poor countries (Utzinger & de Savigny, 2006). Many if not most of the diseases that could potentially be treated with stem-cell-based therapies affect people in both developed and developing countries; but access is likely to be uneven – at least in the beginning – because of the high costs but also because of the healthcare infrastructure required.

What are the appropriate priorities for healthcare, globally? These questions of social justice become even more dramatic when they are considered in an international context (Dresser, 2010). Stem cell research is “concentrated in wealthy nations and much of this research targets conditions arising later in life” (Dresser, 2010), thus raising the question whether justice requires that prosperous nations devote more of their research funds to conditions that, e.g. cause premature death in poor countries (Utzinger & de Savigny, 2006). It should be said, however, that many of the diseases that could potentially be treated with stem cell-based therapies affect people in both developed and developing countries – e.g. Parkinson’s and Huntington’s diseases – but at least in the beginning, the results of stem cell research are not likely to benefit people in developing countries as much as the ones in developed countries, as it can be anticipated that stem cell-based therapies are likely to be expensive and their administration would require a certain health care infrastructure, which is more likely to be available in developed countries. Many new therapies, however, which are expensive and not widely accessible in the beginning, become with time accessible to larger numbers of patients.

Although stem cell research “might eventually deliver benefits to some patients, benefits could also be achieved by investing resources in other kinds of research” or expanding healthcare access for currently disadvantaged groups (or just ensuring access to e.g. clean drinking water). Existing “standard health care interventions have been studied and found to be reasonably effective” – and relatively affordable (Dresser, 2010). After all, lack of access to basic health care, clean water, and other public health services produces high death rates in poor countries (Grady, 2009). It has therefore been argued that in stem cell research, as in other research areas, “the relative value and likely cost of any potential therapeutic benefits should be part of the decision making about research priorities” (Dresser, 2010).

The questions of accessibility of stem cell-based treatment and fair access to already established therapies on a global scale are examples of the types of information where uncertainties and knowledge gaps need to be filled to enable ethically justifiable decision-making concerning ethical questions that are likely to arise only at T₃ level of translation, in priority-setting decisions.

Unless it can be known which population has greater difficulty to exercise their rights to health care in terms of access to new therapies and in terms of access to alternative therapies, rational priority setting decisions cannot be made – at least according to certain types of ethical theories, such as some utilitarian approaches and virtue ethics.

Another example is cost effectiveness and clinical efficacy of stem cell-based therapies. Unless such effectiveness and life-long evaluation of clinical efficacy is compared to cost effectiveness and clinical efficacy of alternative therapies, if any, rational priority setting decisions concerning newly established stem cell-based therapies cannot be made.

Effects of right-to-withdraw for research on human biological specimens

Issues of access to treatment mainly apply at T_3 . Issues of right-to-withdraw and its effects on research are most relevant at T_0 , even though they remain important in later stages (T_3). The effects will be greatest where they involve cells with rare qualities, or where the donor is allowed to withdraw not just the use of the donated materials but of all products that may have been derived from them.

When utility is considered in decision-making, knowledge gaps concerning the objective estimates of harm and benefit which can result from individual donor's unlimited and/or limited right to withdraw from research on donated tissues and/or cells and/or products derived thereof would be mostly relevant at T_0 translation. At later, clinical stages of translation, however, if stem cell-based therapies are applied to patients, the question of the limits of cell donor withdrawal from research would also be important. In some cases, these limits might affect the availability of stem cell-based therapies to patients, if these therapies are based on cells with rare qualities and if the donor of these cells is allowed to withdraw the use of the donated biological materials as well as the products derived thereof.

When improving the state of knowledge discussed above, it is crucial to pay close attention to the methodology of studies the results of which are supposed to improve that knowledge. The results can depend on the way the studies are designed, and because of differences in study design, the results may be lacking a common quality on which to make a comparison.

Need to be specific about epistemic issues

Underlying all these issues is a need to formulate questions in an accurate and precise way. Numerous authors have pointed out the dangers of generalizations in discussing ethical and epistemic issues of translational stem cell research (Lo *et al.*, 2008; Goldstein, 2010; Magnus, 2010; Hyun, 2010; Fung & Kerridge, 2011). Consider safety for example: “just because a cell is safe in one place does not mean it is safe somewhere else”; just “because there has been a phase 1 trial that reported a positive outcome, it does not mean that every patient who has that disorder should find a way to get that treatment right now” (Goldstein, 2010).

It is important to be clear about what is known and what is not known. “For a disorder like Lou Gehrig’s disease, there are forms of it where there is a 99 percent chance that a patient will die within a year”; one might therefore conclude that “the early phase trials

of cells derived from human embryonic stem cells” should be “for disorders where we knew the prognosis with a great deal of certainty” (Goldstein, 2010).

Decisions about first-in-human trials depend, among other things, on the likely adverse effects of the intervention compared to the outcomes of the disease itself – and the ability to distinguish between them; if “a disease often leads to death from liver failure and liver failure is the major risk factor” related to the experimental intervention, “then there must be ways of determining differences in the cause of liver failure” (Magnus, 2010). This will require being precise about e.g. the exact location of cell injection, the type of cells used, and the type of patients treated.

Experimental stem-cell-based interventions may “involve adult (somatic) stem cells used in novel ways, derivatives of human embryonic stem (hES) cells, or derivatives of reprogrammed somatic cells, such as induced pluripotent stem (iPS) cells”; they may involve the patient’s own cells (autologous transplantation), donor cells (allogeneic transplantation), genetically modified cells, cells used in their site of origin (homologous transfer), or cells used outside their site of origin (non-homologous transfer) (Hyun, 2010). Transferred cells can be delivered systemically or transplanted directly into a specific site, “with or without a bioengineered medical device seeded with cells”; cell dosage, cell-transfer frequency, and the disease stage at which intervention is attempted all vary (Hyun, 2010). All these variables raise epistemic issues.

Future research

This thesis makes no attempt to address all ethical questions arising at all levels of stem cell clinical translation. Both empirical and normative issues remain.

Empirical research into patients’ opinions on quality-of-life issues seem especially valuable. Such data could help researchers determine what stem-cell-based therapies should try to achieve. Patients may prefer to tackle those symptoms which most prevent their participation in social life: e.g., problems with bowel and bladder control.

Empirical research could be conducted as well into how family interests weigh against patients’ interests in e.g. deciding whether to accept experimental stem-cell-based therapies offered in clinical trial; or how the *perceived* benefits of stem-cell-based therapies compare to the *perceived* benefits of alternative therapies (where, perhaps, no current access exists); or how – to take a historical view – similar issues have been handled in the past, when treatments based on what was then new and emergent technology were introduced. Any resulting analogies should be used with caution, but something important can be learned from them.

Normative research could include detailed comparison under various scenarios of e.g. utilitarian and deontological approaches to choice of patient groups for first-in-human studies or setting of priorities for treatment. It could also include exploring what “worst

off” means when setting priorities for treatment, while refining the lottery argument from Paper II.

As discussed earlier, some have questioned whether more patients would benefit globally if, instead of introducing stem-cell-based therapies affordable only in certain countries, current therapies were made available in countries where most patients cannot presently access them. In the case of Parkinson’s disease – as discussed in Paper III – the present wide range of medications and surgical interventions is far from universally available. Providing e.g. dopamine agonists more widely could help many more patients than developing new therapies.

In any case, T₄ translation “is vital to fully salvage investments” in T₀-T₃; bringing a therapy to market without knowing how to deliver it to patients “undermines its larger purpose and can only diminish its profitability for investors” (Woolf, 2008). Discovering better ways to ensure that patients safely receive the therapies they need, when they need them, is at least as important as the discovery of new therapies. T₄ translation requires further exploration from both the perspective of economics and the perspective of ethics. A final thought: at all levels of translation, it would be useful to explore the impact on productivity of different research environments: e.g., whether permissive regulation translates to increased productivity (Caulfield *et al.*, 2009).

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SAMMANFATTNING PÅ SVENSKA

Avhandlingen behandlar ett antal etiska problem som är relaterade till stamcellsforskning. Problemen uppkommer under olika steg i översättningen av grundläggande laboratorieforskning till klinisk tillämpning, ”from bench to bedside”. Alla de fyra studierna i avhandlingen pekar på behovet av att förbättra nuvarande kunskapsläge innan man kan fatta etiskt försvarbara beslut i de frågor som diskuteras i dessa studier.

Det problem som står i centrum för *Studie 1* är om det är etiskt försvarbart att reglera grundläggande forskning på humana embryonala stamceller (hES) annorlunda än forskning på humana inducerade pluripotenta celler (hiPS). Forskning på hES-celler har givit upphov till häftig debatt både i Europa och i USA. Detta beror på att det när stamcellslinjer skall skapas är nödvändigt att ta ut den inre cellmassan ur blastocysten och därmed förstöra det befruktade ägget. Frågan är om dessa problem undviks av hiPS-celler, som ju kan vara omprogrammerade hudceller. Om inte, så bör forskning på de båda celltyperna behandlas och regleras på samma sätt. Frågan är också om andra problem aktualiseras av dessa celler, exempelvis beträffande risker för patienter behandlade med terapier baserade på dessa stamceller, behandlingens effektivitet eller tillgänglighet. Om forskningen regleras på olika sätt, bör detta motiveras med hänvisning till etiskt relevanta skillnader mellan celltyperna. Syftet med Studie 1 är därför att utreda den etiska relevansen av huvudlikheter och huvudskillnader mellan behandlingar baserade på hES- och hiPS-celler och att, i fall några av dessa skillnader eller likheter är etiskt relevanta, diskutera om, givet nuvarande kunskapsläge, dessa likheter och skillnader skall betraktas som viktiga för vårt beslutsfattande. Studie 1 analyserar också några hypotetiska scenarier, t.ex. mer effektiva behandlingar versus mer säkra eller mer tillgängliga stamcellsbaserade behandlingar. Studien visar att det är för tidigt att säga att vi kan klara oss utan forskning på hES-celler. Först måste ett antal stora kunskapsluckor utredas och det är viktigt att öppet erkänna dessa kunskapsluckor, eftersom de påverkar riskbedömning och hantering av risker. Dessutom finns det ett behov av att synliggöra och hantera oenighet beträffande de normativa utgångspunkterna. Samtidigt är det naturligtvis så att stamcellsforskning behöver vara reglerad, trots att det idag är för tidigt att säga om forskning på hES-celler och forskning på hiPS-celler bör regleras på olika sätt.

Studie 2 analyserar frågan vilka grupper av patienter som bör tillfrågas om att vara försökspersoner i de första kliniska studierna av stamcellsbaserade terapier på människa. Skall man till exempel välja dem som befinner sig i ett långt framskridet stadium av sin grundsjukdom och har mindre att förlora? Skall man välja dem som inte har några alternativa behandlingar? Eller skall man välja patienter vilkas sjukdom inte gått så långt

och där chansen att lyckas kanske är bättre? Situationen kan variera beroende på vilka sjukdomar som diskuteras. Men är svaret på denna fråga om urval av patientgrupp sjukdomspecifikt, eller beror det på vissa faktorer som är gemensamma för flera sjukdomar? Det ser ut som en teknisk fråga, men den är också värdeladdad. Svaret på frågan beror på vilka värden vi vill skydda eller främja, och hur vi rangordnar dessa värden i betydelse: till exempel patienternas säkerhet och pålitliga, generaliserbara svar angående val av behandling.

Tre typer av kunskapspremissor verkar vara viktiga i ett sådant beslutsfattande och diskuteras i Studie 2. Den första typen berör egenskaper hos stamcellsbaseade behandlingar, särskilt säkerhet och effektivitet. Den andra typen berör karaktäristik av patienter som är kandidater till att få sådana behandlingar. Den tredje typen av kunskapspremissor berör karaktäristik av sjukdomar som skall behandlas med stamcellsbaseade interventioner, inklusive förekomst av alternativa behandlingar av dessa sjukdomar. Studie 2 utvärderar den etiska relevansen av dessa kunskapspremissor för beslutsfattandet om vilka grupper av patienter som skall tillfrågas om att delta i de första studierna av experimentella stamcellsbaseade behandlingar. För att kunna analysera och konkretisera dessa allmänna frågor används Parkinsons sjukdom och Huntingtons sjukdom som exempel. Dessa sjukdomar exemplifierar några viktiga medicinska och samhällsliga skillnader, och det pågår translationell forskning syftande till att hitta stamcellsbaseade behandlingar av dem. I studien jämförs patienter med Huntingtons sjukdom och Parkinsons sjukdom. Dessa patienter skiljer sig åt i en rad avseenden som gör att svaren på de frågor som står i centrum i Studie 2 inte behöver vara desamma. Också här behöver många kunskapsluckor fyllas igen för att ett motiverat och rationellt ställningstagande skall bli möjligt. De viktigaste av dessa luckor preciseras. Även de etiska utgångspunkterna behöver klargöras. Vad är det man hoppas uppnå eller undvika med denna forskning, och hur viktigt är det i jämförelse med andra värden som står på spel? Vilken roll spelar tillgången på terapier? I undersökningen hävdas att även detta bör vägas in i ställningstagandet.

Utan att förbättra det nuvarande kunskapsläget går det inte att från en normativ synpunkt avgöra om det är patienter i de tidigare eller senare stadierna av de sjukdomar som skall behandlas som kommer att vara de bästa kandidaterna till att delta i de första studierna av experimentella stamcellsbaseade behandlingar. De viktigaste kunskapsluckorna berör hur vi definierar och mäter behandlingens säkerhet och effektivitet, patientens hälsa och livskvalitet samt de ekonomiska följderna av sjukdomen för patienten och hans/hennes familj. Det finns kunskapsluckor också om hur vi definierar och mäter effekten av behandlingens säkerhet och effektivitet för patientens hälsa, för livskvalitet, ekonomiskt tillstånd, livslängd samt ökning och minskning av patientens autonomi. Studie 2 argumenterar, från en normativ synpunkt, för att de viktiga faktorerna i urvalet av patientgrupper som skall tillfrågas om att delta i de första studierna av experimentella stamcellsbaseade terapier är sjukdomsstadium, tillgång till effektiva alternativa behandlingar eller alternativa metoder för att lindra sjukdomens

symptom, samt de stamcellsbaseade behandlingarnas effektivitet, beroende på hur effektivitet definieras.

Studie 3 fokuserar frågan hur och på vilka grunder prioriteringar bör göras mellan olika stamcellsbaseade terapier, givet att de når kliniken. Resurserna är begränsade, och det är inte självklart vilka och vems sjukdomar som skall prioriteras. Prioriteringsproblem när det gäller vård och forskning är inte identiska, och kriterierna är inte heller desamma. Stamcellsbaseade behandlingar kommer sannolikt att vara dyrbara och förutsätta en väl utvecklad infrastruktur. Skall man satsa på de vanligaste sjukdomarna (störst prevalens), de farligaste sjukdomarna (högst dödlighet) och/eller de behandlingar som sannolikt har bäst chans att vara effektiva? Eller på de sjukdomar som kostar samhället mest? Problemet analyseras med utgångspunkt i en jämförelse mellan Parkinsons sjukdom och Huntingtons sjukdom. Som i Studie 2 kan analys av prioriteringsproblem – om man inte är tydlig beträffande exakta skillnader mellan de sjukdomar som är aktuella – leda till missvisande generaliseringar. Parkinsons och Huntingtons sjukdomar skiljer sig åt i en rad avseenden som är relevanta för prioriteringsproblematiken. Även här spelar kunskapsluckor och osäkerheter stor roll för beslutsfattandet.

Kunskapen som behövs för prioritering berör många olika aspekter. När det gäller nya experimentella behandlingar är prioriteringen beroende av kontextuella faktorer som befintliga hälsovårdssystem, resurser i olika länder och vad som täcks av hälsoförsäkringar och i vilken utsträckning, men prioriteringen är också sjukdomsspecifik och behandlingsspecifik. Detta innebär att prioriteringen beror också på sjukdomens allvar och allmänna förekomst samt de möjliga behandlingarnas kvaliteter, exempelvis deras säkerhet och effektivitet. En förbättring av kunskapsläget angående de sista två faktorerna samt behandlingens långsiktiga konsekvenser är särskilt viktig för prioriteringen av stamcellsbaseade behandlingar. Kunskapen om alternativa behandlingars tillgänglighet, kvalitet och kliniska konkurrenskraft är också viktig, eftersom bedömningen av stamcellsbaseade behandlingars effektivitet kan vara beroende av dessa faktorer. Kunskapsläget angående kostnader för Parkinsons och Huntingtons sjukdomar behöver också förbättras, eftersom sådana uppgifter kan vara relevanta för prioriteringen givet vissa normativa utgångspunkter.

Prioriteringsbeslutens etiska försvarbarhet beror på vad vi vill uppnå och vilka konsekvenser vi vill undvika. Vissa problem kvarstår, vilket visas i studien, även sedan kunskapsluckorna fyllts, och riskbilden kan till och med bli mer komplicerad med nya kunskaper. En viktig poäng i Studie 3 är att det är nödvändigt att vara tydlig när det gäller att ange exakt vad som ingår i hälsorelaterade konsekvenser av sjukdomen respektive av behandlingen.

Studie 4 diskuterar ett problem där stamcells forskning på ett intressant sätt skiljer sig från mycket annan klinisk forskning. I den senare gäller enligt Helsingforsdeklarationen att försökspersoner när som helst har rätt att återkalla sitt samtycke utan att detta medför sämre vård eller behandling för dem. Rättigheten att dra sig ur en studie när som helst

och utan att förklara varför är en av de grundläggande principerna i forskningsetiken. Men biobanksforskning, inklusive forskning på stamceller och deras linjer, skapar nya utmaningar för denna grundläggande princip. Det pågår en debatt där den obegränsade rättigheten att dra sig ur biobanksforskning har varit ifrågasatt, men samtidigt finns det många argument för att behålla denna rättighet även i denna kontext. Återkallandet av samtycke kan betyda flera olika saker och ta sig olika former, till exempel återkallande av samtycke till att bli kontaktad i framtiden, återkallande av samtycke till att använda identifierbara donerade celler och vävnader i forskningen, att använda oidentifierbart donerat biologiskt material, att använda data som framgår av denna forskning och till och med att använda produkter som stamcellslinjer, baserade på dessa donerade vävnader. Det finns ingen konsensus i forskarvärlden beträffande vad ett återkallande av samtycke skall innebära mer exakt, och frågan är därför viktig att utreda, särskilt då olika regler för återkallandet av samtycke kan försvåra samarbete mellan institutioner och forskare i olika länder. Studie 4 argumenterar för att debatten om återkallande av samtycke – om, under vilka villkor och i vilken utsträckning återkallandet av samtycke skall vara tillåtet i biobanksforskning – inte kommer att göra några betydande framsteg förrän vissa frågor får mer uppmärksamhet.

Studie 4 presenterar olika argument som har framförts eller hade kunnat framföras i debatten om dessa viktiga frågor och föreslår ett antal punkter som borde få större uppmärksamhet, detta i syfte att främja debatten. Dessa punkter inkluderar avvägningar angående autonomi, skada för donatorer av biologiskt material, plikt att delta i (god) forskning, möjliga ekonomiska och icke-ekonomiska kostnader relaterade till återkallande av samtycke och deras påverkan på förtroendet för vetenskaplig forskning. Studie 4 argumenterar för att det finns viktiga skäl att inta en försiktig hållning i beslutsfattandet i frågan om återkallande av samtycke i biobanksforskning skall vara tillåtet, på vilka villkor och i vilken grad. För det första, om argument grundade i faktisk information – om kostnader, skada eller nytta – kommer att användas, är det nödvändigt att först fylla i nuvarande kunskapsluckor med robust kunskap. En annan viktig sak är att enbart empiriska uppgifter inte kommer att avgöra alla frågor om huruvida återkallande av samtycke skall vara tillåtet i biobanksforskning, under vilka förutsättningar och i vilken utsträckning. Svaret på dessa frågor kommer att bero på vilka mål vi vill uppnå och vilka värden vi vill skydda eller befordra. Vissa fundamentala moraliska frågor måste vara avklarade för att den slutliga vägningen av intresse och angelägenheter skall bli så välgrundad som möjligt. Studie 4 betonar också att bedömningen av relevans och försvarbarhet av argument för och emot återkallandet av samtycke inte är möjlig utan att vara specifik beträffande vilka former av återkallandet dessa argument berör. Studie 4 argumenterar för att det är viktigt att skilja mellan en rättighet att återkalla samtycke och en obegränsad rättighet att återkalla samtycke.

Paper I

Do we Still Need Human Embryonic Stem Cells for Stem Cell-Based Therapies? Epistemic and Ethical Aspects

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Abstract While scientific community disagrees about similarities and differences between human embryonic stem (hES) cells and human induced pluripotent stem (hiPS) cells, some politicians embrace translational hiPS cell research as a replacement for translational hES cell research. We examine the ethical relevance of the main differences between hES and hiPS cell-based therapies and discuss whether, given the current state of knowledge, certain differences are essential. We discuss whether well-founded preferences can be made in hypothetical scenarios with varying levels of patient safety, treatment efficacy, treatment accessibility and ethical controversy.

Keywords Human embryonic stem cells · Human induced pluripotent stem cells · Patient safety · Treatment efficacy · Treatment accessibility · Ethical controversy

Introduction

To answer the question in the title of this paper, reliable and precise knowledge about similarities and differences between

human embryonic stem (hES¹) cells and human induced pluripotent² stem (hiPS³) cells is essential. While the scientific community disagrees about similarities and differences between these cells, many would probably today be inclined to answer the question of the title of this article in the negative. For example, some politicians in countries like Italy and Germany are likely to applaud the development of translational hiPS cell research and argue that funding of translational hES cell research should be stopped. However, can we already today say that we no longer need such research?

In this article we shall try to show that the problem is much more complicated. Any position on this issue will have to be backed up by both scientific and normative reasons. As to the scientific reasons, there are still many disagreements, uncertainties and knowledge gaps concerning questions such as patient safety, treatment efficacy, suitability of these cells for drug testing and disease studies or their theoretical ability to contribute to a human embryo under suitable conditions. Disagreements and knowledge gaps

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¹ hES cells are pluripotent cells derived from the inner cell mass of the blastocyst. They are primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types [1].

² Pluripotent cells: cells capable of differentiating into all germ layers (endoderm, mesoderm and ectoderm) and the germline (e.g. inner cell mass, ES, EG, EpiSC, iPS cells) [2].

³ iPS cells are pluripotent cells derived from any differentiated cell type through ectopic expression of transcription factors [2]. Originally they were derived through retroviral expression of Oct4, Sox2, Klf4 and C-Myc, as reported by Shinya Yamanaka [3]. Other combinations and ways of generating iPS cells have been developed over the past 2 years [4]. iPS cells are pluripotent cells that are derived from adult stem cells using reprogramming [1]. In 2006, a group of Japanese scientists made pluripotent stem cells by introducing murine somatic cells [3]. iPS cells share many characteristics with ES cells but are derived from somatic tissues [4].

also concern more social questions, like the accessibility to treatment or the impact of stem cell research on women.

We will argue that it is premature to say that we no longer need hES cell research aimed at finding hES cell-based therapies or that we need hES cell research only for comparative purposes, that is, when we want to compare stem cell lines derived from hES cells and hiPS cells as to stability, purity, tumorigenicity etc. If we have to determine whether hES cells or hiPS cells are more suitable for stem cell-based therapies, we have to consider which similarities and differences between these cells are ethically relevant, and if yes—from what perspective? We will argue that we will only be able to make rational choices when more knowledge is obtained and the currently existing knowledge gaps are filled.

The aim of this paper is (1) to examine the ethical relevance of the main similarities and differences between hES and hiPS cell-based therapies mentioned in contemporary scientific literature and, in case several or all of them are ethically relevant; (2) to discuss whether, with the currently available state of knowledge, certain similarities and differences should be considered essential to our decision-making; and (3) to analyze, given the current state of knowledge, several hypothetical scenarios of, for instance, more efficacious versus safer stem cell-based therapies.

Method

In order to achieve these aims we will: (1) on the basis of the available scientific literature, indicate current state of knowledge and knowledge gaps; (2) outline possible courses of action; (3) identify stakeholders concerned by the alternative courses of action; (4) describe their interests; (5) evaluate and examine these interests in the light of certain value premises, for example, values endorsed by certain ethical theories or values enshrined in European and international guidelines, declarations, directives or conventions; (6) apply these values to the alternatives and argue what should be done in the light of the knowledge we have and in the light of value premises.

To achieve (1), a literature review encompassing the period of the last 4 years until April 2010 has been performed. The ethical relevance of differences between hiPS cell- and hES cell-based therapies will depend on the chosen normative point of departure. The same differences may turn out not to be ethically relevant if, for example, one takes utilitarianism as a point of departure instead of the ethical theories based on human dignity or human rights. The ethical relevance of differences between hES cell- and hiPS cell-based therapies is therefore examined in the light of these three types of ethical theories. In this

article, we deliberately refrain from mentioning any names of ethical theorists for the simple reason that we are interested in exploring the consequences of types of ethical theories concerning which differences between hiPS cell- and hES cell-based therapies should be considered as ethically relevant. We want to avoid exegetical discussions of how particular sentences of a specific ethical theorist should be interpreted.

The sources of information about what in a given culture or at a given time are regarded as values may be, for example, historical documents [5] or legal documents and ethical guidelines. We will analyze the latter two sources of information, investigating what may be considered as important values in the context of translational stem cell research aimed at finding stem cell-based therapies. Although the legal documents reviewed are European ones, we do not claim that the values discussed here are exclusively European values—but rather the values that happen to be protected by European legislation. The debate regarding what may or may not be considered as European values is beyond the scope of this article, and has been discussed elsewhere [6].

Debated Differences Between hiPS Cell- and hES Cell-Based Therapies—what do We Know Today?

Most scientists note that it is important to examine the levels of similarity between the applications of hES cell- and hiPS cell-based therapies in regenerative medicine [2]. Therapies based on each type of cells have their advantages and limitations [1]. However, there are some who argue that hiPS cell-based therapies are identical to hES cell-based ones concerning certain aspects, such as patient safety, treatment efficacy and the theoretical ability of hiPS cells and hES cells to contribute to a human embryo in the right circumstances. Because of the limitations of the scope available, we present only some of these arguments and their counter-arguments. The arguments are more or less taken verbatim from the papers referred to, but in some cases they have been abbreviated for the sake of simplicity.

Differences Between hES Cell- and hiPS Cell-Based Therapies Concerning Patient Safety

Some scientists have argued that no differences between hES cell- and hiPS cell-based therapies concerning patient safety exist. For example, some have pointed out that both hES cells and hiPS cells have the potential to form teratomas⁴ if transplanted into patients [7, 8], the risk of tumorigenesis [7, 9–11] as well as the potential of aberrant

⁴ Teratoma is a tumor characterized by the presence of cells corresponding to all three embryonic germ layers [7].

reprogramming [12]. Others have objected, however, that using for therapies hiPS cells, generated from somatic cells that might have been altered by aging or toxins contrary to a pure unaffected hES cell line, would add unpredictable risks⁵ [15]. The difference between hiPS cells and hES cells regarding their possibility to be rejected by a patient's immune defense system has been mentioned in the scientific literature. Immune rejection hinders the use of non-autologous hES cell lines for therapeutic purposes [16]. It is practically impossible to align genotypes of the embryos from which hES cells originate with those of patients in order to avoid the immunological reaction associated with transplanted hES cells [17]. Contrary to hES cells, hiPS cells can be patient-specific and hence will not be rejected by the patient's immune defense system⁶ [7, 9, 10, 12, 15, 17, 19].

This overview suggests that there is considerable disagreement among the scientists concerning safety of hES cell- and hiPS cell-based therapies and that there are essential knowledge gaps which need to be filled by more research. The overview also suggests that it is still an open question to what extent hiPS cells can replace hES cells in stem cell-based therapies—and with what success. Moreover, it indicates that we should consider the issue of safety from different aspects, such as the risk of tumorigenicity, the risk of immune reaction, or the risk of encountering unpredictable adverse effects after receiving either the hES cell- or hiPS cell-based therapy. The safety of hES cell- or hiPS cell-based therapy is a complex issue, and if we consider all the aspects of safety, it is hardly possible to determine which therapy based on which type of cells would be safer according to the present state of knowledge.

⁵ This latter view has been contested arguing that reducing the extent to which the cells need to be reprogrammed could reduce the potential for genetic damage [13]. A possibility has also been mentioned, that if hiPS cells are derived from cord blood, the younger age of cord blood cells may mean that such hiPS cells may harbor fewer genetic abnormalities and thus offer advantages for use in hiPS cell production [14]. However, the safety and efficacy of this option is not crystal clear. Extensive *in vitro* manipulation during the derivation and subsequent differentiation of cord blood hiPS cells may increase their immunogenicity as a result of upregulation of major and/or minor histocompatibility or other loci [14]. Similarly, it is not known how well units of cryopreserved and fresh cord blood compare in terms of their hiPS cell-derivation efficiency, the genetic stability of resulting lines and how the length of time spent in frozen storage influences these parameters [14]. It is also not known whether hiPS cells derived from cord blood will be better able to generate non-hematopoietic cell types than hiPS cells derived from other tissues [14].

⁶ This statement has been contested by Dressel et al. who have argued that the adaptive immune system has in principle the capacity to kill pluripotent and teratoma-forming stem cells [18]. If that is the case, this would mean that the difference between hiPS cells and hES cells regarding their possibility to be rejected by the patient's immune defense system would at least become less significant.

Differences Between hES Cell- and hiPS Cell-Based Therapies Concerning Treatment Efficacy

Scientists have debated whether there are likely to be differences between the treatment efficacy of hES cell- and hiPS cell-based therapies. On the one hand, some have argued that the notion of generating individually tailored cell populations for every patient, as in “therapeutic cloning” involving hES cells, will not be achieved with either hES cells or hiPS cells, since even with hiPS cells patient-specific therapy is impractical⁷ and costly [11, 15]. Therefore, some authors have suggested that the most likely approach for stem cell-based therapy will be to create banks of cell lines, generated from donated embryos, iPS cells, or cell lines gained through somatic cell nuclear transfer (SCNT),⁸ with different immune properties that would provide acceptable matches with most of the population⁹ [15, 17].

It has also been argued that to date it is unclear how transplanted hES or iPS cells might achieve lasting organ regeneration and repair [20]. Although much of the research conducted with hES cells has already been replicated with iPS cells, with the therapeutic potential in the latter demonstrated in mouse models regarding certain diseases, there is little direct proof of therapeutic benefit in humans for either cell type [20].

On the other hand, direct reprogramming provides a realistic way of generating sufficient numbers of patient-specific pluripotent stem cells for regenerative medicine,¹⁰ in contrast to SCNT [2]. SCNT procedure is technically challenging, inefficient and dependent on voluntary donation of a large number of unfertilized oocytes¹¹ [2], whereas hiPS cell research would not face at least some of these problems.

⁷ To support their opinion, some scientists have argued that: a) for patient-specific stem cell-based therapy millions of stem cell lines would be needed [15], b) there is no time to generate the cells if they are needed rapidly, as after a heart attack or spinal injury—it may take several months of really hard work to make a cell line [11, 15], c) it is not realistic to repair the disease causing genetic mutations and epimutations in iPS cells and replace with the somatic cells in patients [11], d) it is impossible to treat large tissue degenerations [11].

⁸ SCNT is the injection of a nucleus derived from a somatic cell such as fibroblast into an enucleated egg [17]. SCNT-derived ES cells have the same genetic information as the donor except for mitochondrial DNA [17].

⁹ However, some have expressed the hope that it is probable that the generation of patient-specific hiPS cell lines would become much easier and less labour-intensive in the near future [10].

¹⁰ This view could also be contested by arguing that a) in order for iPS cells and their direct derivatives to be approved for therapeutic use, each patient-specific batch will have to conform to FDA regulations for both biologic product development and gene transfer research [21], and b) the end result of FDA tough regulatory requirements might make it financially and logistically impractical to attempt to develop patient-specific iPS cell therapies using the patient's own cells [21].

¹¹ The same authors have also pointed out that donation issue might be overcome by using fertilized embryos [2].

Supporting the view that there would be differences between the efficacy of hES and hiPS cell-based therapies, some have argued that hES cells can only be derived from early-stage embryos thus precluding the establishment of autologous cell lines for patients [16], whereas this would not be the case with hiPS cells [7, 9, 10, 12, 15, 17, 19, 22]. Furthermore, in cases where sporadic form of a disease is solely due to epigenetic alterations, hiPS cell-derived somatic cells could be therapeutic, as the reprogramming process should reverse the disease-causing epigenetic modifications [7].

This overview suggests that there is considerable disagreement among the scientists concerning efficacy of hES cell- and hiPS cell-based therapies and that there are essential knowledge gaps which need to be filled by more research. However, provided that these knowledge gaps are filled, the safety of hiPS cells-based therapy is proven and provided that a reproducible, inexpensive and rapid method to determine the quality of newly established iPS cell lines is found [7], direct reprogramming seems to provide a possible way of generating sufficient numbers of patient-specific pluripotent stem cells, at least for the treatment of some diseases.

It is worth mentioning that hiPS cell-based therapies may have to face regulatory hurdles by FDA standardization requirements [21] which would make hiPS cell-based therapies more cumbersome and problematic to carry out.

Difference Between hES Cell- and hiPS Cell-Based Therapies Concerning the Accessibility of Stem Cell-Based Therapies to Large Numbers of Patients

Most authors in the reviewed literature seem to agree that there is a potential difference concerning the accessibility of hES cell- and hiPS cell-based therapies. For example, some authors have argued that the discovery that iPS cells can be derived from cord blood may lead to enhanced therapeutic applicability of this cell source¹² [14, 23]. Others have argued that hES cell- and SCNT-based therapies involve the ethical dilemma raised by blastocyst destruction¹³ and

¹² The reasons supporting this argument are, for example: a) pluripotency induction from cord blood or amniotic cells would allow ample time for cell expansion of the iPS cells themselves [23], b) pluripotency induction from cord blood or amniotic cells would allow ample time for differentiated from iPS cells tissue or cell products that could be propagated, cryopreserved and banked for rapid “off-the-shelf” therapies in the future [23], and c) there is some suggestion that the more immature the adult starting cell population (like the one contained in cord blood), the easier and more efficient it may be to generate iPS cells [14]. It has been pointed out, however, that hiPS cells generated from cord blood have not yet demonstrated therapeutic efficacy [14].

¹³ It has been pointed out, however, that it is possible to establish pluripotent ES-like cells without destroying the embryo [17]. Realistically, however, only wealthy individuals may reap benefits from this technology [17] if used for establishment of pluripotent ES-like cells for stem cell-based therapies.

oocyte donation necessary to generate patient-specific pluripotent stem cell lines [13, 16, 17]. This would make this therapy non-accessible in the countries where hES cell research is viewed as morally unacceptable.

These arguments suggest an advantage of hiPS cell-based therapies concerning their accessibility to large numbers of patients, provided that both therapies are proven to be safe and efficacious, and provided that therapeutically efficacious hiPS cells can be obtained from cord blood banks and similar easily accessible sources of cells. But as long as knowledge gaps exist, it is not yet clear whether hiPS cell-based therapies are advantageous over hES cell-based ones concerning their potential accessibility to large numbers of patients.

It is worth mentioning, however, that administration of either hES- or hiPS-based therapies would require a functioning infrastructure, highly educated physicians, advanced healthcare, etc. It is therefore quite probable that these therapies will not be accessible to all those who need them for a long period of time. Therefore, when considering the choice of a stem cell-based therapy, it is important to consider when and to whom these therapies should be available. Will they be available to the rich in the already rich countries, or will they be accessible also to those who need them in the developing countries? At the present time it seems difficult to identify any clear differences between hES or hiPS cell-based therapies in this respect.

Differences Between hES Cell- and hiPS Cell-Based Therapies Concerning Ethical Controversy

One of the most controversial issues surrounding hES cell- and hiPS cell-based therapies is this. On the one hand, some have argued that direct reprogramming of iPS cells initiates a cellular process that, given appropriate supportive interventions and the right circumstances,¹⁴ has the biological capacity or natural potentiality¹⁵ to generate an organism intrinsically capable of developing into a fetus [24]. Others have pointed out that with additional DNA reprogramming, scientists can move the cells from plurip-

¹⁴ It has been argued that the combined results of some scientific studies provide persuasive evidence that reprogrammed human cells could develop into a human fetus if they were placed in an environment that would provide a placenta and uterine support [24].

¹⁵ With direct reprogramming, pluripotent cells can be generated with the potential to form a clone of the cell donor if the reprogrammed cells are placed in an environment that would allow formation of a placenta and are gestated in a uterus [24]. Hence, directly reprogrammed cells can form cloned organisms capable of developing into fetuses just as it can occur in the case of SCNT [24]. The wider significance of reprogrammed cells, whether produced by SCNT or by the direct method of Yamanaka, is that the beginning of what could become personal human life is associated with any ordinary cell in the body [24].

otent status to totipotency¹⁶ and turn the iPS cell into an embryo, which, once implanted, can lead to pregnancy and birth [27]. Furthermore, it has been argued that although the zygote makes its own placenta, while the iPS cell must be provided with one, the placenta never becomes part of the embryo itself¹⁷ [24]. In support of the view that there are no scientific differences between hES cell- and hiPS cell-based therapies concerning the theoretical possibility of these cells to contribute to a human embryo, some have pointed out that both iPS cells and “clonotes” that result from SCNT involve reprogramming the nucleus of a human somatic cell¹⁸ [28]. The same authors have also argued that in tests of their pluripotency iPS cells produce the embryoid bodies of teratomas, and therefore they have the same capacities as embryos from which hES cells are derived¹⁹ [28]. Finally, it has also been pointed out by many scientists that some iPS cells can pass the most stringent test of pluripotency—the ability to what is called a tetraploid

complementation²⁰ assay, to build a healthy and fertile animal with no contribution from cells other than the iPS cells themselves [13, 23, 25, 31–33].

On the other hand, some authors have argued that empirical research shows that at least some but not all iPS cells are pluripotent [30], which, if true, would make them different from ES cells, which all are pluripotent. Others have pointed out that the possibility to convert one cell type into another by human technological intervention does not prove that there are no meaningful differences between different cell types²¹ and that “passive potency” of the cell (i.e. what it can be converted into by technological intervention) should not be confused with its active potency for self-development [26]. These authors stressed that it is the cell’s active potency for self-development that determines what the cell actually is²² [26]. They also pointed out that the “innate” potency of a pluripotent stem cell is not identical to that of an embryonic organism²³ [26]. There is an important distinction²⁴ between a living organism and a living cell: the interaction of parts in the context of a coordinated whole is the distinguishing feature of an organism [26].

This overview shows that there are essential knowledge gaps concerning the following questions:

- a) Whether the fact that only some somatic cells can be reprogrammed into iPS cells affect the “natural poten-

¹⁶ This view has been contested arguing that, for example: a) totipotency is not merely the ability to produce all cell types, it further requires the ability to generate specific types of cells in a controlled, integrated, and developmentally appropriate pattern and to organize these cells into a coherent body plan, b) unlike pluripotency, totipotency is not merely a function of the cell’s DNA; the state of the cytoplasm is a critical component of totipotency, c) due to the highly structured elements of the oocyte cytoplasm, it is essentially impossible to “reprogram” a somatic cell to be the equivalent of an oocyte by simply altering its pattern of gene activation or the epigenetic state of its DNA, d) simple reprogramming of a nucleus does not reproduce the complex process of oogenesis, where oocytes are produced by a process that requires information from other cells in the ovary, or establish the cytoplasmic components required for totipotency [25] and e) even if factors were identified that could reprogram the nucleus of a somatic cell to be *identical* in every respect to that of a *bona fide* zygote, such a reprogrammed cell would not be totipotent, because it lacks the non-genetic factors—proteins, mRNA and spatial distribution of these components—that are a critical component of “totipotency” [26].

¹⁷ This argument has been contested, however, pointing out that that tetraploid complementation is not merely a supportive intervention that supplies an appropriate environment for production of a fetus [26] because a) trophoctoderm-derived tissues are clearly part of the *embryo*, not part of the mother or of some other entity that co-exists with the embryo, and b) like all embryonic structures, those derived from trophoctoderm are generated by the embryo, physically continuous with the embryo, genetically identical to the embryo, and critically required for embryonic function and survival [26].

¹⁸ In support of this statement, the author has argued that to develop an iPS cell, one must reprogram a somatic cell, such as a skin cell, by inserting new genes into its genome, whereas to develop a “clonote,” one must reprogram that cell by inserting it into an egg, where the gene products residing in the cytoplasm of the egg do the job [28].

¹⁹ This view has been contested, however, by arguing that while these embryoid bodies consist of tissues derived from all three embryonic germ layers (indicating pluripotency), they are not organized like an embryo and would not develop like an embryo if implanted in a woman’s uterus; they would continue to be a tumor [29].

²⁰ In tetraploid complementation, two blastomeres are fused and cultured to produce a tetraploid morula or blastocyst. iPS cells are then combined with this tetraploid embryo, usually by injection into the blastocyst. When this entity is transferred and implanted into a uterus, the cells originating from the tetraploid blastocyst for the trophoblast and ultimately the placenta, whereas the developing fetus is derived from the iPS cells [30]. To date, tetraploid complementation has only been done in the mouse.

²¹ For example, a neural cell and a liver cell from the same individual contain identical DNA, and yet they are radically different kinds of cells, with distinct function, morphology, and composition, and these differences are critical to the roles neural and hepatic cells play in the overall physiology of the body [26].

²² For example, they have argued that simply because a house can be converted into a pile of rubble by the action of a tornado does not eliminate the important differences between a house and a pile of rubble [26].

²³ This difference stems from the fact that a) zygotes act in an orchestrated fashion to generate the structures and integration required for it to continue developing towards the orderly production of the mature body [26], and b) both in normal development and in experimental situations, such as tetraploid complementation, pluripotent stem cells are able to produce a fetus only if they become part of a new or an existing embryo [26, 34].

²⁴ This distinction is due to the fact that iPS cells on their own exhibit those structures and relationships that are required to maintain cellular life, but not the higher level of organization required to produce the complex, interrelated cellular structures such as tissues, organs, and organ systems that are observed in a one-cell human embryo (i.e. a zygote) [26].

- tiality” of iPS cells to contribute to an embryo, and thus the moral value attached to these cells;
- b) Whether the structure of the oocyte cytoplasm and further organization of a zygote is an indispensable component for the existence of “natural potentiality” to contribute to an embryo;
 - c) Whether hiPS cells can contribute to a human embryo—so far the ability to contribute to embryos and live animals has been proven only in mice.

These knowledge gaps indicate that it is still an open question whether hiPS cells really have the so-called “natural potentiality” to contribute to a human embryo and subsequently a human being, and whether there are any morally significant differences between hiPS and hES cells. However, if hES cells have a special moral status because they can contribute to a human embryo under appropriate conditions, and if also hiPS cells can contribute to a human embryo, at least theoretically, then consistency would require that they should have the same special moral status. But if we provide hiPS cells with a special moral status, consistency would require that the special moral status should be attributed also to the skin cells from which they were derived. If fibroblasts are considered as potential persons, Giuseppe Testa has argued, developmental potential will become “a question of molecular context amenable to our intervention” and speaking of “boundaries of potential” will become “an exercise of political freedom and accountability” [35].

It is worth mentioning that the ethical controversy now attached by some to hES cell-based therapies may extend to hiPS cell-based ones even in case hiPS cells are proven not to have the “natural potentiality” to contribute to a human embryo. For example, Demetrio Neri has argued that directing the attention to the sources of the cells—hiPS or hES cells—fails to identify the meaning and scope of the moral requirements involved in the demand of some opponents to hES cell research not to exploit human life [36]. What exactly does the term “exploit” mean in this context? There can be a number of scenarios involving the exploitation of a human embryo without directly destroying it, e.g. using the cell lines already derived by or differentiated cell lines obtained from other scientists [36]. It can be mentioned that some opponents to hES cell research consider that “using cells already derived by others always implies complicity, which exists independently of whether the last user approves or disapproves of the first agent’s act”, as Neri points out [36]. Even if research on iPS cells would not require the use of hES cells derived by others, it is based on knowledge obtained by hES cell research conducted earlier. Neri has argued that the fact that one exploits human embryos by using derived materials or

derived knowledge should be deemed as morally irrelevant [36].

Less Debated Differences Between hES Cells and hiPS Cells

There are also other, less debated differences between hES cells and hiPS cells, concerning their use as tools for drug testing and disease modeling, their possible application in reproductive medicine as well as the impact of hES cell and hiPS cell research on women. We will provide only a brief overview of these differences since they do not constitute ethical dilemmas to at the same extent as the earlier reviewed differences do.

Some scientists disagree whether hES or hiPS cells are more suitable as tools for drug testing and disease modeling. Some argue that iPS cell technology offers the unique opportunity to assess the quality of disease-relevant cell types by directly comparing cells derived *in vitro* with their genetically identical *in vivo* counterparts [7]. Although it takes many years for the pathological features of some diseases (e.g. amyotrophic lateral sclerosis (ALS) or Parkinson’s disease) to become evident, the disease process might be initiated much earlier, and the analysis of iPS cell-derived neurons might identify more subtle early phenotypic changes in these diseases [7]. Some have argued that, although for most diseases hiPS cells are good models, in some disorders, especially where the phenotype is epigenetically regulated, the model in hiPS cells may differ from that in hES cells [37]. For modeling phenotypes iPS cell-based model is a good one, but for modeling genotypes hES cell-based model is a more suitable one [37]. The phenotype difference observed in the patient-specific hiPS cells may be caused by the genetic background of patients as well as the artificial genetic and epigenetic aberration introduced in the process of iPS cell methods [11]. However, there seem to be a consensus that at least for studying some diseases, such as psychiatric diseases, neurological and genetic disorders or unexplained infertility, patient-specific hiPS cell lines are invaluable tools [13, 23, 38, 39].

Some Difficulties

Comparing and contrasting the work of different scientists on a particular subject, especially in cases where they arrive at different conclusions, raises several issues. Why have the authors arrived at different conclusions? This can reflect not only different ways of phrasing the problems but also different conceptions of what constitutes evidence and/or different ways of constructing certainty. In other words, it

need not be related to different ethical views on some of the underlying controversial issues. It could have to do with the way the studies are designed. In fact, this strengthens the point we are making in this paper that at present it would be premature to answer the question raised in the title of our paper with “no”—in view of the many still existing uncertainties and knowledge gaps. Are their papers designed in such a way that they are commensurable? In order to make meaningful comparisons between studies a number of critical points are essential, such as type of stem cells, type of culture, dosage, type and stage of disease and whether patients suffer from one or several conditions and whether stem cell-based therapies have been combined with others. If a number of parameters are different, comparisons may not be meaningful.

Alternative Courses of Action, Affected Stakeholders and Their Interests in the Light of Value Premises

The analysis made in the previous section has shown that currently available state of knowledge does not provide any clear guidance as to which type of stem cell-based therapy is safer, more efficacious, more accessible to large numbers of patients or less ethically controversial.

Why consider safety, efficacy, access and the extent to which the research raises ethical controversies? There are two reasons: (1) these concerns refer to important values in our culture, and (2) they may pull in somewhat different directions. In the latter case, it will be necessary to make decisions concerning the relative importance of these concerns: which is more important, in case there is a clash or a tension between them?

Safety without efficacy is pointless and a waste of resources. Efficacy without safety is dangerous and raises issues of which risks a person ought to be willing to take, and should be (allowed to be) exposed to, for a certain chance to some benefit. Obviously, both safety and efficacy are desired and desirable. But the specific features of stem cells and stem cell-based research give some of these recommendations a special twist.

Variations in accessibility raise issues of justice, another important value in our culture. To be sure, in the history of medicine, there are several examples of expensive therapies, first accessible only to a few rich people. But if the therapy was successful, and cooperation with industry could be established, the therapy became less expensive and available to more people. However, this does not show that concern for social justice is unimportant—on the contrary, as is underlined in the ISSCR guidelines for translational stem cell research.

What is the reason for considering the extent to which certain avenues of research are ethically controversial? This is in our view relevant to the extent that these avenues of research are funded by money collected by taxpayers, directly or indirectly. Clearly, then, many different interests are at stake here, and they have to be considered and balanced against each other; and in the end, the decision taken will not be ethically neutral. The interests of some may be favored, the interests of others not.

It may turn out that each type of therapy will have some of these characteristics, but not all. It is possible therefore that in the future we might be facing a choice between, for example:

- (a) A safer but less efficacious versus more efficacious but less safe therapy,
- (b) A safer and more efficacious but accessible to a small number of patients versus less safe and less efficacious therapy accessible to many, or
- (c) A safer and more efficacious but more ethically controversial versus less ethically controversial but also less safe and less efficacious therapy.

There can be many other combinations between different characteristics of stem cell-based therapies, and it would be beyond the scope of this paper to describe and discuss them all.

Who would be the stakeholders affected by such scenarios? Present and future patients as well as their health care providers and clinicians can be directly affected by safer or more efficacious stem cell-based therapies. The part of the society currently opposing hES cell research might, although not necessarily, review their position if hES cell-based therapies prove to be safe, efficacious and accessible to large numbers of patients. Safety and efficacy of such therapies would also make an impact on the whole society, interested in more cost-effective healthcare.

Accessibility of stem cell-based therapies would also directly affect the present and future patients as well as their health care providers. Those who are able to afford such therapies and/or who live in the countries where such therapies are available would be affected positively, whereas the interests of those unable to afford or access such therapies would be defeated. This situation might affect the society at large in terms of increasing gaps between economic classes or the differences between the countries with and without the infrastructure and necessary qualifications to offer such therapies.

Differences between the ethical controversies raised by hES cell- and hiPS cell-based therapies could affect the opinions of many groups in society at large. These opinions might in their turn affect the researchers and

research institutions in terms of political decisions regarding research activities on a certain type of cells, or the funding available for such research. They may also affect present and future patients in the cases when political decisions would allow or limit access to stem cell-based therapies.

Looking for the guidance on what may be considered as relevant values in the context of applying stem cell-based therapies, either in a research or a therapeutic context we will now turn to legal documents and ethical guidelines.

Autonomy of research subjects and patients and their safety is protected according to many European and international documents (see Table 1). The table provides the examples of values which are especially important in this context. They are few among numerous values of different kinds that are either protected by the so-called “hard law”²⁵ or promoted by the so-called “soft-law”²⁶ in Europe. The table does not claim to cover all the values protected and promoted by the documents analyzed. In the table, we make a distinction between international documents protecting and promoting human rights in general, documents regulating biomedical research on humans, and documents regulating research involving human cells. Some provisions of the international human rights documents protect or promote certain values only indirectly, as they do not deal specifically with, for example, autonomy or safety of biomedical research subjects and individual patients.

The analysis of hard law and soft law documents has shown that the following values, relevant to translational stem cell research, are protected or promoted (listed in the

alphabetical order to avoid any ranking): advancement of medical research,²⁷ autonomy of individual patients,²⁸ autonomy of research subjects,²⁹ safety of individual patients³⁰ (in the case of innovative stem cell-based therapy),

²⁷ This value is promoted by, for example, Art. 13 of the EU Charter of Fundamental Rights, which states that “scientific research shall be free of constraint” and “academic freedom shall be respected” [48], and by Recommendation 34 of the ISSCR Guidelines, which states that in some very limited cases, “clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial”, provided that certain conditions are fulfilled [47]. This value is also protected by Art. 15 of the Oviedo Convention, demanding that “scientific research in the field of biology and medicine shall be carried out freely, subject to (...) provisions ensuring the protection of the human being” [44].

²⁸ This value is protected by Art. 5 of the Oviedo Convention, requiring individual’s free and informed consent for any intervention in the health field as well as the right to freely withdraw this consent at any time [44]. It is promoted in the Recommendation 28 of the ISSCR Guidelines, which also stresses the importance of free and informed consent, and specifically states that patients need to be informed “when novel stem cell-derived products have never been tested before in humans and that researchers do not know whether they will work as hoped”, about “the possible irreversibility of a cellular transplant” and “the source of the cells so that [research subjects’] values are respected” [47]. It may be argued that individual patient’s autonomy, as a value, is indirectly protected by Art. 10 (the right to freedom of expression) of the European Convention on Human Rights [43], as well as promoted by Art. 1 (protecting human dignity) and Art. 3 (protecting the right to integrity of the person) of the EU Charter of Fundamental Rights, and, for minor patients, by Art. 24 (1) (protecting the rights of the child) of the same Charter [48].

²⁹ This value is protected and promoted by the same provisions as protecting or promoting autonomy of individual patients, and, in addition, by several other provisions, indicated in Table 1. All of them require research subject’s informed consent which is free (e.g. Art. 3 (2b) and Art. 3 (2e) of the Clinical Trials Directive [40] or Art. 22 and Art. 24 of the Declaration of Helsinki [45]), as well as express and specific (e.g. Art. 16 of the Oviedo Convention [44]).

³⁰ It may be argued that safety of individual patients, as well as safety of research subjects is indirectly protected and promoted by Art. 2 of the European Convention on Human Rights [43] as well as Art. 2 of the EU Charter of Fundamental Rights [48] respectively, both protecting the right to life, as well as, for minor patients, promoted by Charter’s Art. 24 (2), protecting the rights of the child. This value is also protected by Art. 2 of the Oviedo Convention, requiring that “the interests and welfare of the human being shall prevail over the sole interest of society or science” [44]. In a much more specific manner, it is also protected by Art. 5 (1) of the Tissues and Cells Directive, which requires that “tissue and cell procurement and testing are carried out by persons with appropriate training and experience and that they take place in conditions accredited, designated, authorised or licensed for that purpose” [41]. Art. 35 of the Declaration of Helsinki also promotes this value by making sure that the interests of the individual patient are protected: “in the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient (...) may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering” [45].

²⁵ The term “hard law” refers to documents that are binding to the EU member states and thus protecting certain values by requiring these states to, for example, grant certain rights and freedoms to the individuals under their jurisdiction. An example of hard law in the European context would be the directives and regulations of the European Union (such as the Clinical Trials Directive 2001 [40], the Human Tissues and Cells Directive 2004 [41] or the Regulation on Advanced Therapy Medicinal Products 2007 [42]), as well as the international conventions (such as the European Convention on Human Rights 1950 [43] and later protocols, or the European Convention on Human Rights and Biomedicine 1997 [44], the so-called Oviedo Convention)—the latter only when ratified by the member states. International conventions may thus be both hard law and soft law, depending on whether they have been ratified.

²⁶ The term “soft law” refers to documents that are not binding unless they are incorporated in the national legislation or ratified by the parliaments of the member states. Soft law thus normally promotes certain values by providing guidelines and recommendations. Example of soft law would include various declarations and guidelines (e.g. Declaration of Helsinki 2008 [45], Council for International Organizations of Medical Sciences (CIOMS) Guidelines 2002 [46] or International Society for Stem Cell Research (ISSCR) Guidelines for the Clinical Translation of Stem Cells 2008 [47]).

and safety of research subjects.³¹ This analysis has also demonstrated that safety of research subjects, which the first patients receiving stem cell-based therapies would be, is an important value, protected or promoted by all the reviewed documents.

In the context of translational stem cell research on humans, autonomy and safety of research subjects or patients as well as advancement of medical research have been presented as values also in the recent academic literature. For example, Yim [50], Lo et al [51], Sugarman [52], Tzamaloukas et al [53], Maienschein et al [54], and Marks [55] to name but a few authors, have stressed the importance of advancement of medical research while ultimately preserving the safety of research participants and patients, whereas the first four authors have stressed the importance of obtaining a truly informed consent, and thus safe-guard the autonomy of research participants.

Besides the above-mentioned sources of information we may also receive guidance from different types of ethical theories as to what should be regarded as values. For example, classical utilitarians like Bentham [56] focus on pleasure or happiness, while preference utilitarians like Singer [57] focus on maximizing interest satisfaction. From a utilitarian perspective, the consequences of using hiPS

cell- and hES cell-based therapies would be the most important factor when deciding which type of therapy should be preferred. It means that both types of utilitarians would attach importance to safety of patients, the advancement of medical science, and the interests of groups opposing hES cell-based therapies depending on how strong these interests are, or how much happiness their satisfaction generates, and by how many they are expressed. But it is possible that for some utilitarians, the stronger interests of fewer stakeholders would outweigh the weaker interests of a larger group of stakeholders.

From a human rights' perspective, the key is respect for individual human rights [58]. This theory claims that humans have rights and these rights must be taken seriously, but it remains debatable who precisely qualifies for such protection [58]. The scope of the protection offered is important to clarify. It is sometimes debated whether such protection extends to unborn human beings or to human embryos. A therapy which involves a violation of human rights—even if these are the rights of one single person—would be considered as unacceptable. An example could be a therapy which is unsafe to the extent that it could pose a threat to patient's right to life.

From the viewpoint of human dignity-based theories, the interests of present patients would also be of the highest importance, and a therapy involving a violation of human dignity—even of one single person—would be deemed immoral. The dignitarian perspective condemns any practice, process, or product which will compromise human dignity [58]. One interpretation of human dignity originates in Kantian ideas. Although it is notoriously unclear what constitutes the positive content of “human dignity”, the negative content of this concept is sufficiently clear—actions or omissions that could violate human dignity, such as slavery, torture, eugenics, stigmatization and discrimination. According to Kant, human beings should always be treated as ends in themselves, and never merely as means to an end. From this perspective, the autonomy of patients or research subjects to decide for themselves would be seen as an important value, founded on human dignity.

One version of dignitarianism states that human life should be protected and respected starting from the point of conception [58]. According to this view, an entity that has a potential to become a human embryo deserves protection. The potentiality argument as stated and discussed by Anne Fagot-Largeault [59] plays a crucial role in the controversies over the scope of human dignity and whether it applies to human embryos. Is, for example, the basis of the human dignity rationality, as in Kant's ethics, and does that exclude embryos from the scope? Or does the potentiality argument help to include embryos so they are protected by human dignity? If the notion of human dignity applies also to

³¹ Besides the provisions, listed in Table 1, which protect and promote both the safety of individual patients as well as the safety of research subjects, the latter is protected by numerous other provisions, indicated in the table. Some of these provisions require that very specific measures are taken to ensure research subject's safety. For example, Art. 14 (2) of the European Regulation on Advanced Therapy Medicinal Products requires the establishment of a risk management system designed to identify, characterise, prevent or minimise risks related to advanced therapy medicinal products [42], Art. 20 of the Declaration of Helsinki—satisfactory risk management [45], Recommendation 24 of the ISSCR Guidelines suggests that subjects are “selected to minimize risks, maximize the ability to analyze results, and enhance the benefits to individual subjects and society” [47], and Art. 16 of the Declaration of Helsinki requires that medical research involving human subjects is conducted only by individuals with appropriate scientific training and qualifications [45]. Most other provisions emphasize that biomedical research may be undertaken only if foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients (e.g. Art. 3 (2a), Clinical Trials Directive [40]), or the importance of knowledge to be gained (e.g. CIOMS Guideline 8, which also requires that risks are minimized [46]), or the potential benefits of the research (e.g. Art. 16, Convention on Human Rights and Biomedicine [44]). Several provisions also emphasize that in medical research “the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society” (Section 2.3 of the Guideline on Good Clinical Practice, ICH [49]), or “over all other interests” (Art. 6, Declaration of Helsinki [45]). Regarding medical research combined with medical care, Art. 31 of the Declaration of Helsinki requires that such combination may only be acceptable “to the extent that the research is justified by its potential (...) value and if (...) participation in the research study will not adversely affect the health of the patients who serve as research subjects” [45].

Table 1 Examples of values protected or promoted in Europe relevant to translational stem cell research

| Values protected or promoted | International documents protecting/promoting human rights in general | | International documents regulating biomedical research on humans | | International documents regulating research involving human cells | |
|---------------------------------|--|---|---|--|---|--|
| | Hard law | Soft law | Hard law | Soft law | Hard law | Soft law |
| Autonomy of research subjects | Art. 10, ECHR ^a (indirectly) | Art. 1, 3, CFR ^b Art. 24 (1), CFR (minor research subjects) | Art. 3 (2b), 3 (2e), CTD ^c Art. 5, 16, Oviedo CHRB ^f | Art. 22, 24, DoH ^d Guideline 4, CIOMS ^g | | Rec. 28, ISSCR Guidelines ^e |
| Autonomy of individual patients | Art. 10, ECHR (indirectly) | Art. 1, 3, CFR Art. 24 (1), CFR (minor patients) | Art. 5, Oviedo CHRB | Section 2.9, GGCP (ICH) ^h | | Rec. 28, ISSCR Guidelines |
| Safety of research subjects | Art. 2, ECHR (indirectly) | Art. 2, CFR (indirectly) Art. 24 (2), CFR (indirectly) | Art. 14 (2), Reg. ATMP ⁱ Art. 3 (2a), CTD | Art. 6, 16, 18, 20, 21, 31, DoH Guideline 8, CIOMS | Art. 5 (1), TCD ^j | Rec. 24, ISSCR Guidelines |
| Safety of individual patients | Art. 2, ECHR (indirectly) | Art. 2, CFR (indirectly) Art. 24 (2), CFR | Art. 16, Oviedo CHRB Art. 2, Oviedo CHRB | Sections 2.2, 2.3, GGCP (ICH) Art. 35, DoH | Art. 5 (1), TCD | |
| Advancement of medical science | | Art. 13, CFR | Art. 15, Oviedo CHRB | | | Rec. 34, ISSCR Guidelines |

^a *ECHR* European convention for the protection of human rights and fundamental freedoms [43]

^b *CFR* charter of fundamental rights of the European union [48]

^c *CTD* European clinical trials directive [40]

^d *DoH* declaration of Helsinki [45]

^e *ISSCR guidelines* international society for stem cell research guidelines for the clinical translation of stem cells [47]

^f *Oviedo CHRB* convention on human rights and biomedicine [44]

^g *CIOMS* CIOMS guidelines [46]

^h *GGCP (ICH)* guidelines on good clinical practice (CPMP/ICH) [49]

ⁱ *Reg. ATMP* European regulation on advanced therapy medicinal products [42]

^j *TCD* European tissues and cells directive [41]

embryos, how should we define the potentiality of human embryos to become persons? Is it morally wrong to interfere with this potentiality because the embryo might have become a potential genius, or because it “cuts short the development of a potential human being and prohibits its actualization” [59]?

If there is a scientific difference between hiPS cells and hES cells concerning their ability to contribute to a human embryo, this difference is ethically relevant according to this version of dignitarianism. Such dignitarians would not make any difference between stem cell-based therapies including material obtained from spare IVF embryos, SCNT embryos or hiPS cells if they all have the potential to contribute to a human embryo. If hiPS cells do not have natural potentiality to become a human embryo, then hiPS cells and hiPS cell-based therapy would be preferred to therapies based on hES cells. However, the qualifier “natural” is not part of all dignitarian arguments. Apart from that, it should be remembered that the existence of natural or scientific “boundaries of potential” of hESCs and hiPS cells to develop into a human embryo has been questioned by Giuseppe Testa. He has argued that the existence of such boundaries is a political rather than a scientific question [35].

The dignitarian view could be criticised by both utilitarians and human rights’ theorists. Although utilitarians count the benefits and harms in relation to all those who are affected by an action, they restrict the calculation to those who are capable of experiencing pain or pleasure, having preferences and so on [58]. Like the utilitarians, human rights theorists do not usually recognize pre-sentient life as a bearer of rights [58].

Having outlined the stakeholders affected by our preferences, the values involved in our decision-making and the importance of the interests of different stakeholders in the light of these different value premises, we return to the scenarios in the light of current knowledge and the value premises.

Alternative Ways of Action in the Light of Current Knowledge and the Value Premises

Grounding our decision on current knowledge and the explicitly stated value premises, can we make our preferences in the case of above-mentioned alternatives? Since the current state of knowledge contains uncertainties and gaps, let us reconsider the alternative options in the light of value premises.

Greater Safety Versus Greater Efficacy The interests of present patients would be considered as important by all three types of ethical theories. However, the focus on the

interests of present patients would not help us to choose between safety and efficacy, since different patients may have different interests. However, if we take into consideration the values endorsed by European and international ethical guidelines and legal documents, safety of patients and research subjects is considered as an important value.

It has to be noted that safety is not black and white, but is a matter of degree, also depending on the target group—e.g. children, pregnant women or other adults,—on the disease, and the alternatives available. Based on the present state of knowledge, both hES cell- and hiPS cell-based therapies can be considered as risky, depending on the aspect of risk chosen. Just which of these aspects will be considered as more “risky” and “safe” depends on the value that we attach to the probability and severity of, for example, graft-versus-host disease (GVHD), cancerous tumor formation or the currently unknown long-term effects. Both GVHD and cancer can be lethal, but in many cases both can be effectively treated. Unknown risk, however, is different from the risk of cancerous tumor formation or GVHD. We may be likely to perceive something as more dangerous when it is unknown than when it is known. As Sahlin, Persson and Varemans have argued, it is the known unknowns and unknown unknowns that make the risk-assessment immensely difficult [60].

Greater Safety and Efficacy Versus Greater Accessibility to Large Numbers of Patients Taking into consideration that the therapies based on hES and hiPS cells would mostly be used for the treatment of currently untreatable diseases, treating a few patients could be considered as a greater utility than treating none, at least from a viewpoint of some utilitarians. Just how much happiness or interest satisfaction launching of such a therapy would generate, if we take a utilitarian view, is unclear unless we know how safe, efficacious and accessible that therapy is. There is a problem with the “double maximization” often advocated by utilitarians: to do as much good for as many as possible. If we want to do good for as many as possible, one alternative ought to be chosen. But if we want to do as much good as possible, perhaps another alternative ought to be preferred.

When discussing the consequences of choosing “less safe and efficacious but more accessible” therapies, we should also consider the impact of such therapies on the advancement of medical science and the trust in scientific research or innovative therapies. London, Kimmelman and Emborg have argued that “adversities in isolated trials can have cascading effects, undermining institutional and social supports for new initiatives” [61]. Choosing less safe and efficacious therapy that is accessible to all, at least at the stage of clinical research, may have negative consequences to a large amount of stakeholders—not only the patients

that have been harmed by the experimental therapy but also future patients and researchers if further research initiatives are suspended on the grounds of the first disaster.

From the viewpoint of human rights, everyone should have the same right to access the therapy needed, and a “lottery” option would most probably be preferred in the case of scarce resources and there are patients with the same need of a treatment that only is available to a few of them. Furthermore, in the case of less safe and less efficacious therapies, it would be important what exactly is meant by “safe” and “unsafe”, when discussing the general acceptability of such therapies. If “unsafe” would amount to the threat to at least one patient’s right to life, such a therapy, no matter how accessible and how beneficial to the rest of the patients, would be unacceptable from the point of view of human rights. Similarly, if the complications suffered by the patient and caused by unsafe therapy would amount to inhumane treatment, dignitarians would also disapprove of such a therapy.

Greater Safety and Efficacy Versus Lesser Ethical Controversy The public, especially in some states in the US and some member states of the EU, remain uncomfortable with the use of hES cells for clinical applications. There are situations in which policy-making does not require consensus, for example, when the rights of minorities are threatened. For example, if there is a clash between the interests of those suffering from incurable diseases and who want to promote any promising line of research, and those who treat hES cell research as a human rights issue, there will never be consensus. Nevertheless, policies have to be made.

From the point of view of utilitarians who focus on the satisfaction of the interests of the greatest number, this dilemma could not be solved merely by counting how many stakeholders are on which side of the argument. As was mentioned earlier, the satisfaction of interests would depend on what exactly is meant by “safe” and “efficacious”. Regarding one type of human dignity arguments, extending the protection of human dignity to human pre-implantation embryos, the use of hES cell-based therapies, however beneficial to patients and the whole society, is not acceptable. But on the one hand, the knowledge gaps regarding the theoretical possibility of hES cells or hiPS cells to contribute to a human embryo under the right circumstances need to be filled. On the other hand, if we take the perspective proposed by Demetrio Neri [36], it becomes irrelevant whether these knowledge gaps are filled—both hES cell-based and hiPS cell-based therapies can be considered as equally ethically controversial from the viewpoint of dignitarians, who extend the protection of human dignity to human pre-implantation embryo.

No conclusion can be drawn from these different types of ethical theories unless it is clarified what exactly is meant by “safe” and “unsafe”, “efficacious” and “inefficacious”, “accessible” and “ethically controversial”. It is especially important to fill the knowledge gaps concerning patient safety, as this is a value endorsed, to a different degree, by all three types of ethical theories reviewed in this article, as well as an important value protected or promoted by European and international guidelines, declarations, conventions and directives.

Conclusions

Returning now to the question posed in the title of our paper: “Do we still need human embryonic stem cells for stem cell based therapies?” there are at least three possible answers: “yes”, “no”, and “too early to tell”. If the problem is interpreted as referring to the present situation, our answer would be “yes”. This is consistent with the findings in the literature, and in particular with the differences recently discovered between disease models based on hES cells and hiPS cells of Fragile X [37]. But if the problem is understood as referring to the future, our answer will be the third one. In view of the infancy of the fields, the existing uncertainties and knowledge gaps, it is premature to take a dogmatic position at the present.

Research in the area of both hES cells and hiPS cells is in rapid development, and this paper provides an overview of the scientific and other arguments actual at present. If the scientific picture changes, the moral relevance of scientific and other differences must be re-assessed.

Do we still need hES cells for stem cell-based therapies after the discovery of iPS cells? The analysis in this paper illustrates and emphasizes that the answers to this question are relative to:

- 1) The scientific state of the art, where there are still considerable disagreements among scientists and many uncertainties, as well as
- 2) The normative starting points, where there are considerable disagreements among many ethicists and many uncertainties.

From this point of view, black and white thinking and dogmatic conclusions concerning the question in the title of this article seem premature at the present time. The knowledge gaps and uncertainties should be openly acknowledged, since they influence the risk assessment and risk management. Research efforts should be directed at filling the knowledge gaps. Thus, it is premature to say that we do not need translational hES cell research aiming

at finding stem cell-based therapies or that we need such research only for comparative purposes.

The most contested differences between hES cell- and hiPS cell-based therapies outlined in this article, namely, concerning patient safety, treatment efficacy, accessibility to large numbers of patients and ethical controversy, are ethically relevant in the light of different value premises, endorsed by different types of ethical theories. The differences concerning patient safety can be considered as ethically relevant from the viewpoint of all three types of ethical theories considered in this article, whereas other differences are given varying level of importance, depending on the value premises.

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Paper II

WHAT PATIENT GROUPS SHOULD BE ASKED TO PARTICIPATE IN FIRST-IN-HUMAN TRIALS OF STEM CELL-BASED THERAPIES? THE CASES OF PARKINSON'S AND HUNTINGTON'S DISEASES: ETHICAL AND EPISTEMIC CONSIDERATIONS (Paper II)

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Abstract: The aims of this article are: (1) to discuss whether there are any types of medical and societal differences among diseases that are relevant for decision-making as to what patient groups should be asked to participate in first-in-human (FIH) trials of stem cell-based therapies; (2) to analyze these differences in the light of values generally endorsed by different types of ethical theories, since the question in the title of this paper is a value-loaded and the answer to it depends on which values one wants to promote and protect, and how they are ranked in importance relative to each other; (3) to discuss whether the answer to this question is disease-specific or whether it depends on factors common to several diseases. To illustrate these problems, we use Parkinson's disease (PD) and Huntington's disease (HD), between which there are important medical and societal differences. Moreover, research on stem cell-based therapies for these diseases is in

translation. We argue that this approach to the problem can be applied to decision-making about similar problems raised by other diseases, exhibiting the same types of differences.

Keywords: First-in-human trials, experimental stem cell-based therapies, values, Parkinson's disease, Huntington's disease

1. Introduction

In many research areas, where healthy volunteers are not an appropriate population for Phase I or first-in-human (FIH) studies, which usually test the safety of the experimental intervention, the contemporary standard is to use the sickest patients, because they are not as likely to be harmed as less sick patients.¹ Dosages in Phase I studies are usually not tailored to maximize benefit to the participants, since the primary goal of such studies is usually to determine if an intervention is safe, and not whether it works.² It is Phase II studies which usually test efficacy of the experimental intervention, and inclusion of the sickest patients may not be appropriate in Phase II studies, as such patients would be least likely to benefit from the experimental intervention.³ Their involvement in Phase II studies may lead to false conclusion that the intervention provides no benefit when in fact it might work in healthier patients.⁴

“First-in-human” can mean different things. Although this term refers to the first time an intervention under investigation is used in a human clinical trial, it can include a range of different types of interventions, from an intervention that is very similar to other interventions to the one which is not only first in human, but also the first intervention using that particular type of mechanism, and finally, to a new kind of intervention, sufficiently different from other kinds of approved interventions in clinical use.⁵ In this article, we will use the term “first-in-human” meaning the latter type of intervention.

In the context of FIH clinical studies of stem cell-based interventions, not much can be known about the likelihood that the intervention will actually lead to efficacy testing and subsequently to clinical use.⁶ The risk-benefit ratio of cell replacement trials is therefore unlikely to be particularly favourable, and therefore it would be difficult to justify serious and potentially irreversible risks associated with such interventions.⁷ To name a couple of examples, it has thus been argued that such studies should involve patients who suffer from diseases or conditions where no current therapies are available or, when there are treatment options, participation should be restricted to patients for whom existing treatments are not an option.⁸ It has also been argued that the less serious the condition or disease the patient is suffering from, the less justification there is for such patients to participate in Phase I studies, if the harm-benefit ratio for such participants is relatively poor.⁹

However, should that always be the case regarding all FIH experimental stem cell-based interventions? Such interventions may range from treatment of life-threatening diseases without alternative therapies to cosmetic therapies, thus involving a different risk-benefit ratio".¹⁰ Finally, stem cell therapies are based on different kinds of stem cells.¹¹

A question therefore arises which patient groups should be asked to participate in FIH trials of stem cell-based therapies. Is the answer disease-specific or does it depend on factors common to several diseases? This may look like a technical question, but on closer inspection it is also value-loaded. In other words, the answer depends on which values one wants to promote and protect, and how they are ranked in importance relative to each other: safety of patients, reliable and generalizable answers to choice of therapy and dosage, etc. Although such questions are usually addressed during the ethical review process, the effects of FIH stem cell-based interventions would be more difficult to detail because there are still many known and unknown unknowns related to such interventions.

To answer these questions in the context of stem cell-based interventions, similarities and differences between diseases have to be examined, and that is what we will try to do in this paper. Then two different scenarios are possible, relevant for the decision strategy to be preferred. If the comparative analysis provides us with relevant information about differences between diseases, one type of decision-making strategy is called for. If however, there are considerable gaps of knowledge, many known unknowns, a different decision-making strategy suggests itself.

Three types of knowledge premises seem important in such decision-making. The first type of knowledge premises relates to the qualities of stem cell-based therapies, especially their safety and efficacy. The second type of knowledge premises relates to the characteristics of patients that are candidates for such therapies. We discuss these types of knowledge premises in section 2 of this article. The third type of knowledge premises relates to the characteristics of the diseases intended to be treated by stem cell-based therapies in FIH trials, including the existence or non-existence of alternatives to such therapies. These premises are discussed in section 3 of this paper. Whereas in section 4, we evaluate the ethical relevance of these knowledge premises for decision-making about what patient groups should be asked to participate in FIH trials.

To analyze and concretize these general questions, we will use the examples of Parkinson's disease (PD) and Huntington's disease (HD). These diseases exemplify important medical and societal differences, and research on stem cell-based therapies for these diseases is in translation from laboratory to clinic. Obviously, the problems raised by first in human trials with stem cell-based therapies will resemble in several ways first in human trials with therapies based on other new and emergent technologies. Problems with desperate patients will be similar, for example. But in our decision-making we need to be more explicit about the knowledge premises and the value assumptions. What is essential in the present paper is, we believe, the focus on quality-of-life issues, the

discussion of the role of health and non-health related consequences, the importance of alternative treatments (if any), the early *versus* the late stage arguments, the role of “changed facial expression and voice”, the disparity of inside feelings in the patient groups, and the inherent coercion of caregivers.

We argue that the approach to the problem we use in this paper can be applied to similar decision-making in the case of other diseases, exhibiting the same types of differences.

2. When can FIH trials begin and what patient groups should be selected to participate in them?

To answer the question in the first part of the title of this section, we first have to examine the requirements that stem cell-based therapies to be tested in FIH trials have to meet and to investigate which of these requirements are necessary, and which of them sufficient conditions to start FIH trials of such therapies.

2.1 What conditions have to be fulfilled before FIH can begin?

Safety. A necessary condition for the start of FIH trials is the safety of stem cell-based therapies. See table 1 for examples of requirements concerning safety and risk management in biomedical research in general or translational stem cell research in particular that are present in different international guidelines and declarations as well as European conventions, directives and regulations.

Researchers have also emphasized the importance of safety of FIH trials. For example, Sugarman has argued that it is only acceptable to move to a FIH trial with a cell-based intervention, if there is scientific agreement about safety¹² based on preclinical studies. Moreover, safety should be reasonably ensured as well as the possibility of benefit in terms of answering an important scientific question determined.¹³ However, it is important to be precise what this scientific agreement is actually about. It would only be ethically acceptable to proceed with FIH trials if the scientific community agrees about the stability of knowledge regarding safety. The scientific community may also agree that there are still many knowledge gaps regarding safety, which would not justify the commencement of FIH trials. Moreover, safety is not just a scientific issue – there should also be an agreement about what is an acceptable level of risk, and such agreement will involve value judgments. It is equally important to be precise about how many knowledge gaps are “too many”. The distinction between “many” and “too many” is value-laden; it is not ethically neutral.

To ensure safety, sound research design is indispensable. Kimmelman et al have stressed that design of preclinical studies strengthening their internal and external validity and their execution with scientific rigor is “a critical factor in assuring favorable benefit profiles – whether this involves direct, therapeutic benefits or knowledge benefits”.¹⁴

These considerations imply that research subjects should not be asked to participate in research the safety of which is questionable, and that safety is thus a necessary condition for FIH trials.

Efficacy. Another necessary condition to be met by animal research is demonstration of proof-of-principle for a desired therapeutic effect in a relevant animal model.¹⁵ It must be demonstrated in animal models that stem cell-based approach induces substantial improvement of functional deficits that resemble the debilitating symptoms in patients.¹⁶ With knowledge gaps regarding both known and unknown risks, substantial improvement seems to be necessary in order to justify taking these risks. In the future, provided such gaps are eliminated or reduced, less substantial improvement may become acceptable, depending on what the risks are. It is important to consider, however, who should decide whether the improvement is substantial or not.

Given today's state of knowledge, animal models may not fully predict either the safety or efficacy of stem cell-based therapies. For example, such models may not fully predict the toxicity of stem cells or their derivatives, occurrence of immune and other biologic responses, risk for tumor formation¹⁷ and other behavior after implantation in patients.¹⁸ Similarly, they may not mimic all aspects of the pathology of the human condition, leading to lack of efficacy of the stem cell-derived product in the clinical trial.¹⁹

Clinical competitiveness. According to the ISSCR Guidelines, "stem cell-based approach must aim at being clinically competitive or superior to existing therapies".²⁰ If current knowledge is to be translated into a stem cell-based treatment for a certain disease, it is necessary to define what is required for the stem cell-based approach to be clinically competitive and what risks to patients are acceptable.²¹ For example, in order to be clinically competitive in PD, a stem cell-based therapy "has to provide advantages over current, rather effective treatments for alleviation of motor symptoms in PD patients".²² More specifically, such therapy "should give rise to long-lasting, major improvements of mobility and suppression of dyskinesias without the need for further therapeutic interventions".²³ Alternatively, stem cell-based therapy "should improve symptoms that are largely resistant to current treatments."²⁴ In addition or alternatively, it should be advantageous as a single procedure versus lifelong drug therapy with associated side effects, and/or cost-effectiveness,²⁵ or it should counteract disease progression.²⁶

The potential of stem cell-based therapies to improve different areas of health-related quality of life (HRQoL) of patients should also be taken into consideration when evaluating their clinical competitiveness: improvement of emotional reactions, energy, sleep, decrease of pain and social isolation.²⁷ Measurement of HRQoL provides important information on the outcome following transplantation not gained by traditional assessment protocols.²⁸

If efficacious therapy is lacking, as in the case of HD, the severity of a disease might justify the potential risks of a stem cell-based experimental intervention in patients.²⁹

According to the ISSCR Guidelines, certain knowledge gaps are not seen as a barrier to commencement of FIH trials aiming at the treatment of serious and untreatable diseases: “complete understanding of the biological mechanisms at work after stem cell transplantation in a preclinical model is not a mandatory prerequisite to initiate human clinical experimentation, especially in the case of serious and untreatable diseases for which efficacy and safety have been demonstrated in relevant animal models”.³⁰

Informed consent. Finally, obtaining free and informed consent is a necessary but definitely not a sufficient requirement in the context of FIH trials. If scientific knowledge regarding the safety of stem cell-based therapies is not stable, turning to a FIH trial as a last remedy may possibly cause an even greater suffering of the patient, especially bearing in mind the possible irreversibility of a cellular transplant. Similarly, if the scientific community does not agree that the efficacy of stem cell-based therapy can reasonably be expected, including consenting “hopeless” patients into a FIH trial may expose them to an additional burden of futile treatment.

Informed consent is also essential to respect the potential research subject’s values. According to the Recommendation 28 (c) of the ISSCR Guidelines, subjects should be informed about the source of the cells so that their values are respected.³¹ It can be discussed what this may mean in practice. For example, should this mean that the subject should not be informed – if he/she expressly states that he/she does not want to know about this – whether the experimental intervention is based on human embryonic stem cells? On the one hand, one may imagine a situation where it may be easier for some persons with “pro-life” views to accept such an intervention when they do not know whether the intervention is based on human embryonic stem cells. On the other hand, in FIH trials, which tend to involve significant risk, disclosure should not be based on potential research participant’s preferences for research-related information. Limited or partial information would not meet the requirements for informed consent, e.g. the requirements of the FDA.

2.2 What patient groups should be selected to participate in FIH trials?

In testing of most therapies or medications, FIH trials involve healthy volunteers. As mentioned earlier, the main aim of such trials is usually to test the safety of the administered treatment, and safety can be best evaluated when tested on a healthy human to eliminate possible confounders. However, there are some exceptions to this rule, namely when the tested therapy or medication can be so dangerous or so toxic that it would not be acceptable to offer it to a healthy person. Because of the risks related to stem cell-based therapies for PD and HD, the FIH trials of such therapies would have to include PD and HD patients rather than healthy volunteers.

When considering which categories of patients should be chosen as research subjects in FIH trials of stem cell-based therapies, we have to bear in mind that safety of research subjects, which is a value protected and promoted in many European and international

documents, is not black and white, but is a matter of degree, depending on the target group – e.g. children, pregnant women or other adults, – on the disease, and the alternatives available.³² The level of risk and safety of experimental stem cell-based therapies can be judged depending on the aspect of risk chosen³³ as well as on the aim of administering stem cell-based therapies. Are they meant to restore, maintain or improve the patient’s health and quality of life? These goals can be defined in many different ways³⁴ and can be very important in deciding which categories of patients should be asked to participate in FIH trials of stem cell-based therapies. These goals will be considered in greater detail in section 4 of this article, in the light of value premises.

Patients at early stages of their disease. From the ISSCR Guidelines’ requirement that stem cell-based clinical researchers “monitor research subjects for long-term health effects”³⁵ it seems that the stage of disease is important for deciding which patient groups should be chosen to participate in FIH trials. Monitoring for long-term health effects is hardly possible if terminal patients close to death participate in FIH trials. However, as Sugarman points out, if healthier patients participate, and the cell-based intervention proves to be harmful, the subjects may have shortened their lives or harmed their health as a result of participating.³⁶ If cell-based interventions are proven to be safe and can reasonably be expected to be efficacious, in earlier stages of the disease, ideally patients who can be monitored for long-term effects would be preferable for FIH trials. However, the efficacy of the administered stem cell-based treatment may also depend on the stage of the disease, and the latter may vary depending on the disease. For each disease a road map should be developed “that defines the necessary scientific and clinical advances required for stem cells to reach the clinic”.³⁷

Patients at late or final stages of their disease may have the least to lose, but the scientific usefulness of FIH trials might be compromised if such patients have a range of other health problems that confound the results.³⁸ Potentially efficacious therapy, had it been tested on patients in earlier stages of their disease, might then be not developed and the value of research may be reduced. This is an important concern, especially in the light of the requirement of the Declaration of Helsinki that it is acceptable to combine medical research with medical care only “to the extent that the research is justified by its potential (...) value (...)”.³⁹ Having “the least to lose” should therefore not be the decisive factor.

Can the stage of the disease alone be a decisive factor in deciding which groups of patients should be selected to participate in FIH trials? According to the ISSCR Guidelines, subjects should be selected to (1) minimize risks, (2) maximize the ability to analyze results, and (3) enhance the benefits to individual subjects and society.⁴⁰ Taken separately, however, these three requirements may pull in different directions. Various stages of the disease may meet these requirements differently. According to the Declaration of Helsinki, “in the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician (...) may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or

alleviating suffering”.⁴¹ These requirements can be fulfilled only if the applied therapy is more efficacious than already existing alternatives, if any. It means that it is not the stage of the disease but rather the efficacy of therapy – the latter can vary depending on the former – that would be the decisive factor about which group of patients should be included in a FIH trial.

Desperate patients for whom alternative therapies do not work, independently from the stage of the disease, are yet another group to be considered. According to the ISSCR Guidelines, “if an efficacious therapy is not available, then the severity of the disease, especially if the disease to be treated is severely disabling and life-threatening, might justify the risks of a stem cell-based experimental intervention in patients”.⁴² This implies that, besides the efficacy of treatment, the availability of alternatives is another important factor in deciding which type of patients to include in FIH trials. However, the Guidelines warn not to “take advantage of the hopes of patients with poor short-term prognoses”.⁴³ Patients may be desperate not only because of the lack of efficacious treatment alternatives, but also because of inaccessibility of such alternatives. According to the Guidelines, “clinical research should compare new stem cell-based therapies against the best medical therapy currently available to the local population”.⁴⁴ This requirement, introducing an explicit geographical and temporal limitation to the local population at the present time, is noteworthy as different from the Declaration of Helsinki requirement of comparison with the best proven therapy.

It can be summarized that enrolling patients at earlier stages of their disease is to be preferred when more or less efficacious therapeutic alternatives do not exist or are locally unavailable, and/or where the successful administration of stem cell transplants is likely to be in early stage patients. We will reconsider these statements in section 4 of this article, in the light of values endorsed by different types of ethical theories. The next section will outline the factual differences between PD and HD, the two diseases chosen as examples in our analysis.

3. Examples of medical and societal differences between Parkinson’s and Huntington’s diseases

“Living with Parkinson’s is like living with a thief”, said one patient affected by PD. “It controls all my functions, my visual perception, cognition, my mind, blood pressure and body temperature and my sex life. Like a thief in the night, it sneaks up on me and my dignity so that I lose my motor skills and power to control; it also ruins my night’s rest”.⁴⁵ In the words of patients, suffering from HD, “With Huntington’s one does not have a fear of dying, one has a fear of living. The disease forces impossible choices under the most difficult conditions and there is nothing that can prepare you for the horror of Huntington’s disease”.⁴⁶ As these testimonies illustrate, both diseases change the suffering

person's quality of life considerably. There are many similarities between both diseases in terms of their impact on the patient, on the health caretaker in the patient's family and on the society, but there are also differences. The differences between PD and HD, outlined in this section, in many cases are not unique to these two diseases: there can be other (neurodegenerative) diseases with similar differences.

We will only outline the differences relevant for decision-making concerning which patient groups should be asked to participate in FIH trials, without aiming at completeness. Other medical and societal differences between PD and HD may be relevant for other issues, such as setting therapeutic priorities, and will be discussed in another article.

3.1 Medical differences

Of the many medical differences between HD and PD, the following ones seem, from the perspective of different types of ethical theories discussed in section 4 of this paper, particularly ethically relevant for deciding which patient groups should be chosen to participate in FIH trials.

Impact on life expectancy. PD by itself does not directly cause people to die, but complications can lead to death, and after some time, the medication can also cause side effects.⁴⁷ Contrary to PD, HD is a lethal incurable disease, the average duration of which is 16 years,⁴⁸ but it can vary greatly.

Availability of alternative therapies. In treatment of PD both pharmaceutical and surgical interventions as well as rehabilitation and medical nursing are available.⁴⁹ Conversely, there are no treatments that can cure, delay onset or slow the course of HD; from onset onwards progressive degeneration occurs and the sufferer requires increasing levels of care and maintenance.⁵⁰ However, provision of a full range of supportive medical nursing and social care can help improve the patient's quality of life.⁵¹ Different treatments are available in HD to reduce the severity of some symptoms.⁵² For the summary of the parameters above see table 2.

Chances of success of stem cell-based therapies. This may in practice be a decisive factor whether such therapies should be tested clinically. The importance of proving chances of success is also recognized in the ISSCR Guidelines (Recommendation 34), which states that clinician-scientists "may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial", provided, besides meeting other requirements, "that there is a written plan for the procedure that includes scientific rationale and justification explaining why the procedure has a reasonable chance of success". Significant scientific advancements have already been made in preclinical testing of stem cell-based therapies for both diseases, and they are constantly advancing.⁵³ Chances of success of stem cell-based therapies, in terms of inducing "substantial improvement of functional deficits"⁵⁴, are likely to be evaluated

differently in the context of a disease with and a disease without efficacious alternative therapy. What will count as “substantial improvement” may depend on the availability of other efficacious treatment alternatives. If an efficacious therapy already exists, as in PD, the risk of an adverse effect “must be low and the stem cell-based approach must offer a substantial advantage”, such as “better functional outcome” or “single procedure versus lifelong drug therapy”.⁵⁵ If an efficacious therapy does not exist, as in HD, “the severity of the disease” might “justify the potential risks of a stem cell-based experimental intervention in patients”.⁵⁶ Considering safety of FIH studies, Kimmelman et al have argued that the nature and degree of risk for invasive FIH studies puts “particular pressure on the requirement that risks be favorably balanced against benefits for human studies”.⁵⁷ A similar way of thinking could also be used when considering efficacy of stem cell-based therapies.

Even after FIH trials have started, many knowledge gaps will still exist regarding the safety and efficacy of stem cell-based therapies. In the course of these trials, it may turn out that stem cell-based therapies are safe and efficacious, safe but inefficacious, efficacious but unsafe or, in the worst case, both unsafe and inefficacious. Until the knowledge gaps concerning safety and efficacy of such therapies are filled, we need to consider all four scenarios.

3.2 Societal differences

Psychological effects of the disease on the patient and patient’s family. For both PD and HD patients their diseases have very similar effects on their social life, although the causes of these effects may be somewhat different. Both types of patients may experience the perceived effect of their disease on their human dignity in the form of (sometimes very much) reduced social life, which becomes affected by their inability to perform social activities they used to engage in. Social life is also affected by possible misunderstandings because of the changed facial expression, inability to express feelings through body language and changed voice in PD-affected patients⁵⁸ and personality changes in HD-affected patients. In both cases, the progression of the disease and the extent of its symptoms can affect not only an individual’s ability to take an active role in everyday life, but also his/her desire to do this.⁵⁹ The difficulties such patients are facing may be symptoms-related, treatment-related or emotional-related.

For example, one study found that 76% of surveyed PD patients had difficulties in walking outside their homes, to a degree that affects their daily living, and 73% found that maintaining their balance affected their lives (symptoms-related difficulties).⁶⁰ The same study found that 77% of surveyed PD patients had to plan their day around taking medication⁶¹ (treatment-related difficulties), with higher frequency for taking medication meaning a higher level of inconvenience for the individual.⁶² Another study reported that 78% of surveyed PD patients claimed that feelings of depression or misery affected their participation in life (emotional-related difficulties).⁶³ 76% experienced difficulty in

remembering things, 64% had difficulty in getting to sleep, and 92% reported that tiredness during the day has an adverse effect on day-to-day living.⁶⁴ Feeling depressed or miserable, having difficulty remembering things and thinking things through have consequences on all aspects of their lives, social activities, leisure and work.⁶⁵ Yet another factor that has been found to contribute to the reduced social life is the patient's physical appearance: about 79% rated the importance of their physical appearance as very important or moderately important.⁶⁶

The social life of PD-affected patients may also be affected by communication difficulties concerning speech, facial expressions, body language and handwriting.⁶⁷ PD-affected persons can easily be misunderstood: Some say they cannot show on the outside how they feel on the inside.⁶⁸ Their slow or reduced muscle movements can be misinterpreted as annoyance, disinterest or as lack of understanding.⁶⁹ Changes to the function of facial/throat muscles can also affect the voice, producing speech that may be quiet, hoarse, hurried or hesitant.⁷⁰

HD-affected patients may have problems in their social relations due to anger outbursts that may be misunderstood, wrong choice of words, constant disorganization, changed sexual behavior, and increased dependence on others.⁷¹ They may experience problems in relations with colleagues due to forgotten duties, deadlines, names, dates, and due to inability to organize themselves as before, long time taken to perform simple tasks, making mistakes at work and inability to concentrate.⁷² Before Huntington's disease is diagnosed all these changes in personality may be taken personally by others and affect relations negatively.⁷³

Unlike in the case of PD, the psychological effects of HD start even *before* the disease actually manifests itself, and affect even those family members who do not carry the HD gene and will never get the disease. In most cases HD is a hereditary disease and it is possible to undergo genetic testing to determine whether, e.g., a child or a sibling of a HD patient also carries the HD gene. The psychological effects start already with the anguish when deciding whether to get tested for the HD gene or not. One HD-affected patient has said: "There are not enough words to describe the emotions involved in the decision of opening up "Pandora's Box",⁷⁴ and there are many important personal, legal and financial considerations involved. Moreover, hereditary nature of HD may contribute to family breakdown, and to secrecy which can be so great that it becomes impossible to discuss the subject within the family.⁷⁵

For those who have tested positively, the fear of future may lead to extremes, such as depression with each passing year, or spending too much time or money on things that one would otherwise do moderately. The fear of future may also lead to self-restrictions. One study has found that some people who had tested HD-positively avoided getting into situations in which HD may express itself: e.g. they had given up driving, before they were incapable of doing so.⁷⁶

For those who have tested negatively the psychological effects may take the form of feelings of guilt for not having inherited the HD gene when some other family members have tested positive. Even the HD-affected patient may experience the feelings of guilt for having passed HD on to one's children, for having created a family knowing that he/she has inherited the gene. Such feelings of guilt may cause abnormal family relations.⁷⁷

Impact of the disease on the health care providers in the patient's family. Family relationships in PD- and HD-affected families can change. Being a spouse or partner to somebody with PD or HD can be physically and emotionally challenging almost from the time of diagnosis, and becoming a caretaker can be associated with very mixed emotions.⁷⁸ At later stages of the PD and HD, the affected patient may require a lot of care, which may result in great emotional and physical charge for the non-professional caretaker (such as spouse or child) and lead to caretaker's exhaustion,⁷⁹ ruin of life or career plans, and negative effect on health (often due to lack of sleep and constant stress). One Italian study focusing on PD found that 60% of care-takers of PD patients are spouses/partners, 21% are sons or daughters, with 19% said to be "others". 35% provided care 24 hours a day.⁸⁰

Although the onset age of both PD and HD may vary, HD usually affects an individual at a time when they have many responsibilities to their family.⁸¹ This means the partner who acts as caretaker is often placed in the position of total responsibility, taking on the roles and responsibilities of their partner as well as their own.⁸² Contrary to PD, due to the hereditary nature of the disease, HD does not disappear with the death of the affected individual, and the caretaker may end up caring for more than one generation of sufferers.⁸³

Economic consequences of the disease to the patient and the family. PD, especially in medium and advanced stages may make it impossible for the affected patient to keep his/her job. For example, one study found that only 17% of surveyed PD patients had a job.⁸⁴ HD-affected patients are in a similar situation. Families having PD or HD patients usually experience a drop in their standard of living after the patient (especially if he/she had been the "breadwinner") had developed the disease.⁸⁵ The family members that become the caretakers of the patient often have to give up their jobs, if they had been employed, in order to provide care for their affected family members.⁸⁶ These families may therefore experience a great deal of struggling to make ends meet and the feeling of personal restriction that accompanies involuntary unemployment.⁸⁷ It is important that these financial difficulties do not prevent patients from fair access to well-designed clinical trials, as it is stressed in ISSCR Guidelines (6.2.5) on fair subject selection. The patients' financial status, insurance coverage, or ability to pay should not become a hinder to access such trials.

In summing up this section 3, the findings of the studies mentioned here represent the examples of factual knowledge about PD and HD available to us today. This knowledge

has been collected by studies in different countries, using different methodologies, at different times, and exhibiting different levels of representativeness. There can be country-dependent or disease-dependent factors that may have influenced the findings of the reviewed studies. For instance, more extreme examples could have been found in the studied HD-affected population because it is a smaller population than the PD-affected one. These findings cannot therefore be considered as universal truths regarding societal differences between PD and HD, but rather as examples of differences found in the above-mentioned studies.

4. Ethical relevance of the medical and societal differences between PD and HD

We will now analyze the ethical relevance of these differences in the light of different types of ethical theories and the values endorsed by these theories. In this article, we will deliberately refrain from mentioning many names of ethical theorists for the simple reason that we are interested in exploring the differences values endorsed by different types of ethical theories make in adopting – or arguing for – decisions as to what should be done in the described situations of choice. We want to avoid, if possible, exegetical discussion of how the writings or particular sentences of a specific ethical theorist should be interpreted.

Although utilitarianism is not the only ethical theory that considers the consequences of an action relevant for the ethical evaluation of that action, *only* the value of the consequences are considered in the classical forms of utilitarianism, of which there are several versions. From such a utilitarian viewpoint, *availability of alternative therapies* represents an important medical difference between PD and HD, since a basic utilitarian principle is to do as much good for as many as possible. How important is the availability of alternative therapies when deciding about the acceptability of experimental stem cell-based therapies? Let us consider all four possible scenarios regarding the efficacy and safety of such therapies.

HD patients would certainly benefit from safe and efficacious stem cell-based therapies, as they have no alternative cure, and the methods for alleviation of symptoms are limited (see table 2). However, if these therapies turn out to be safe but inefficacious to FIH trial participants, HD patients, especially those in the later stages of their disease, may be harmed by participating in such a trial due to lack of access to their usual treatment alleviating the symptoms of the disease as long as the trial continues. Even if the effect of the alternative treatment is limited, it is still better than nothing, especially when symptoms become more difficult to support in the later stages of the disease. However, it is not easy to estimate whether such patients would suffer more than patients in earlier stages of HD in case of safe but inefficacious experimental therapies. At early stages of

HD patients may still be active professionally and experimental therapy, administered instead of the alternative limited treatment for alleviation of symptoms and proved to be of limited efficacy may harm such patients in accelerating the process of losing their position, for instance at work.

Stem cell-based therapies that turn out to be unsafe and inefficacious may be harmful to HD patients in the same way, whereas the positive and negative effect of such therapies that turn out to be efficacious but unsafe can be debated. In this case, the inability to use the usual treatment for alleviation of symptoms due to participation in a trial would be compensated by the efficacy of stem cell-based therapies, and the risks posed by them would need to be evaluated in the light of the risks of these alternative methods of symptom alleviation as well as in the light of actual benefit to the patient due to efficacy of the administered therapies.

If the experimental treatment turns out to be efficacious and safe for the patients participating in the FIH trial, it is not certain that HD patients in later stages of their disease as well as the health care providers in the patients' family would benefit from this treatment more than respective stakeholders at the earlier stages of the disease, if they were participating in such a trial. It is not certain because the magnitude of benefit will depend on how "benefit" is defined: for instance, in terms of prolonged life expectancy or in terms of improved life quality of the patient or improved life quality of the patient's health care providers in the family. It will also depend on how efficacious and safe the experimental therapy is compared to the available alternatives. From a utilitarian perspective, it is therefore not possible to estimate whether it is patients in earlier or in later stages of HD that should be asked to participate in FIH trials of stem cell-based therapies. However, if the limited alternative methods of alleviation of symptoms are not effective in the case of particular patients, such patients could be seen as suitable candidates for FIH trials from a utilitarian perspective.

This analysis clearly indicates that the problem we encounter is not only that of value preferences, but also the problem of definition and measurement of values such as safety, efficacy, health, quality of life or economic prosperity. It is very important to raise and discuss the question how the various relevant factors can be measured. Not only safety and efficacy can be graded, this is also true of the other factors such as quality of life or economic prosperity, which can not only be vague but also ambiguous. Since different methods of measurement give different results, it is hardly possible to discuss the exact risks and benefits of participation in FIH trials unless these definition and measurement problems are solved.

If the experimental therapies turn out to be unsafe, inefficacious or both for the PD patients participating in the FIH trial, such therapies would have more negative consequences on PD patients than in the case of HD patients, as PD patients have limited alternative treatments and alternative methods for alleviation of symptoms. It could therefore be argued that FIH therapies in PD patients would be justifiable only in

cases when alternative therapies, for treatment as well as for alleviation of symptoms, are inefficacious.

From a classical utilitarian viewpoint, but also according to other ethical theories, *impact on life expectancy* is another ethically relevant difference between PD and HD. Safe and efficacious stem cell-based therapies could increase the life expectancy of HD patients, whereas unsafe and inefficacious ones have a potential to reduce life expectancy. Therapies that turn out to be inefficacious but safe would not decrease life expectancy of HD patients, as these patients have no alternative cure. The situation is not so clear if such therapies turn out to be unsafe though efficacious, as the total amount of benefit for the patient in terms of life expectancy would depend on how unsafe the treatment was compared to its efficacy. Taking into consideration only life expectancy of patients, it is not possible to estimate whether it is patients in earlier stages of HD or in later stages of HD that should participate in FIH trials. Similarly, it is difficult to estimate whether it should be patients for whom alternative methods of alleviation of symptoms are inefficacious, as it is not certain that stem cell-based therapies will increase life expectancy.

Whether safe and efficacious stem cell-based therapies would increase the life expectancy of PD patients will depend on how much more safe and efficacious they would be compared to alternative treatments. Considering life expectancy of PD patients from utilitarian viewpoint, administration of such therapies would be acceptable only to PD patients for whom alternative therapies are not efficacious.

Yet another important factor from a utilitarian viewpoint is the *consequences of the disease to the patient and the patient's family*. The consequences may differ depending on how they are defined and measured. For example, in terms of lost income due to the patient's unemployment, lost income due to the involuntary unemployment of the health care taker in the patient's family, the expenses spent on patient's treatment, care or adaptation of the facilities at home, etc. Unless the definition and measurement problem is solved, it is not possible to estimate whether the administration of an experimental therapy, the safety and efficacy of which also has to be defined and measured, will contribute to reducing the economic consequences of the disease on the patient and his/her family. Therefore, it is not possible, given the present state of knowledge, to determine whether patients in earlier stages or later stages of their disease should be asked to participate in FIH trials. However, the economic situation of families of patients who have no efficacious treatment alternatives may improve if the experimental therapy, administered in the context of FIH trials proves to be efficacious and safe for these patients. If it proves to be inefficacious but safe, however, there would be no expected change in the family's economic situation. It has to be mentioned, however, that Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) usually do not consider economic prosperity when conducting an evaluation of risk and benefit. However, some kinds of economic aspects may be considered. For example, the IRB

Guidelines intended to assist University of North Texas researchers, list among the risks that researchers must state in their application to the IRB, social or economic risks to the prospective research subjects, which include “changes in relationships with others that are detrimental to the subject and may involve embarrassment, loss of respect of others, or that diminish the subject’s future employability or eligibility for insurance”.⁸⁸

Considering rights-based arguments. So far we have focused only on the consequences of FIH trials in PD and HD patients. According to a different, deontological way of thinking, the consequences of FIH trials do not decide their moral rightness. FIH trials are only morally right if they do not violate any human rights or human dignity.

The care of PD and HD patients often requires quite a lot of sacrifice on the part of *health care providers in such patients’ family*. It may therefore be argued that at least in some (or even many) cases, these family members are “forced” into the caretaker situation because they do not have a choice. It follows that the labor of these caretakers is used to achieve good consequences (care of PD or HD patients) without their consent. Even though there is no “forced labor” in the literal sense, in many cases one cannot consider becoming a caretaker (e.g. 24 hours 7 days a week) a matter of personal choice. If we take into account that consent of financially vulnerable healthy volunteers in a phase 1 pharmaceutical trial offered very high financial remuneration may not be free (though it can be informed), we may likewise consider that consent of caretakers is not free if they have made this choice because other forms of care are unavailable (e.g. too expensive, too far away or both). Furthermore, it can be argued that advanced forms of PD or HD affect not only the autonomy of the patient, but, in some (or many) cases – also the autonomy of the caretaker in the family. The caretaker may have limited autonomy to make decisions, which may be “dictated” by the situation. It has to be mentioned, however, that the contribution to the patient’s care by his/her family members may be a necessary condition to protect the patient’s human rights, such as the right to life, and in this way the two rights would come into conflict.

Successful application of stem cell-based therapies has a chance not only to lead to improvement of the health and quality of life of PD- and HD-affected patients, but at the same time to improve the quality of life (and indirectly – also health) of health caretakers in the patients’ family. Efficacious therapies thus have a potential to enhance the autonomy of both patients and familial health care providers. However, application of such therapies would only be morally acceptable if free and informed consent of patients receiving therapies is obtained. In later stages of PD or HD, where patients’ capacity to provide such consent is limited, an informed proxy decision-maker has to make the decision for the patient. However, the freedom of such proxy decision-making may be questionable in cases where the decision-maker is a family member of the patient, and especially if he/she is the caretaker of the patient. It cannot be excluded that there can be cases where an exhausted caretaker would see the enrollment of the patient in a trial testing stem cell-based therapies as the last hope of improvement of the situation –

not only the patient's but also his/her own. In such cases the patient may be used as a means to improve the caretaker's quality of life.

If patients' participation in FIH trials can contribute to enhancing the autonomy of their familial health care providers, participation may be considered even more appropriate from the human rights perspective. Even if the latter situation is more likely to happen in the later stages of HD or PD, especially when available alternative therapies in the case of PD or alternative methods of alleviation of symptoms in the case of HD are not efficacious or locally unavailable, it cannot be argued that from human rights perspective the patients at later stages of their disease would be seen as more suitable candidates for participation in FIH trials.

Considering the arguments based on *human dignity*, the *psychological effects of the disease on the patient and patient's family* are of ethical relevance. From the viewpoint of human dignity-based theories, the psychological and physical effects of the disease may endanger the human dignity of PD and HD patients in terms of their loss of autonomy due to difficulty to communicate, physical appearance, difficulty of movement, etc. From the perspective of human dignity-based theories, stem cell-based therapies would be justified as means to achieve the goal of least possible infringement of human dignity by the disease. In the case of HD, there is a lack of alternative therapies that could eventually prevent the patient's loss of autonomy. It could be argued that stem cell-based therapies would be acceptable means, in the absence of other more effective means, to prevent this loss of autonomy. To sum this up, from the viewpoint based on human dignity, such therapies would be acceptable in the cases when patient's autonomy is lost or becomes very limited due to the psychological, physical or both effects of the disease. It also has to be pointed out that according to one interpretation of human dignity, the protection of such dignity extends also to human embryos or fertilized eggs, if one considers that such entities are worthy of the same level of protection as born human beings. We have discussed this position more extensively elsewhere.⁸⁹ According to this interpretation of human dignity, therapies based on embryonic stem cells would not be acceptable, regardless of the possibility of such therapies, if safe and efficacious, to contribute to the enhancement of patient's autonomy.

Psychological effects of the disease on the patient and the patient's family or the impact of the disease on the patient's familial health care providers would also be ethically relevant factors from the utilitarian viewpoint, but for different reasons. At least some forms of utilitarianism would consider these factors in terms of happiness or unhappiness that they contribute to. However, the "amount" of unhappiness cannot be discussed unless there is a consensus about its definition and its measurements.

5. Conclusions

The similarities and differences between PD and HD highlighted in this paper are of varying importance depending on the chosen normative point of reference. For example, the availability of alternative therapies, the impact of the disease on life expectancy or the economic consequences of the disease to the patient and the family are important differences from a utilitarian viewpoint. But the difference concerning the impact of the disease on the patient's health care providers in the family may be a particularly important one from the human rights' perspective. The psychological effects of the disease on the patient can be seen as important from the view based on human dignity, at least to the extent they affect the patient's autonomy and human dignity. Despite focus on different characteristics of the disease, the treatment or the patients who would be asked to participate in FIH trials, all the reviewed ethical theories arrive at a consensus concerning the following issues:

First, from a normative perspective, it cannot be determined whether patients in the earlier or in the later stages of PD or HD would be the best candidates to participate in FIH trials unless certain knowledge gaps are filled. The most important of them are (a) how we define and measure safety of treatment, efficacy of treatment, health, quality of life or economic consequences of the disease on the patient and patient's family and what are the results of applying these definitions and methods of measurements to the diseases compared, and (b) how we define and measure the impact of the safety or efficacy of treatment on patient's health, quality of life, economic situation, life expectancy or loss or reacquisition of autonomy and what are the results of applying these definitions and methods of measurements to the diseases compared. If one particular method of measurement is chosen, the result may point in one direction; if a different method is used, the result may not be the same.

Secondly, it is not the stage of the disease but rather the availability or existence of efficacious alternative therapy in the case of PD or alternative method of alleviation of symptoms in the case of HD that is the determining factor of whether or not the patient should participate in a FIH trial of stem cell-based therapies. The patients who have no efficacious alternatives are the most suitable candidates for the FIH trials of stem cell-based therapies, provided that free and informed consent of patients or their legal representatives has been obtained and rigorous preclinical research has demonstrated the safety and the proof of principle for a desired therapeutic effect of stem cell-based therapies.

Thirdly, the ethical guidelines reviewed in Table 1 also imply that it is not the stage of the disease but rather the efficacy of therapy that is one of the decisive factors about which group of patients should be included in a FIH trial. However, from the point of view of some of the reviewed ethical theories, a precise definition of efficacy is crucial in order to evaluate its importance in this decision-making.

The result of this analysis suggests that many knowledge gaps need to be filled before it can be decided in a non-arbitrary way which patients or patient groups should be asked to participate in FIH trials of PD and HD. Then the ethical starting points also need to be made explicit, including the positive and negative goals, what one wants to achieve and avoid with the FIH trials of these diseases. Unless this is clarified, it is difficult to estimate whether the answer to the question analyzed in this article is disease-specific or whether it depends on factors common to several diseases.

Topics for further research include both empirical and normative issues. For example, there are probably considerable individual variations in how family interests are weighed against patients' interests. This can be the subject of empirical studies, using research interviews, focus groups, and other methods. Normative issues include a detailed analysis of which conclusions different versions of utilitarianism and deontological theories would support, given various scientific scenarios.

Points that need to be further developed are: the consideration of prioritizing treatment for those who are worst-off (in senses that need to be made clear), as well as the lottery argument. Here two situations need to be distinguished. The first is this: in most cases, we know very little about the effect of stem cell-based interventions. Animal studies have been tried, but the next step needs to be taken. That is why small scale FIH trials are necessary. Then a lottery can be justified, provided that other conditions in terms of information, consent, and safety are met.

The situation is not the same, if we have reason to believe that patient selection makes a difference to the outcome, that the SC-based therapies will be more efficacious on some patients than on others. Every participant in the lottery has a fair chance and equal opportunity to "win" the possibility to receive an experimental stem cell-based intervention. But if we have reason to believe that some interventions are more efficacious on certain patients than others, the lottery means that scarce resources (in terms of such interventions) to some extent are wasted. If we want to optimize the effects of stem cell-based interventions, we have to abandon the lottery and apply these interventions on patient populations where we have reason to believe that they will be efficacious. Behind "optimization" hide different value premises that will need to be spelled out, as details here may point to different conclusions.

An interesting possibility, worth a paper of its own, would be to examine the history of medicine to see how similar cases in the past have been handled, when treatments based on what was then new and emergent technologies, were introduced. Which heuristic devices were then used in thinking through these challenges? Analogies are to be used with caution, but something can be learnt from them, if similarities and differences between the examined cases are carefully spelled out.

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Table 1

Examples of safety-related requirements in the international guidelines and declarations and European conventions, directives and regulations

| International guidelines and European legislation | Requirements for clinical trials regarding safety and risk management that: |
|---|---|
| Sect. 2.3, ICH Guideline on Good Clinical Practice; ¹ Art. 2, Oviedo Convention ² | Prevalence of the interests and welfare of the human being over the sole interest of society and/or science |
| Arts. 6 & 20, Declaration of Helsinki ³ | Prevalence of the interests and welfare of the human being over all other interests and satisfactory risk management |
| Art. 3 (2a), Clinical Trials Directive ⁴ | Balance of foreseeable risks and inconveniences against the anticipated benefit for the individual trial subject and other present and future patients |
| Guideline 8, CIOMS Guidelines ⁵ | Minimization of risks and balance of foreseeable risks and inconveniences against the importance of knowledge to be gained |
| Art. 16, Convention on Human Rights and Biomedicine ⁶ | Balance of foreseeable risks and inconveniences against the potential benefits of the research |
| Recommendations 16 & 18, The ISSCR Guidelines ⁷ | Assessment of risks of tumorigenicity for any stem cell-based product and rigorous characterization of cells to be employed in clinical trials to assess potential toxicities through <i>in vitro</i> studies and, where possible for the clinical condition and tissue physiology to be examined, also in animal studies |
| Art. 14 (2) of the European Regulation on Advanced Therapy Medicinal Products ⁸ | Establishment of a risk management system designed to identify, characterise, prevent or minimise risks related to advanced therapy medicinal products |

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Table 2

Examples of medical parameters of PD and HD

| Disease | Properties | | |
|---------|-------------------------------|-------------------------------|---|
| | Is the disease fatal? | Is there an alternative cure? | Is there an alternative method for alleviation of symptoms? |
| PD | No (but progresses with time) | Yes (limited) | Yes |
| HD | Yes | No | Yes (limited) |

Paper III

DIFFERENCES BETWEEN PARKINSON'S AND HUNTINGTON'S DISEASES AND THEIR ROLE FOR PRIORITIZATION OF STEM CELL- BASED TREATMENTS (Paper III)

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Abstract: The problems of allocation of scarce resources and priority setting in health care have so far not been much studied in the context of stem cell-based therapeutic applications. If and when competitive cost-effective stem cell-based therapies are available, the problem of priority setting – to whom should stem cell-based therapies be offered and on what grounds – is discussed in this article using the examples of Parkinson's Disease (PD) and Huntington's Disease (HD). The aim of this paper is to examine the presently known differences between PD and HD and analyze the role of these differences for setting priorities of stem cell-based therapeutic applications to treat these diseases. To achieve this aim, we (1) present the theoretical framework used in the analysis, (2) compare PD and HD in terms of health related and non-health related consequences of these diseases for patients, their relatives and third parties; (3) analyze the ethical relevance of observed differences for priority setting given different values and variables; (4) compare PD and HD in terms of social justice related consequences of stem cell-based therapies and (5) analyze the ethical relevance of these differences for priority setting given different values and variables. We argue that the steps of analysis applied in this paper could be helpful when setting priorities among treatments of other diseases with similar differences as those between PD and HD.

Keywords: Differences, ethical theories, Huntington's disease, Parkinson's disease, priority setting, stem cell-based therapies, values

1. Introduction

Allocation of scarce resources and priority setting in health care has been discussed in the academic literature for more than 25 years. However, these problems have so far not been much studied in the context of stem cell-based therapeutic applications [1]. If and when competitive cost-effective stem cell-based therapies are available, to whom should stem cell-based therapies be offered and on what grounds? [1] We will illustrate this discussion with the examples of Parkinson's Disease (PD)¹ and Huntington's Disease (HD)².

In this article, we will examine presently known differences between PD and HD and analyze the role of these differences for setting priorities of stem cell-based therapeutic applications to treat these diseases. To achieve this aim, we will: (1) present the theoretical framework used in the analysis, (2) compare PD and HD in terms of health related and non-health related consequences of these diseases for patients, their relatives and third parties; (3) analyze the ethical relevance of observed differences for priority setting given different values and variables; (4) compare PD and HD in terms of social

¹ Parkinson's Disease (PD) is a progressive neurological disorder, considered to be one of the most common neurological conditions [2]. Of all the neurodegenerative disorders it is second to Alzheimer's disease in the number of cases [2]. PD is caused by the destruction of nerve cells in the brain that produce the neurotransmitter dopamine [2]. A similar destruction occurs naturally with ageing, but in PD the process is much faster [2]. Typical major symptoms are tremor, stiffness of muscles and slowness of movement, but every PD-affected person experiences individual symptoms [2]. The average age of onset is 60, but PD can also affect younger people (e.g. young-onset PD at age 40 or younger is estimated to occur in 5-10% of people with PD) [2].

² Huntington's Disease (HD) is a terminal incurable inherited progressive neurodegenerative disorder of the central nervous system, characterised by a variety of symptoms that affect the patient's physical and mental health [3]. HD has a range of motor, cognitive and psychiatric symptoms [4]. The motor symptoms include involuntary and uncoordinated movements of the limbs and disturbed speech, and the psychiatric symptoms include depression, aggressive outbursts, psychotic behavior, progressive dementia [5], and personality change [4]. Symptoms can start at any age, but typically occur between the ages of 35–40, often after the affected individual has reproduced and possibly transmitted the faulty gene to his/her offspring [6]. Each child of an affected person has a 50% risk of inheriting the condition and developing HD [6]. However, it is estimated that approximately 1%-14% of persons with HD do not inherit the HD allele from a parent, but instead acquire it from a newly formed mutation [7].

justice related consequences of stem cell-based therapies and (5) analyze the ethical relevance of these differences for priority setting given different values and variables. As these consequences can be measured in various ways using different scales, and the result will be relative to the method and scale used, we will be explicit on these matters. We argue that the steps of analysis applied in this paper could be helpful when setting priorities among treatments of other diseases with similar differences as those between PD and HD.

2. Theoretical framework

Dimensions relevant to priority setting. Different countries employ somewhat different approaches to priority setting of already established therapies. These approaches may vary depending on the context in which decisions are made, such as the health care system, coverage of the health care insurance, the extent of private care, economic and technical development of the country, existing infrastructure, historical background, political majority, religious traditions, etc.

The approaches may also vary depending on dimensions which have been identified as relevant for priority setting in the actual prioritization of already established therapies [1] and how these dimensions are interpreted. These dimensions include: (a) the seriousness or severity of the condition, (b) the positive effects of the intervention on the health and/or quality of life of the patient or the patient group in question, (c) the negative effects to the patient including the secondary risks to which others may be exposed, (d) the costs of the intervention in relation to positive and negative effects and (e) the prevalence of the disease [1].

However, in priority setting of newly established, still experimental therapies, some aspects of these dimensions seem to be particularly relevant for decision-making: chances of success of the experimental intervention; costs of non-intervention to the patient, to the patient's family and to the society; availability of alternative, already established therapies; and fair access to already established therapies on a global scale. Depending on which of these dimensions is given priority, the relevance of differences between PD and HD for priority setting will vary. In this context, uncertainties of scientific knowledge regarding safety and efficacy of such experimental therapies as well as knowledge gaps are especially important.

Ethical points of departure. Agreement on which dimensions are relevant to consider is, however, not enough. Various other issues are raised, having to do with the basic ethical assumptions made. For example, what is the role of the personal responsibility of the patient? What should the state provide? To what extent are undeserved inequalities to be compensated for – by whom and in what way? If we have to choose between trying to cure or relieving very severe suffering of a few and relieving moderate suffering of many,

what is to be chosen and on what grounds? Should there be limits to extremely costly treatments?

The answer to the question of how prioritization between stem cell-based therapies for PD and such therapies for HD *should* be made will vary depending on the ethical principles chosen as the points of departure. Different ethical principles promote partly different values. Depending on what values are considered as important, the relevance of certain differences between PD and HD for priority setting will vary. We will explore if and to what extent the consequences of priority setting will vary depending on which ethical principles are chosen as a point of departure.

We do not here want to argue, for instance, for an egalitarian view, that just principles of health care presuppose equal treatment for equal need, taking into account the variations in capabilities of persons, and a human-rights based approach encompassing a human right to health care, though these are our personal views, similar to the ones proposed by Denier [8]. But to argue for this has to be left for another occasion. The point here is rather to examine the implications of what is presently known about the differences between HD and PD for the hypothetical problem of setting priorities (not in research but in health care). The sections on the dimensions and on the ethical platform then serve as an analytical framework that helps to select the differences that are relevant – given different ethical principles as starting points.

3. Empirical premises

3.1 Seriousness or severity of the disease

PD by itself is not a direct cause of patients' death³ [2], whereas HD is a lethal incurable disease⁴ [6]. Unlike in the case of PD, the psychological consequences of HD start even *before* the disease actually manifests itself: in most cases HD is an inherited disease and testing positive for carrying the HD allele will most likely lead to psychological distress [9-11]. However, we lack information today about how these psychological consequences compare with those of PD in terms of their severity, duration or impact on the patient's quality of life. Yet another important difference between PD and HD is that HD has been reported to display clinical anticipation, which means that more severe forms of the disease or earlier age of onset of the disease occur with successive generations [12-14].

³ However, complications of PD can lead to death, and after some time, the medication can also cause side effects [2].

⁴ The average duration of HD is 16 years [6], but it can vary greatly.

3.2 Availability of alternative therapies

In treatment of PD and HD both pharmaceutical [15, 16] and surgical [2, 17] interventions as well as rehabilitation [18] and medical nursing [15] are available. However, with the treatment of PD that is now available⁵, life expectancy for a PD-affected patient is fairly normal and none of the used medications have any side effects that could cause death [2]. Conversely, there are no treatments that can cure, delay onset or slow the course of HD [6], although provision of supportive medical nursing and social care can help to improve the patient's quality of life [20].

3.3 Chances of success of the intervention

The chances of success of stem cell-based therapies may in practice be a decisive criterion whether such therapies should be administered to patients and whether the treatment of one disease should be prioritized over the treatment of another. However, the present state of knowledge about safety and efficacy of these therapies for PD and HD (see for example articles by Lindvall and Kokaia [21] and by Nolte [22]) contains both known unknowns and unknown unknowns. Therefore, the chances of success of these therapies are difficult to estimate. When such estimation is possible, the safety and efficacy of stem cell-based therapies should be evaluated in the light of safety and efficacy of alternative therapies if any. When no alternative therapies exist, the risks of stem cell-based therapy should be evaluated in the light of risks of non-treatment.

3.4 Costs of non-intervention to the patient

The difference between the economic consequences of PD and those of HD to the patients can be measured not only in terms of disease-related expenses, e.g. for buying medication, but also in terms of patients being able to go back to work or getting a job. These differences can depend on at least two factors: (1) the lack of efficacious therapy for HD, thus implying that returning back to work is very unlikely once the disease has started to advance, whereas the existing therapies for PD may make this possible; and (2) the possibility to test for carrying the HD gene. The latter may result in economic consequences for the patient who has tested positive even *before* the disease actually manifests itself. For example, participants of one study reported perceptions of consequences following disclosure of such genetic test results for employment and insurance, among other areas [23]. Test results negatively affected participants' decisions to pursue career advancement or to seek new employment [23].

⁵ However, there is still an important knowledge gap related to present limitations of therapy, lack of effective preventive treatments, lack of restorative treatments, and lack of effective therapies to prevent or symptomatically improve long-term motor and non-motor complications [22].

3.5 Costs of non-intervention to the patient's health care provider in the family

The difference in the economic consequences of PD and those of HD to the patients' health care providers in the patients' families can depend on at least two factors: (1) the difference between PD and HD in the usual disease onset age and (2) the hereditary nature of HD. As to (1), HD usually affects an individual at a time when they have many responsibilities to their family, although the onset age of both PD and HD may vary. This means that the partner who acts as caretaker often is obliged to take on the roles and responsibilities of their partner as well as their own [5, 24]. As to (2), HD is often carried on to the following generation due to the hereditary nature of the disease, and the patient's caretaker may end up caring for more than one generation of sufferers [5].

At later stages of PD and HD, the affected patient usually requires a lot of care, which may result in great emotional and physical stress for the familial health caretaker, such as spouse or child, and lead to caretaker's physical exhaustion, ruin of life or career plans, taking on the previous role of the PD- or HD-affected individual in addition to his or her own [5] and negative effect on health, often due to lack of sleep and constant stress. For example, one Italian study found that 60% of caretakers of PD patients are spouses/partners, 21% are sons or daughters, with 19% said to be "others", and that 35% provided care 24 hours a day [25]. The patterns of caring for PD and HD patients in families are likely to vary from country to country depending on factors such as culture or the level of average income. Examples from particular countries should therefore not be generalized but they can be useful as illustrations of what the situation can be like in some cases. The above-named consequences of the disease to the patient's health care providers in the family can often have an economic expression in terms of lost opportunity income or even expenses directly related to worsening of their own health. This is especially true for those unable to pay for external aid.

3.6 Costs of non-intervention to society

Differences in economic impact of the diseases on the society. Estimation of the exact difference between PD and HD regarding their economic impact on society is difficult, since this impact depends on a number of factors, such as accessibility to health care delivery and medications, which is quite variable in different regions of the world [19], the age of the patient at the onset of the disease or the correct diagnosis and efficacious treatment at an early stage of the disease. As to the latter, the need for infrastructure and the involvement of human resources varies according to the progression of disease [19]. If the disease can be treated, such as PD, early and proper treatment results in substantially less cost to society than non-treatment [26]. For example, one study found that almost 40% of advanced PD patients needed to be admitted to long-term care facilities when the need for complex care exceeded the possibilities of primary caregivers at home [27]. Considering the costs of non-intervention to the society, the costs of PD, the progression of which can be slowed down by timely treatment, will be higher than the costs of HD.

The comparison of the cost of PD and HD to society is problematic for several reasons: (1) the underrepresentation of the studies focusing on HD compared to studies focusing on PD and (2) the limited comparability of existing empirical studies exploring the cost of PD. The latter may be influenced by many different variables, for example:

Method of data collection. The data can be collected using the “top-down approach” that calculates costs by splitting highly aggregated statistical data (e.g. reports of national statistics), or by “bottom-up approach”, collecting data from individuals [28]. The latter provides more precise data, but is time consuming and allows for recruitment of a limited number of patients [28], which may affect representativeness. Even in the same country, the results of studies using different approaches may differ.

Availability and quality of health care. Reported direct costs of the disease in different countries are not always comparable, since direct costs are associated with the availability and quality of health care [28-31]. For example, in India health insurance is available only for 7% of the population, resulting in lower direct costs of PD [32].

Method of patient recruitment. Recruitment of patients from specialist offices may result in higher costs of outpatient care [33]. The mean medical cost may be approximately twice as high among PD patients followed by neurologists compared to those followed by general practitioners [34]. Direct health care costs may therefore be higher in areas with good availability of specialized health care resources [35]. The reported costs of the disease may also be influenced by the age of patients. For example, patients in advanced stages of PD consume higher health care expenditures than the younger ones [36]. Availability of timely or more expensive treatment may likewise be influential: reported inverse association between age and the costs of pharmacotherapy (not health care in general) has been explained in another study by administration of costly dopamine agonists to younger patients with PD [37, 38].

Inclusion and exclusion of certain costs into the calculation of total costs. Including only direct costs, such as healthcare resource use and drugs, or also indirect costs, such as mortality costs, lost productivity and care provider replacement costs, will affect the total costs [39]. Including costs for adaptations to the patient’s home [33], or excluding the costs of help provided by family members, which may vary depending on the definitions of home care as well as cultural differences between various countries [35], will also be influential to the reported total costs. Moreover, variations in indirect costs, such as the cost of productivity loss can be influenced by the labor cost in the country of study and/or inclusion of older than work age patients [40]. Inclusion (or not) of opportunity costs, such as lost income due to reduction or termination of paid employment, will also influence the total costs [41].

Gender of patients who are sources of data. One UK-based study found that women were more likely to be informal care providers than men, and therefore if a patient with PD was female, then she was less likely to receive informal care from a spouse than a male

patient [42]. However, the perspective of costs taken in this study included services provided by health and social care agencies as well as informal health care providers in the families, but excluded societal costs, such as lost employment [42]. From this perspective, men had higher costs than women [42]. As the authors point out, social norms and expectations of the caring role could have influenced such results [42]. The findings of this study should not be generalized, but should rather serve as a reminder that gender of the patients studied may have an impact on the study results, although this impact may vary depending on factors such as social norms or gender-role expectations in a given country.

Misdiagnosis of PD. Empirical research has shown that there can be high rates of misdiagnosis in Parkinson's disease. A UK-based study has found that at least 1 in every 20 patients taking medication for PD had been misdiagnosed [43], and pathological studies based on brain bank material from Canada and the United Kingdom have shown that clinicians diagnose the disease incorrectly in about 25% of patients [44]. Diagnosing PD can be difficult: PD has symptoms similar to a number of other neurological disorders,⁶ every case is unique [45], and there are no diagnostic tools such as an X-ray or blood test that can confirm PD [2], only diagnostic tools to rule out other conditions with similar symptoms [2]. PD patient's quality of life could be improved if the treatment was started as soon as possible [19, 25]. Contrary to the difficulties in diagnosing PD, genetic testing can be used to confirm HD. However, this does not exclude the possibility that there can be patients suffering from HD who have never been diagnosed and are considered by the familial health care providers to be suffering from another condition, such as senility. This situation can be more likely in countries where the population is less informed about HD and/or largely preoccupied by other types of problems such as famine, armed conflicts and the like.

Long time span between the onset of the disease and the official diagnosis. Due to low rates of neurologists per patient – even in some European countries, such as Ireland, the rate is one per 200,000 patients – PD patients often have to wait one or two years to see a neurologist [46]. Due to the difficulty of diagnosing PD, it may sometimes take another several years before the diagnosis can be made confidently [45].

Geographical differences in financial burden of diseases. Empirical studies conducted in Western European, Asian and Eastern European countries prove that there is a difference in financial burden of neurodegenerative diseases on patients depending on the level of the development of the country in which they reside. For example, in Russia, PD patients' expenditures accounted for 43% of their private income and more than 90% of home care in Russia was provided by family members and friends [30]. Similarly, in

⁶ There are similar conditions, often referred to as Parkinson's Plus syndromes or atypical-Parkinson syndromes, which make diagnosis and treatment problematic [45].

Czech Republic, 40% of patients' income was consumed by PD-related expenditures [28]. In India, costs of treating PD were out of reach for most Indian patients [32], and the economic burden of Chinese PD patients was also found to be heavy [40]. In comparison, the relative economic burden of PD on patients in Germany accounted for 9% of their income [47]. This difference on a global scale can be explained by higher mean gross income in Western Europe [28]. These findings can be important if we consider that there are differences in prevalence of PD and HD concerning their social, ethnic, economic and geographical boundaries.

PD affects both men and women in almost equal numbers, with no social, ethnic, economic or geographic boundaries [2]. Some cases of the so-called secondary parkinsonism may be drug-induced by pharmaceuticals such as flunarizine and cinnarizine, if they are misused frequently, as in some Latin American countries where they are used to prevent cerebrovascular disorders [19]. But drug-induced parkinsonism accounts for only a small proportion of cases of PD [19].

HD is also found in many different countries and ethnic groups around the world, but according to some sources, the highest frequencies of HD are found in Europe and countries with many inhabitants of European origin, such as the United States and Australia, whereas the lowest documented frequencies of HD are found in Africa, China, Japan and Finland [7, 48]. However, documentation in African countries remains poor and evidence is inconclusive, and there have not been many studies conducted in Asia either [7]. Although the existing data suggest that HD affects mainly people of European ethnicity, including such people in European-origin countries, the lack of documented cases of HD in some native populations of the Americas, Australia and New Zealand does not necessarily signify that HD is non-existent among these populations. The cases of HD can be underreported among these populations. The possibly shorter life expectancy among these populations may also be a confounding factor.

It can probably be argued that today HD is mainly a problem of European-descent populations most of which happen to live in developed countries. However, the apparently greater importance of HD in these countries does not necessarily depend on genetic differences between the populations in these countries and the "native" populations in, e.g. Africa or Australia. The greater importance of HD for European-descent populations can be the result of greater knowledge about the disease among these populations as well as greater resources for its diagnostics and research.

The equal prevalence of PD in both developed and developing countries and the higher burden of the disease in the latter may result in a more disadvantaged situation of PD-affected non-European descent population than such HD-affected population in developing countries. However, this argument is tenable provided that the problem is considered from a global perspective and provided that only the cases of confirmed diagnosis are considered.

Difference between the age of the usual onset of PD and HD. The difference between the economic consequences of PD and HD on the society as well as on individual patients may also be conditioned by the difference in the age of the usual onset of PD and HD. These consequences are of a different nature than the consequences for familial health care providers, discussed earlier.

The symptoms of HD usually manifest themselves when the patient is around 35 and still employed. But PD is not common among young persons, although cases of early-onset PD do exist. In many cases the disease starts after the retirement age and thus does not prevent PD patients and the society from enjoying the economical profit and labor input resulting from their employment. Such profit for most HD patients could be possible in case of successful treatment, if the patients were able to go back to work.

The difference in the usual onset age of PD and HD can also imply shorter quality adjusted life years of PD patients and longer quality adjusted life years of HD patients if stem cell-based therapy proves to be successful. This would also imply a similar difference in the quality of life of their respective health care providers in the family. However, this difference could only be relevant if we consider the *amount* of quality adjusted life years rather than their actual *quality*. A significant improvement of a shorter duration can be more beneficial for the patient or the patient's health care provider than an insignificant improvement of a longer duration, and *vice versa*. The difference in the usual onset age of the disease can therefore only be considered given that the improvement in the quality of life is equal, which is difficult to estimate.

Differences concerning risks of patient causing public danger. Although both PD and HD patients can find themselves in situations where they can cause danger for themselves and for the public, the types of this danger as well as potential health and non-health related consequences of PD and HD for the society differ. In the case of PD, a typical example would include a PD-affected patient suddenly unable to move while crossing a busy street and thus potentially causing an accident. The risk of HD-affected persons causing public danger due to their cognitive losses is especially real at the early stage of HD, and particularly if a person is not aware that he/she has inherited the HD allele. Deterioration of intellectual speed, attention and short-term memory [49], as well as ability to multi-task, plan and organize effectively is potentially dangerous both for the patient and for the society, especially if the HD-affected person occupies a post that requires a lot of responsibility or if the symptoms of HD worsen while the patient has not quit driving. Due to impaired judgment and ability to know when something is wrong, lack of self-control, impulsiveness and loss of forward or consequential thinking [50], HD-affected persons can get involved in criminal behavior such as cheating, stealing or inappropriate sexual behavior without willing to do so.

3.7 The prevalence of the disease

From a global perspective, there is a difference between the prevalence of PD and that of HD: PD is a progressive neurological disorder, considered to be one of the most common neurological conditions [2], whereas HD is much less common. However, this difference may not always be as significant in all countries. The prevalence of Huntington's disease has been reported to vary from 1:143 in Venezuela to 1:10,000,000 among the Black population in South Africa [48]. It is therefore important to be explicit about whether the differences in prevalence are discussed from a global or from a local perspective. Moreover, it has been documented that the variability of the expression and the age of onset of Huntington's disease influence the estimates of its prevalence [48]. The estimation of the prevalence of PD can also be affected by similar factors, including misdiagnosis of the disease. The methodology of the studies and the risk of possible bias should be taken into consideration when comparing the prevalence of these two diseases.

The difference in prevalence is likely to increase in a global perspective. The prevalence of PD continuously increases with age [28, 35] and the number of PD patients is expected to increase as the worldwide population ages [29, 35, 51-53]. According to the existing estimates, the number of PD patients is expected to double in the next decades [52]. The progressive nature of PD and its increasing prevalence have already resulted in a substantial economic burden to society, health care providers, individual patients and their families [33, 54], and due to the changing age patterns of many societies, this burden will continuously increase [33, 51, 55, 56]. Since in most of the cases HD is an inherited disease that often begins to manifest itself when the patient is about 35 years old, the increasing life expectancy is not likely to affect the number of HD patients.

3.8 Variable access to treatment in a global perspective

Accessibility to treatment of PD is extremely variable in different regions of the world. In a global perspective, availability of anti-Parkinson drugs is only 60.6%, ranging from an extreme of only 12.5% in Africa to 79.1% in Europe [57]. The same is true for rehabilitation, which is an important aspect of the treatment of PD: worldwide availability of rehabilitation services ranges from just 18.8% in Africa to 88.1% in Europe [57]. Similarly, there are 0.03 neurologists per 100 000 population in Africa and 0.07 per 100 000 in South-East Asia, compared with 4.84 per 100 000 population in Europe [57]. There is a lack of universal access to the presently available wide range of PD medications, surgery and complementary therapies [19]. In the less developed regions of the world, this lack of access to therapy and specialists results in inadequate health care of PD patients [19].

In addition to low availability of adequate health care of PD patients in these regions of the world, the available care results in higher economical burden to the patients than in developed countries. For example, in India, where PD treatment choice primarily depends on costs and affordability of medications [32, 58], only 30% of patients were

reported as having received dopamine agonists [32] as compared to 72% in a German study [47]. If even medicines are unaffordable, newer surgical therapies such as deep brain stimulation are well beyond the reach of most Indians [32]. A somewhat similar situation was observed in Eastern Europe. The absolute figures for drug costs in Czech Republic were 2–4 times lower than in the studies from Western Europe – probably due to less frequent prescription of costly dopamine agonists [28]. These differences between the developed and developing countries illustrate the global problems of social justice and are not unique to PD but are relevant in the case of other diseases as well.

Similar studies reporting the accessibility to treatment of HD in a global perspective are not available, to our knowledge. Possibly, this is because of the lower prevalence of HD as compared to PD, and possibly lower public interest. However, it is quite probable that similar geographical differences in accessibility of adequate treatment also exist in the case of HD. Due to the rarity of HD, many general practitioners and health workers do not have any real understanding of the disease [59] and even in developed countries people living in small isolated places are often forced to relocate to bigger towns and cities to be treated [60]. If access to adequate treatment can be a problem in rural areas of developed countries, it is likely that the problem is even greater in developing countries. So it is actually questionable whether there is any significant difference between PD and HD regarding the accessibility to treatment in a global perspective.

3.9 Other factors

As it has been argued elsewhere [1], there are other factors that should be taken into consideration when making priority-setting decisions. These factors include positive and negative effects of the intervention on the health and/or life quality of the patients as well as costs of the intervention in relation to positive and negative effects of the intervention. With today's state of knowledge, it is not possible to evaluate either the positive and negative effects of such therapies, nor their costs. This is a strong reason to postpone priority setting decisions in health care until these knowledge gaps are filled. Of course, it can be anticipated that stem cell-based therapies are likely to be expensive, at least in the beginning, and their administration would require a certain health care infrastructure, which is more likely to be available in developed countries. However, many new therapies are expensive and not widely accessible in the beginning, but with time tend to become accessible to larger numbers of patients, if scaling up is possible.

4. Ethical premises

The relevance of the empirical premises for priority setting depends on the chosen normative point of reference. Different ethical theories endorse at least partly different values, for example health, happiness, prosperity, justice, etc. We will explore the implications of some types of ethical theories for prioritization decisions in the case of

experimental stem cell-based therapies for PD and HD. We want to avoid, if possible, exegetical discussion of how the writings or particular sentences of a specific ethical theorist should be interpreted.

4.1 Utilitarianism

Although utilitarianism is not the only ethical theory that considers the consequences of an action relevant for the ethical evaluation of that action, *only* the value of the consequences are considered in the classical forms of utilitarianism, of which there are several versions. Consequences of PD and HD can be both health related and non-health related. The broader understanding of health we have, the harder it is to see what makes health special compared to other factors in priority setting [61]. Health and non-health-related consequences can include actual and expected consequences for both patients, their families and for third parties. Utilitarianism is one of the views according to which the relevance of indirect, non-health related consequences in priority setting is not different in principle, from that of direct, health effects. If we must choose between two health care allocations, indirect, non-health related consequences of treatment and non-treatment are no less relevant than, and relevant for the same reason as, such direct, health-related consequences. On this view, we might be morally required to favor an allocation with much worse direct, health-related effects when the allocation in question brings about a greater sum of welfare, if it does so by producing non-health related gains in welfare for a huge number of people [61].

4.2 Deontology: Kantian/Rawlsian approaches

Deontologists would consider that an act is morally justifiable by virtue of its balance of good and bad consequences, *only if* the good consequences are achieved without the necessity of using anyone's body, labor, or talents without that person's consent as the means by which these consequences were achieved. A basic idea in Kantian approaches to ethical problems is that persons are ends in themselves and may not be sacrificed for the benefit of others. Nor may they be sacrificed for the greater good of society. John Rawls makes his anti-utilitarian position very clear in the first pages of his Theory of Justice [62]. His two basic principles of justice are not applied to health care but more generally to any society which would be considered as just. If we refer to the Rawlsian approach, prioritization of therapies for PD and HD should be made from behind of the "veil of ignorance" – not knowing whether the decision-maker or his or her offspring or another relative will be a PD- or HD-affected patient or such patient's relative in tomorrow's society. Prioritization decisions from behind the "veil of ignorance" should be adopted in such a way that they are equally just for any inhabitant of the planet – regardless of that person's ethnic background, income, race, gender, social status, religion and the like. The importance of social justice can be illustrated by incorporation of this principle in various normative texts. For example, in the context of translational stem cell research,

promotion of social justice is an important requirement in the ISSCR Guidelines for Translational Stem Cell Research [63].

Norman Daniels has in a number of works, such as *Just Health Care* [64] applied Rawls' approach to resource allocation in health care by emphasizing that health care is morally important. Protecting normal functioning contributes to protecting a person's normal opportunity range. Hence preventing and treating disease and disability with effective health care services explains the moral relevance of justice in this context. Daniels has discussed which inequalities in health are morally acceptable and which are unjust, and has outlined a fair process for making rationing decisions. Focus in his theory is on procedural justice. However, a presentation of the details of his theory would be beyond the scope of this paper. It is here referred to as an example of a type of theory which in certain cases would lead to different practical conclusions than a utilitarian approach.

4.3 Virtue ethics

According to virtue ethics the most fundamental matter of moral concern is the character of a virtuous person. Virtue ethics goes back to Aristotle. The virtues are not given to us by nature, however. We have to learn and practice. The importance of good habits is stressed by Aristotle. Education and good examples are utterly important (a point stressed repeatedly in his *Nicomachean Ethics*) [65]. There is, however, no single unified virtue theory, but in explaining what is the right thing to do, virtue ethics appeals to what would have been done by the virtuous person in the situation at hand.

Martha Nussbaum is a prominent representative of contemporary virtue ethics, who has contributed also to the contemporary discussion of resource allocation in health care. She takes her starting point in a concept of a person that differs from the Kantian concept. Her conception of a person is more Aristotelian and Marxist than Kantian. Human dignity is contextually embodied. A person is both capable and needy. Rationality and free will are limited; variations in need are pervasive in human life. Dependency is part of the human condition. Nussbaum argues that the care of the disabled, the chronically ill and those with life-long disabilities will not get a fair share of the resources in the type of approach exemplified by Rawls and Daniels [66]. To be a just society, all its citizens, regardless of age, race, sex and disability, would be offered decent life chances in areas like health, education and employment.

4.4 Rights

Ronald Dworkin's seminal *Taking Rights Seriously* [67] has been followed by a number of writings where the notion of equality has been applied to health care [68]. In particular, he has focused on the problem of setting limits in a way that would be consistent with an approach taking human rights seriously. Dworkin argues that distributive justice should be defined in terms of equality of resources. He makes an important distinction between endowments (race, sex, fortune, intelligence, which we

have not chosen) and choices. We have personal responsibility for our choices but not for our endowments. A main ambition is to combine a collective responsibility of political communities to show equal concern for all its citizens with the personal responsibility of each citizen for the choices they have made. He proposes a complicated theory or scheme of distribution, different from the approach favored by Rawls, involving the use of auctions, insurance schemes, markets and taxation models, in order to be able to combine efficiency and long-term care within a theory of justice.

A central idea in Dworkin's approach is that the market is the best means of enforcing equal division of resources, as measured by the opportunity cost of such resources to others. Efficiency is required by justice. Denier has rightly suggested that his theory could be called "a second-best theory" in the sense that it "does not and cannot fully compensate for undeserved inequalities" [8]. But to go into the details of his approach would be beyond the scope of this paper. As was made clear earlier, the ethical points of reference are presented in this section as a basis for a discussion of which of the previously mentioned differences between PD and HD are ethically relevant.

5. Discussion

In section 3 of this paper we have identified and discussed a number of differences between PD and HD in dimensions potentially relevant for priority setting. This relevance depends on types of ethical premises, discussed in section 4. There are quite a few dimensions containing differences between PD and HD which are relevant for priority setting given the approaches grounded on utilitarian, deontological, virtue ethics-based or rights-based theories. The consensus regarding this relevance is, however, based on different reasons.

5.1. Same conclusions, different reasons

Seriousness or severity of the disease would inform priority setting given all four perspectives – (1) utilitarianism, (2) deontology, (3) virtue ethics as well as (4) rights-based theories – but for different reasons. Given (1), the objective is the greatest happiness/benefit for the greatest number. Benefit can be increased by reducing the severity of the disease, which can be affected by prioritizing therapy of a more serious disease over therapy of a less serious one. Given that prioritized therapy is safe and efficacious, benefit for patients in need of this therapy would be a consequence of such prioritization. Many utilitarians believe it is possible and meaningful to add harms and benefits. In that case many small benefits to a large number of people may outweigh big benefits to a much smaller group. From that point of view it is not at all clear that health care resources should be spent in the first place on those with most serious or severe condition. We will discuss this conflict later in this section.

Given (2), the seriousness of the disease will be relevant for priority setting depending on which deontological position is considered. From a Kantian position, this variable would be a central one, provided that a failure to prioritize a treatment for a disease with no alternative therapies amounts to inhumane or degrading treatment of patients suffering from this disease and provided such prioritization would help avoid such treatment. Given a Rawlsian view, the position of the worse-off in society deserves special importance [62]. The notion of worse-off can be understood in terms of health or in terms of being worse-off in some other respect [69], and both would be considered relevant for priority setting.

From the perspective of (3), the inequality concerning life chances in areas like health and employment between HD and PD patients could be decreased by prioritizing the treatment of a more serious disease, in our case HD, over that of a less serious disease. Finally, given (4), it can be argued that failure to treat HD patients with the newly established therapy would violate their right to life, which would not be the case in PD, where alternative treatments are available. When discussing the violation of rights, however, it is important to be specific what rights are considered: equal rights to access health care, or human right to life. Only in light of the latter priority setting could make a difference provided safety and efficacy of prioritized therapies is proven.

Whether it will be possible to assess the tenability of the positions based on the various ethical premises and applied in this particular context, will depend on a couple of factors: (a) whether health related consequences of PD and HD for patients, their familial health care providers and society as well as such consequences of stem cell-based treatments of these diseases can be measured and compared. The difficulty here lies in agreement on the definition of health related consequences as well as on methods of their measurement, and in ensuring comparability of these measurements. In order to perform a reliable comparative analysis, the variables compared should be evaluated under the same circumstances. The number of medical and societal differences between PD and HD, also reviewed elsewhere [70] would make such comparability difficult.

Moreover, the tenability of positions based on (1), (2), (3) and (4), depends on (a) safety and efficacy of stem cell-based therapies for PD and HD and, in case of utilitarianism, also on (b) the definition of health related consequences of PD and HD and their treatments. The tenability of a deontological position would also depend on (c) – the ability to prove that failure to administer an existing treatment for HD, which has no alternative therapies, amounts to inhumane or degrading treatment of HD patients. The choice of criteria of “inhumane” and “degrading” will play a crucial role here.

Regarding (a), it cannot be estimated what consequences will result from prioritization of a therapy for one disease over a therapy for another unless the knowledge gaps about the safety and efficacy of these therapies are filled. For example, it is unclear whether prioritization of treatment of HD over that of PD would reduce inequalities of life chances in areas like health and employment between HD- and PD-affected persons. It is

also questionable whether such prioritization would improve the situation of HD-affected persons provided that failure to treat them amounts to degrading treatment or violation of their right to life. Safety and efficacy of prioritized therapy would also be decisive in determining whether its prioritization would result in the best consequences for the greatest number. Those utilitarians who include even the expected consequences in their calculations of harms and benefits would consider the difference between PD and HD regarding clinical anticipation – the fact that HD is likely to have a more severe expression or earlier onset in the future generations. However, to enable decision-making about priority setting it would be important to estimate whether administration of stem cell-based therapies could reduce the seriousness of the expression of the disease or retard its development.

Regarding (b), if health related consequences are defined in terms of physical health only, different conclusions will follow than if they were defined also in terms of mental health and quality of life. In the case of the former, treatment of HD should be given priority over that of PD according to some utilitarians, since PD, contrary to HD, is not a fatal disease and has alternative therapies. If even mental health is included in the evaluation of the severity of the disease, prioritization decision can be different. However, it can be very difficult to estimate how the psychological consequences of HD compare with those of PD in terms of their severity, duration or impact on the patient's quality of life. Lacking information today about such estimation, the seriousness of the disease, if interpreted as including psychological health, cannot inform prioritization decision-making given some of the utilitarian views.

Regarding (c), the definition of inhumane and/or degrading treatment would be crucial in estimating the tenability of deontological position. Can a failure to prioritize a treatment of an incurable disease which is especially debilitating and considerably reducing the quality of life over a treatment of a disease that has alternative therapies amount to inhumane treatment of patients suffering from that incurable disease? Some deontologists may consider HD patients as being treated inhumanely if such patients are “forced” to remain in a debilitating and degrading situation when this situation could be avoided.

The use of severity of illness as a basis for informing healthcare priorities has been reported by some empirical studies. For example, respondents in one study preferred to prioritize either equally or in favor of the most severely ill patient groups, regardless of the potential efficiency gains [71]. Where a patient group with severe health problems was unable to benefit greatly from treatment, compared to a group competing for the same resources that had moderate health problems and that was able to show greater benefits from treatment, the majority of respondents wished to give at least equal priority to the more severely affected patient group [72]. Respondents of these studies gave a unit of health gain for the more severely affected group greater social value than the same unit of health gain for the less severely affected group [72]. It has also been argued that claims

should be satisfied in proportion to their strength [73]. This implies that each person with a need for healthcare has a claim to such care the strength of which is proportionate to the patient's medical needs – the more serious the illness, the greater the claim – and the improvement in health that the patient will enjoy, if the necessary healthcare resources are devoted to him [73].

Chance of success of stem cell-based therapies is a dimension relevant for priority setting given all normative starting points above: non-efficacious treatments are not needed though the criteria of success may be interpreted in somewhat different ways. However, the knowledge available today about the differences between PD and HD regarding chances of success of stem cell-based therapies is fragmentary and uncertain.

Availability of alternative therapies would also be relevant for priority setting given all types of ethical theories here reviewed. Utilitarians would consider availability of alternative therapies when assessing the total benefit of the consequences of prioritization, but this dimension would not be decisive for priority setting. If safety and efficacy of stem cell-based therapies for PD and HD were equal, treatment of HD, according to some utilitarians, would be prioritized over that of PD since a successful therapy would result in greater benefit to those who do not have any alternative therapies. The tenability of this argument, however, can only be evaluated when the knowledge gaps regarding the safety and efficacy of stem cell-based therapies are filled. According to other utilitarians, who do not estimate benefit in terms of the magnitude of positive change for a separate individual or a group of individuals but rather in terms of distribution of positive change, it is the number of patients experiencing that positive change that is relevant for priority setting rather than availability of alternative therapies.

If safety and efficacy of stem cell-based therapies for PD and HD are not equal, priority setting decisions would depend on what is considered to be more important – the number of persons experiencing good consequences or the level of goodness of these consequences. If the former, the prevalence of the disease would be a more important criterion for priority setting than availability of alternative therapies.

Considering efficacy of therapies, it is important to take into account that the standard of what is considered a “successful therapy” can be dependent on the availability and quality of alternative therapies. This can be illustrated by the fact that the ISSCR Guidelines set higher requirements for stem cell-based therapies where alternative therapies do exist by requiring new therapies to be competitive with existing alternatives [63].

To offer all persons decent life chances in areas like health, education and employment, availability of alternative therapies is relevant for priority setting given the position of virtue ethics. PD patients who can be treated with alternative therapies already have better chances in health or employment than HD patients for whom such therapies are not available. Prioritizing a therapy of HD would reduce the difference in such chances. However, whether prioritization of HD treatment over the treatment of PD would

actually reduce the inequality in such life chances will depend on the safety and efficacy of stem cell-based therapies for HD and PD. As long as stem cell-based therapy for HD has at least acceptable level of safety and some efficacy, availability of alternative therapies will be more relevant for priority setting than chances of therapeutic success, given the view of virtue ethics.

Availability of alternatives would inform the deontological decision-making in priority setting if one holds a Rawlsian view. To provide as equal chances as possible to everyone in tomorrow's society, it would be important to first provide a therapy for those who today have no treatment alternatives, such as HD patients. Given another, Kantian view, however, availability of alternative therapies would be irrelevant for priority setting, except when omission to provide an existing therapy to patients suffering from an especially debilitating disease and having no alternative treatment options can be considered as amounting to degrading treatment. Given the rights-based position, availability of alternative therapies would be relevant for priority setting provided that such omission to treat is considered as a violation to human right to life.

The costs of non-intervention to the patient. First, it is important to be specific whether non-intervention is equal to non-treatment. Non-intervention in terms of non-prioritization of the treatment promising a certain degree of efficacy to treat HD patients may in fact amount to non-treatment, since HD-affected persons have no alternative therapies. This would not be the case for PD patients. The costs of non-intervention to society would therefore be analogous to costs of non-treatment in the case of HD, but not PD. Second, it is important to be specific what types of costs we refer to. For utilitarians, all types of costs – health related and non-health related would weigh equally. For deontologists only these costs of non-intervention that amount to non-treatment and possibly to inhumane treatment of a patient would be relevant for priority setting. From the perspective of virtue ethics, the costs that reduce the life chances in areas like health, education or employment would be considered as relevant, and from the perspective of rights-based theories – health related costs that amount to infringement of the individual's human rights, such as right to life.

The costs of non-intervention to society. Like in the case above, it is important to be specific about what types of costs are considered. The costs to society can have several forms, one of them being the expected consequences of non-treated disease in terms of risk of patients causing public danger. The differences between PD and HD related to namely this form of costs to society would inform decision-making from the perspective of all types of ethical theories. For example, such differences would be relevant for priority setting from the perspective of those utilitarians, who consider both actual and expected consequences of the intervention. The expected consequences for third parties can be measured in terms of risk of PD- or HD-affected person causing physical harm or economical damage to third parties because of the aggravating symptoms of the disease.

The differences between PD and HD regarding this type of costs to society would also be relevant for priority setting given some of the deontological approaches as well as rights-based approaches. The deontologists holding a Kantian view could argue that exposing other members of society to risk of damage of their health or even risk of death would amount to using their bodies without their consent as the means to grant the human rights and human dignity of HD-affected persons. Similarly, those supporting the right-based approach could argue that such risks endanger the human right to life of the third parties. Finally, from the perspective of virtue ethics, securing equally decent life chances of HD-affected persons in areas like education or employment may jeopardize such chances of other members of society, if their health is damaged.

The tenability of these arguments can be evaluated provided (1) the difference in risk can be reliably estimated, especially taking into consideration much higher prevalence of PD, and (2) provided safety and efficacy of HD treatment is proven.

Fair access to treatment in a global perspective. Given some types of the deontological, e.g. Rawlsian, approach, as well as rights-based approach, the most acceptable decision would be the one which would reduce the inequality regarding access to treatment as much as possible. However, unless it can be known which population has greater difficulty to exercise their rights to health care, the estimation of the rightness of decision cannot be made reliably. It is important to fill this knowledge gap also according to virtue ethics and some utilitarian approaches: firstly – to estimate which therapy would lead to the maximization of improvement of life chances in areas like health, education and employment for a greater number of persons; and secondly – to maximize the benefit for the greatest number.

In all four cases, however, all these arguments are tenable provided the differences between PD and HD in this dimension can be reliably estimated. In the case of PD, inaccessibility of treatment is mainly geographically determined, with patients in developing countries having a much worse access to treatment than patients in developed countries. Even if it were proven by further research that HD does not to affect certain native populations in certain continents, there could still be HD-affected persons of another ethnic origin in developing countries, and the problem of access of treatment is likely to be similar to that of access of treatment of PD. As long as there is no reliable estimation of whether it is PD- or HD-affected persons who have greater difficulties to access treatment, this dimension can hardly be informative in priority setting taken all four approaches.

Given all four ethical starting points, the relevance of this dimension can even be questioned considering the following. If stem cell-based treatments will be routinely administered to PD and HD patients, this would not solve the problem of access to treatment automatically or in a short run. In the long run, however, stem cell-based therapies may become accessible to larger numbers of patients and may therefore

contribute to reducing the inequality in access to treatment, if such is proven, between PD- and HD-affected persons.

5.2 Different conclusions, different reasons

There can be some interesting differences among the approaches grounded on different types of ethical theories, and sometimes even between approaches grounded on different traditions within the same type of theory. Table 1 presents types of ethical theories endorsing partly different values, and dimensions that can be considered as relevant for priority setting given these values. It provides a scheme that could be followed when comparing the relevance of different dimensions discussed in this article for priority setting. The table is left blank on purpose to illustrate that there is no unique “correct” way to fill it in and that the answer in each blank cell of the table would depend on the arguments used. Moreover, the answers – in terms of “relevant” or “irrelevant” – can be identical in many of these cells, but for very different reasons, as the discussion following below will illustrate.

Table 1.

Dimensions containing differences between PD and HD that can be relevant for priority setting given the perspectives of different types of ethical theories

| Types of ethical theories Dimensions | Utilitarianism | Deontology | Virtue ethics | Rights-based |
|--|----------------|------------|---------------|--------------|
| Seriousness or severity of the disease | | | | |
| Non-intervention costs to patient | | | | |
| Non-intervention costs to patient’s familial health care provider | | | | |
| Fair access to treatment in a global perspective | | | | |
| Prevalence of the disease | | | | |

We will now discuss which specific difference some ethical premises and the values endorsed by them will make in this context, if interpreted and applied to the problem at hand.

Maximization of the benefit for the greatest number versus maximization of the greatest benefit. As we have already discussed above, there are differences among the approaches grounded on different traditions of utilitarian thought. Striving to achieve “the greatest

happiness for the greatest number”, some utilitarians consider that the total level of goodness achieved is more important than the distribution of the goodness or the number of persons experiencing the benefit. But others give more importance to the greater number of persons experiencing some benefit. For the former, the chances of success of stem cell-based therapies for PD and HD would be a decisive factor in priority setting, if these chances of success were known and could be compared. For the latter type of utilitarians, a big number of PD patients experiencing an insignificant improvement in their health and economic situation would be preferable to a smaller number of HD patients experiencing a significant improvement, provided that other things are equal. This argument would be tenable as long as the levels of safety and efficacy are acceptable, no matter how beneficial both therapies actually are. Whether it is possible to evaluate the tenability of this argument will depend on whether the knowledge gaps regarding the safety and efficacy of stem cell-based therapies can be filled and on chosen criteria of “success” and “improvement”. However, regardless of the possibility of filling these gaps, it can be problematic to measure efficacy. If it is measured also in terms of its ability to improve the patient’s quality of life, rather than in terms of purely clinical criteria, it is important to be explicit regarding the criteria for the evaluation of quality of life. Given the present state of knowledge, it can be very difficult to compare the quality of life between PD and HD patient groups, since, among other things, it depends on the stage of the disease and the availability of treatment in a global perspective.

Protection of human dignity and equal chances versus maximization of benefit. *Consequences of non-intervention to the patient’s health care provider in the patient’s family*, especially when these consequences are expressed in terms of lost opportunity income or expenses directly related to worsening of the health care provider’s own health due to his/her physical exhaustion from the constant patient care, can be interpreted as using such caretakers as means to secure the healthcare of third parties, given a deontological (Kantian) position. As Lippert-Rasmussen and Lauridsen have argued, deontological decision-making would be informed by the presence or absence of a violation of deontological constraints, such as the Kantian formula of humanity as an end in itself, or the equal moral worth of persons [61]. The scope of what exactly is meant by treating someone as an end is not always clear and may include an individual’s claim that costs are not imposed on him/her as an indirect consequence of satisfying other people’s claims to medical treatment [61]. This is especially true in the case of those unable to pay for external aid: allowing them to ruin their lives and their health while serving others can be seen as discrimination. These consequences can also be interpreted in terms of reduction of chances of familial health care providers in areas like health, education and employment, and therefore would be relevant for priority setting from the perspective of virtue ethics.

Familial health care providers of HD-affected patients seem to have a higher chance to end up in such a situation due to usually earlier onset of HD than PD, lack of alternative

therapies and its inherited nature, thus possibly demanding care of more than one generation of HD-affected persons. If consequences of non-intervention to the patient's health care providers can be interpreted as using health care providers as a means to secure the health care of third parties, it can be argued that HD treatment should be prioritized over PD treatment given a Kantian view. However, such prioritization would end up in an ethical conflict with the principle to treat all human beings equally since they have equal moral worth. It is therefore not certain that a deontological viewpoint would advocate any prioritization based on this dimension. This dimension would, however, be important to a utilitarian way of thinking, as one of the actual consequences of non-intervention, and would be considered when calculating the total benefit of a prioritized action.

Economic efficacy versus therapeutic efficacy. From a utilitarian perspective, a highly efficacious therapy which benefits patients very significantly might be given higher priority than a more cost-effective but less clinically efficacious treatment [74] or the other way round, depending on whether priority is given to satisfying the needs of, for example, those who have the strongest claims or those who are more numerous. Cost effectiveness and clinical efficacy of stem cell-based therapies for PD would need to be compared to cost effectiveness and clinical efficacy of alternative therapies, whereas such qualities of a therapy for HD – to those of the available care and the alleviation of symptoms. Without filling the knowledge gaps regarding the clinical efficacy of stem cell-based therapies and without the above-mentioned lifelong evaluations the cost effectiveness in relation to clinical efficacy cannot be estimated. Needless to say, rights-based and at least some deontological schools of thought would consider only therapeutic efficacy in priority setting.

6. Conclusions

This article has shown that in the case of newly-established, experimental therapies, prioritization decisions are not only system-specific, i.e. dependent on the context of priority setting, such as the existing health care system, resources in different countries and coverage by health care insurance, but also disease-specific and treatment-specific. This means that priority setting of experimental therapies also depends on the qualities of the diseases in question, such as the seriousness or the prevalence of the disease as well as on the qualities of therapies being prioritized, such as their efficacy and safety. It is important to take into account that the standard of what is considered a “successful therapy” can be dependent on the availability and quality of alternative therapies.

Priority setting involving treatments based on new and emergent technologies raise special problems. These problems concern the role of uncertainties and knowledge gaps. The uncertain probabilities and the gaps of knowledge discussed above raise important issues, and their implications for priority setting deserve to be analyzed in depth [75, 76].

As Sahlin et al have put it, the problem with the risk of unknown and uncertain long-term effects is “one of not knowing what will happen, and when we know it will, when; and of not being acquainted with the consequences, and therefore being unable to value the unfamiliar” [77]. Even when we are equipped with reliable knowledge, our behavior is influenced by affects and emotions, and as decision-makers we are short-sighted and “prone to serious errors of refraction” [77]. Decision-making when the state of knowledge is unstable and knowledge is incomplete is thus even more difficult and should be approached very carefully.

There are medical and societal differences between PD and HD, which are relevant to priority setting depending on which ethical arguments decision-making is based on: utilitarian, deontological, rights-based or grounded in virtue ethics. However, it is not possible to evaluate the tenability of the positions based on some of the ethical starting points unless the knowledge gaps about the safety and efficacy of stem cell-based therapies for PD and HD are filled with reliable knowledge. However, filling these gaps with reliable knowledge does not necessarily imply that decision-making about priority setting will automatically become easier. It can be even more difficult. There can be other, today yet unknown facts that could be relevant for priority setting given different sets of values. Future research may show that the only differences between PD and HD are those that are considered relevant for priority setting given values that are endorsed or protected only in some societies but not others. However, reliable knowledge is indispensable to enable decision-making about priority setting.

According to some of the utilitarian arguments, the priority setting decision will depend on the definition of health related consequences of PD and HD as well as health related consequences of their treatments. Different interpretations of what consequences are considered as “health related” – concerning only physical health or psychological health as well – also affect the tenability of arguments. The tenability of some of the deontological arguments will depend on whether it can be estimated in a reliable and comparable way that failure to prioritize an existing therapy for an especially handicapping disease with no alternative therapies amounts to inhumane or degrading treatment of patients suffering from this disease or contributes to their treatment as means to achieve certain aims, as well as on the criteria of “inhumane” or “degrading”. In order to evaluate the tenability of arguments presented in this paper, knowledge gaps about the safety and efficacy of stem cell-based therapies for PD and HD as well as about the economic impact of PD and HD on society and differences in accessing the treatment should be filled with reliable knowledge obtained from further research.

The steps of analysis applied in this paper could be helpful when setting priorities among treatments of other diseases with similar differences as those between PD and HD.

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Paper IV

WITHDRAWAL FROM BIOBANK RESEARCH: CONSIDERATIONS AND THE WAY FORWARD (Paper IV)

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Abstract: The right to withdraw one's consent after having agreed to participate in research is a fundamental principle in contemporary research ethics. However, it has been questioned whether this right should apply to research conducted on donated biological samples, including stem cells and tissues from which stem cells can be derived. In this article we present some of the concerns that have been expressed related to this question. We then identify five areas that one needs to pay greater attention to before any conclusions can be drawn as to whether donors should be given the right to withdraw, or under what circumstances withdrawal should be allowed.

Keywords: Right to withdraw, human biological material, biobank research, research ethics, informed consent, autonomy

1. Introduction

The unconditional right to withdraw one's consent after having agreed to participate in a research project is an important principle recognized in both international legal documents regulating biomedical research on human subjects [1, 2] and ethical guidelines concerning such research [3, 4]. According to this principle, research participants have the right to freely withdraw their participation at any time, without providing rationale for their decision. Various reasons can be, and have been, offered in support of this right; reasons to which we shall return. There are many kinds of research,

however, and it cannot be assumed without argument that allowing unconditional withdrawal is equally reasonable in all cases. In particular, the question has been raised whether the ethical requirements for withdrawal from research on human biological specimens should differ from those usually applied in research involving human participants [5, 6]. No doubt there are some possibly relevant differences between the two kinds of research – research on biological samples, after the sample has been collected, involves no risks of direct physical harm, for instance, and seemingly doesn't pose as serious a threat to the individual's privacy or personal integrity as does invasive research [5, 6]. Whether these or other differences are enough to justify different standards concerning the individual's right to withdraw from research remains to be settled.

The literature arguing for or against allowing withdrawal is rather scarce in this specific context of biobank research. However, much has been written about biobanks in general, as well as about the right to withdraw from biomedical research. But a handful of articles and book chapters focus specifically on the issue of withdrawal from biobank research [5-8]. This work has certainly contributed in valuable ways to the debate, by exploring arguments and concerns in different manner related to the right to withdraw from biobank research. Much remains to be done, however, before it can be assessed under what circumstances, if any, withdrawal ought to be allowed. The main purpose of this article is to bring attention to distinctions that need to be made, and to assumptions that still need to be argued for, in order to settle the issue. We shall proceed as follows: in the next section we will briefly present a number of different considerations that have been, or that reasonably could be, put forward in favor or against allowing donors to withdraw from biobank research. Then we suggest a number of areas that need to receive greater attention in order for the debate to make progress. The discussion should be applicable to various types of research involving donated human biological specimens, from research conducted on donated tissues and cells to research conducted on biological products derived from them, such as cell lines, or data originating from such research.

The problem of withdrawal seems to be particularly challenging in the area of the so-called "translational stem cell research". This research translates the results of basic stem cell research into diagnostic and therapeutic applications. When donors of tissues or cells express the wish to withdraw from such research involving, for example, the stem cells that have already been derived from the tissues they had donated, the question how to address this request of withdrawal can be very difficult, especially if these stem cells have already been used to derive products intended for clinical use in patients, such as cells differentiated into the desired cell type.

2. Considerations

Biobank research has presented bioethicists with new challenges. These relate in different ways to the processes of collecting, storing, processing, distributing, and making scientific use of human biological material. To some extent the challenge consists in viewing biobank research through the lenses of traditional ethical principles and concepts, such as respect for autonomy and protection from harm. And it is not always obvious how to make sense of the picture that emerges. To some extent the challenge consists in rethinking basic ethical assumptions [9].

We shall now describe some concerns associated with withdrawal in the context of biobank research. Many, although not all, have been mentioned in previous work on withdrawal. They can all be expressed in somewhat different ways, and we do not wish to claim that we make full justice to all of them. Rather the aim is to introduce the relevant lines of reasoning, and then turn to the issue of how the debate on withdrawal ought to proceed from the present point.

Autonomy

A central concern relates to the idea of individual autonomy [10]. The concept of “autonomy” is a complex one, and in this article it is used in line with other works in this area. Beginning perhaps with the Nuremberg Code it has been a core principle of research ethics that participation in research should in general be optional, not coerced or uniformed, and not something that people can be forced into, and that each individual should have a right to self-determination. The underlying idea is that by participating an individual typically invests herself – her body, time, efforts and more – and that the individual has a right to decide over that which primarily concerns *her*. Obviously, whether an individual participates in research does not only concern her, as others are affected too. But in many types of research, particularly biomedical research, an individual’s participation has generally been seen as falling within the scope of a right to *self*-determination.

Some commentators point out that the right to withdraw implies a respect for research participants’ autonomy “by letting them reconsider their willingness to participate”, as they may have reasons for changing their mind [11].⁷ Such reasons can be related to a change in the assessment of risks that research participants are willing to assume, “a change in their personal situation” [11], or growing older which can influence their

⁷ As we shall return to later, it is neither obvious what autonomy means, nor why it should be promoted. One point is worth mentioning here: Increasing a person’s options is not the same thing as promoting that person’s autonomy [12]. Hence, one cannot simply assume that withdrawal promotes autonomy simply because it opens a possible line of action for the donor.

wishes and values [13]. According to some other commentators, assessment of risks can change due to, for example, improved techniques allowing researchers to extract new information from the samples [5].

While most considerations that have been offered *against* the right to withdraw consent to participation in biobank research relates to other things than autonomy, it could be argued, and it has to some extent been that even if the possibility of self-determination was the sole or dominating value, this value does not support the view that there ought to be a right to withdrawal. Two lines of thought deserve to be mentioned here. Firstly, it could be claimed that research on donated material, in contrast to, for example, invasive studies, no longer concerns the individual from whom the sample was taken, in the sense needed in matters of self-determination. The sample may come from you, and you may certainly have a right to decide whether to offer it to researchers in the first place, but once taken it is perhaps no longer part of you or your body, nothing you can claim any more, and decide what can be done with this sample. This may seem plausible in situations where the donated material has already been anonymized [14]. But if the material can be traced back to the donor, it is not difficult to imagine ways in which the donor can be harmed, something that we will return to in a moment. For example, the personal integrity of the donor can be harmed if unauthorized third parties get access to genetic information about the donor – something which can become increasingly possible with the development of the possibilities to cheaply sequence the whole genome.

Secondly, and perhaps somewhat surprisingly, it has been argued that allowing *unconditional* withdrawal actually risks undermining autonomy [15]. There are at least two ways to understand this idea. First it can be argued that autonomy requires that the donor's decision to withdraw be *informed*, in roughly the same sense as informed consent is required in the first place [16]. A donor who withdraws as a result of being uninformed, or confused, does not act autonomously, or so it could be argued. Some believe that informative and explanatory discussions here are necessary to remove misconceptions. And that continued research is justified when a withdrawing research subject cannot present “sufficient reasons why it is no longer reasonable to ask for his continued participation” [6].⁸ The other way to understand the idea that unconditional

⁸ To determine whether the reasons of withdrawal are sufficient and whether waiving the right to withdraw is acceptable, some commentators [6] have suggested a consultation with an Ethical Review Board. This suggestion may introduce variations of evaluation of what can be considered as “sufficient reasons” among different boards and even more so among such boards in different countries. It has been argued that the sense of what constitutes undue influences in withdrawal procedures likely differs among different stakeholders such as researchers, Ethical Review Boards or research participants [17]. It is also far from clear that shifting the problem of determination of what should count as “sufficient reasons” from researchers to Ethical Review Boards would solve the question of when it should be considered acceptable to withdraw from the study.

withdrawal conflicts with autonomy relates to an account of autonomy that builds on a relation between researcher and participant. Unconditional withdrawal negatively affects this relation, because it undermines dialogue, and hence autonomy too. Or that is the general idea. We shall not here pursue this idea further, but only clarify that there is more than one way to perceive autonomy in the context of bioethics, and that these differences may be relevant to how we perceive withdrawal.

Harm to donors

When it comes to research in general, the right to withdraw can (among other things) be regarded as an additional safeguard against risk or harm. This is because research participants are given the chance to drop out from a study whenever they feel discomfort, are uncomfortable with participation, or sense a risk that they will be harmed.

Here the question is whether biobank research poses comparable risks to those in clinical trials, and if these participants therefore should be allowed to drop out whenever they want. Of course, during the process of collecting biological samples research participants can experience pain and be exposed to risks of being physically harmed. No one denies this, even though the risks often are minimal (as, for instance, when a blood sample is taken).⁹ Neither does anyone deny that the donor should be allowed to drop out during this phase, regardless of whether we are talking about collecting blood samples or biopsies from the lung. Rather, the interesting question is if donors are at risk of being harmed when the samples have been collected.

When the sample has been collected and put in a biobank it does no longer make much sense to speak of risks of direct physical harm [5, 6, 19]. Thus, if withdrawal primarily is justified in terms of allowing participants to avoid such harm, then we should perhaps after all reconsider donors' right to withdraw after the sample has been collected.

Harm, however, may come in many forms, not only directly physical [18]. Some commentators have discussed the possibility that donors can suffer *indirect* physical harm [6]. If, for instance, due to research one has run out of samples that could have been used for clinical purposes, this might have a negative effect on donors' health. Apparently, this would not have been avoided even if the donors exercised the right to destroy (or to anonymize) the material. But it could have been solved if the donors earlier had been given the chance to withdraw their consent to further use of the donated material *for scientific purposes*. This shows the importance of keeping different forms of withdrawal apart, something which we will return to in the next section.

There are other ways in which donors can be harmed. Some biobanks contain vast amounts of information about donors – information that can be used to determine their

⁹ Minimal risk has been defined as “the probability and magnitude of harms that are normally encountered in the daily lives of the general population” [18].

current health status, their genetic predisposition to develop a certain disease, and more. This opens for *informational risks* [6, 19, 20]. Misuse, or unfortunate circumstances, can have the effect that this information leads to harm, and several possibilities have been discussed. Third parties, such as employers and insurance agencies might get hold of sensitive data, which can cause harm to the donor. The donor can suffer financially. She can also be at risk of stigma and adverse psychological reactions related to the information [13]. Also, biobanks can be, and indeed have been, used for criminal investigation [21], although this has been in conflict with their purpose. And one could easily imagine other scenarios too.

Moreover, the donor might be provided with information that causes anxiety, without wanting or having asked for that information. For example, the donor can learn that she, due to her genetic setup, most likely will develop Alzheimer's disease within a ten-year-period, without there being much to do about it.

A somewhat different harm might appear if the donated material is used for a purpose to which the donor strongly objects (which can be seen as a form of *moral harm*) [6]. Pacifists (and, of course, many others too) may not want to see their donated material used in the development of biological and chemical weapons [19], while others care if the donated material is used by the pharmaceutical industry. It may be seen as problematic to frustrate such preferences regardless of whether the donor is aware of purposes for which the sample is used. Also, if a sample is used in a way that serves to discriminate or stigmatize the donor, or a group to which the donor belongs, then some speak of *dignitary harm* [13]. This harm would appear because such a usage would signify a lack of respect for the donor.

Many of these harms seemingly relate to confidentiality breaches, or non-sanctioned usages, in the sense that the information is used in a way it was never intended to, or consented to. Such breaches happen, however, whether they are accidental or deliberate, and should therefore be taken into account when reflecting on the risks associated with donating biological material to research.

Duty

Another concern relates to a supposed duty to participate in (good) research. The worry is that allowing withdrawal undermines the fulfillment of a supposed duty to contribute to the scientific enterprise.¹⁰ By using modern medical services and expecting to receive the best possible treatment, we take advantage of the work done by previous generations, and thus we ought to contribute to the processes by which such treatment is established,

¹⁰ Actually, it has been argued that it could make sense to speak of a duty not to withdraw without good reasons, a duty that “would potentially conflict with unconditionality, since we normally find it acceptable to ask people to explain or justify their *prima facie* breaches of moral duties” [7].

or so it has been argued [6]. Also, of course, we perhaps have an obligation to participate in research in the sense that we ought to help others, irrespectively of whether we ourselves gain something in the process. It has been argued that there is a moral obligation to (a) participate in minimally invasive and minimally risky research projects such as biobank research [6, 22], provided “safeguards against wrongful use” of donated biological specimens are in place [22], (b) remain in research once committed, particularly when research entails little or no risk, or (c) remain in research when a person has consented to a project that promotes public good and if resources would be wasted if research were not completed [6].

Now, the supposed duty to participate in research can be, and indeed has been, questioned [23]. But it is not only handful of bioethicists who believe that we have a duty to participate in research. In a Swedish study, for example, many patients expressed a willingness to contribute to biobank research because they sensed a duty to do so [24, 25].

Possible costs related to allowing withdrawal

Let us turn the attention to some different possible costs related to allowing donors to withdraw from biobank research. Costs, whether economical or of other kinds, play an important role in the debate on withdrawal. In the end, these costs may in different ways hamper scientific progress, and as a result slow down the development of new methods for diagnostics and treatment of severe medical conditions. Hence, potential costs add to the importance of dealing with the issue of withdrawal.

Allowing donors to withdraw can be costly and time-consuming, it has been said, especially given that withdrawals are frequent and/or the process of destroying or anonymizing data takes a lot of effort [7]. The latter may be the case when donated material has spread out to different research institutes, perhaps in different countries [26].

In order to highlight the risks involved in allowing unconditional withdrawal, Søren Holm discusses a hypothetical scenario, where an untrue horror story about a large national biobank, first presented in a populist newspaper, spreads on the Internet, and where as a result 20,000 people withdraw within a week [7]. The problem here is not so much the costs in destroying or anonymizing these samples (even if these costs may be significant), as it is the negative effect on the biobank as a source for research, in terms of numerous future studies that now can never be conducted. It is also likely that the trust of the general public in biobank research would decrease after such an incident, at least for some period of time. Others have also commented on the risk that withdrawals have a negative effect on research. Leaving a study prematurely can, for example, introduce a withdrawal bias in this study, since the individuals dropping out may be systematically

different from those who do not and this difference might affect the study outcome.¹¹ In Holm's catastrophic scenario the ones who withdrew could perhaps belong to the younger part of the population – those, perhaps, most active on the Internet – and hence introduce a systematic bias in some research projects. It should be noted that bias may also be introduced at other occasions. For example, it could have been introduced if certain people had disproportionately agreed to participate in a certain biobank research project at the recruitment stage.

The problem above relates to another worry mentioned in the literature, namely that withdrawals may influence the choice of research to be conducted, which in turn in the long run may influence people's health and well-being [5].¹² For example, research projects where research participants are motivated to stay in the study may be easier and faster to carry out and as a result undertaken more often than projects where participants are likely to drop out frequently.

A different kind of problem discussed in the literature relates to withdrawal as a threat to scientific integrity, in that it is inconsistent with the requirement to keep data "for a reasonable time span so that it can be inspected and assessed by peers" [26]. No doubt, peer review belongs to the very foundation of the scientific community, because it is needed for ensuring the quality of scientific research, and investigating allegations of scientific fraud. Thus, it is a worry to be taken seriously, whether we are conducting research on biobanks or other sources of information.

As we have seen, several concerns have been expressed that maintaining a right to withdraw from biobank research is costly in terms of research quality and, in the long run, reduces expected gains to society in the form of medical information, improved medicines and treatments [5, 15]. Some think that withdrawal therefore undermines most people's general interest in research [29] and that withdrawals may undermine the "right" of such stakeholders to a "complete and unbiased trial result" [27]. Suggestions have therefore been made that the right to withdraw has to be balanced against and outweighed by the benefit, expected to result from limiting it [6, 28] – benefit such as favoring "those that are worst off in society" – the current and future patients [28] and public health interests in general [6].

¹¹ This worry has been expressed in the context of clinical trials [27], but could also be of relevance in some studies involving biobank material if withdrawals are frequent enough.

¹² Some have argued that this is a problem for stakeholders such as patients waiting for trial results [28] or research participants remaining in the study who can be disappointed by the loss of information due to withdrawals [16].

Withdrawal and trust in science

Withdrawal from biobank research has also been related to trust in science. It has been argued that people may start distrusting research, if they think that they have no say [5, 30, 31] and that erosion of trust in medical science could have severe consequences for medical research [32]. One can here picture several different outcomes, such as that it may become more difficult to recruit people to participate in research [5, 30]. If people feel they can trust medical researchers, they might be more likely to consent to research on their samples [5, 33] and less likely to change their minds about doing so [5]. A somewhat more implausible possible consequence, still worth mentioning, is that people may start distrusting scientific methods and results, and perhaps even think twice before donating money to important research.

In the literature, however, there is an opposite line of argument that focuses on trust. The idea is that trust in research could be enhanced, if it were made publicly known that only those who strongly object to participation in research for reasons not based on misconception will be allowed to withdraw, which means that “public health interests in research” are not taken lightly [6]. Hence, making it more difficult to withdraw could under these special circumstances promote trust in science.

It has thus been suggested by different commentators that both allowing withdrawal and limiting withdrawal can promote trust in research in different ways.

3. The way forward

So far a number of different concerns have been presented. Most of them have been expressed in the debate on withdrawal, in one way or another. Some of the worries mentioned need no doubt be taken seriously, since they concern seemingly fundamental values and potentially significant costs. We are however still far from being in a position to draw any conclusions about what the withdrawal policies ought to be, and we shall now explain why.

The many meanings of withdrawal

One of the striking things when going through contemporary work on withdrawal is that it is far from always made clear how to understand withdrawal. Similar difficulties have been acknowledged by several authors [8, 34]. Major ethical guidelines [3, 4] provide little assistance in mapping out the many meanings of withdrawal, but taking into account most of the possibilities touched upon in the literature it can be taken to require that:

- 1) The donator is not contacted further;
- 2) The donated biological material is no longer used for specified purposes (whether research in general, or a certain type of research);
- 3) The donated biological material is anonymized;
- 4) The donated biological material is destroyed;
- 5) The data already collected from donated biological specimens is no longer used for research (data withdrawal);
- 6) The materials obtained from the original donated biological specimens (such as cell lines) are prevented from further distribution or use;
- 7) The information obtained from the use of biological materials transformed from the donated specimens is prevented from further distribution or use.

Finer distinctions can be made regarding some of these possibilities. Holm notes, for instance, that anonymization can be combined with either further generation of data from existing samples, or no such further generation [7].

Allowing some of these forms of withdrawal may seem more reasonable than others. Options 3), 4) and 5) have been much debated [6, 14, 27, 28, 34-36]. And 3) and 4) have also been proposed as a form of withdrawal by some ethical guidelines [5, 37]. For example, according to the UNESCO International declaration on human genetic data, when consent to storage and use is withdrawn, the samples are to be dealt with in accordance with the wishes of the person concerned, but if these are unknown, unsafe, or unfeasible, the samples should instead be destroyed or irretrievably unlinked [37]. Also CIOMS Guidelines 4 and 5 suggest that research subjects should be given the right to request destruction or anonymization of their biobank samples at any time [5]. National legislations sometimes follow these lines as well. For example, the Swedish Biobank Act gives individuals the right to have a sample destroyed or made unidentifiable [38].

Here we neither want to defend nor dismiss allowing any of the seven forms of withdrawal mentioned above. Rather, we want to state what should already be obvious, namely that in order to assess suggested policies for withdrawal, one first needs to have some idea of what withdrawal amounts to. Not living up to this requirement is problematic for at least two reasons. Firstly, it encourages people to talk past each other, which may lead to a confused debate. Secondly, it is simply not possible to judge the relevance and tenability of arguments presented in this paper unless they relate to some specific understanding of withdrawal.

Intermediate positions: a right to withdraw, but with difficulty

To make progress on the issue of withdrawal one might benefit from making the picture more nuanced in other respects as well. For one thing, much of the debate concerns whether there should be a right to withdraw, but many of the concerns raised by those who oppose this right could be given credit without committing us to the rather radical position that research participants should not have any such right. In connection with the discussion about informed withdrawal and “relational notions of autonomy”, we have already touched upon the idea that one should have a right to withdraw, but that this should be a *conditional* right – conditional, perhaps, upon good enough reasons being offered for withdrawing. But other intermediate positions, even weaker ones, are possible too. One might, for instance, consistently claim that everyone has an unconditional right to withdraw their consent, but that the actual withdrawal, in some circumstances at least, should be associated with some *difficulty*.

What kind of difficulties could be appropriate? There are a number of possibilities that one might at least consider. Providing information to the donor, verbally or in writing, about the consequences of withdrawal or about one’s views on the risks of participating in biobank research, might serve as an appropriate form of friction, for instance. Requiring or at least expecting the donors to execute their right to withdrawal by doing it in a certain way, or by first going through certain steps, might also yield the desired difficulty. Having to sign a written confirmation of their decision to withdraw [16], having to explain one’s decision [17], or having to discuss it with researchers are obvious ways in which this can be done. As has been pointed out, no such expectations or requirements should be such that they conflict with the general principle that the research subject’s decision must be voluntary. Generally speaking, however, decisions can be voluntary even when they have been made after input from, or under the influence from, people who prefer that the individual makes a certain choice – as long as that influence isn’t inappropriate, or comes from someone whom the individual is significantly dependent upon. Whether the power imbalance that exists between researchers and research subjects is so strong that the latter cannot make voluntary decisions about withdrawal if they are expected to first discuss the issue with researchers, is one of the questions that need to be discussed further.

According to Holm, *time* might also be a factor worth introducing. The immediacy with which requests for withdrawal typically have to be met in clinical research seems not to be as crucial in biobank research. The material could, he suggests, be placed in a limbo for a period of time and only destroyed if the donor does not, once again, change her mind [7].

Open empirical questions

Several of the concerns and arguments that have been presented in this article refer to the consequences of allowing or disallowing donors to withdraw their participation. As to allowing withdrawal, worries have been raised that this might lead to the most important studies never being launched, to selection bias, significant economical costs, and more. As to disallowing withdrawal, one has pointed to the risk that this might lead to, among other things, distrust in science (with concomitant decrease in funding and less willingness to participate), use of donated tissues by unauthorized third parties, and stigmatization. Many commentators apparently assume that those consequences are sufficiently likely to weigh in favor or against a right to withdrawal. Whether allowing and disallowing withdrawal will have the relevant consequences are open empirical questions, however, and surprisingly little evidence has been offered in support of such assumptions. Several of the concerns mentioned in the previous sections are thus fairly speculative, in the sense that, for all that is known, they concern merely *possible* outcomes related to allowing, disallowing, and making it more difficult for donors to withdraw from biobank research.

Occasionally the need for empirical evidence is explicitly acknowledged. Consider, for example, the argument that the right to withdraw is too costly. Gert Helgesson and Linus Johnsson point out that this argument carries little weight until it can be shown that “granting a right to withdraw consent indeed does unacceptable damage to research” [5]. So far so good. The lesson is not learned, however, as is demonstrated when the authors later on, based on an empirically unsupported claim about the importance of public trust for people’s willingness to participate in research, support the right to withdraw consent.

With uncertainty about matters of fact, one of the things that are needed before we can judge to what extent there should be a right to withdraw also in biobank research is more data. Consider, for example, the worry that limiting the right to withdraw may incur costs in terms of difficult and slow recruitment, on the assumption that people are unwilling to take part in a research project if they have little possibility to withdraw. Would people in fact refrain from participating on these grounds? This is but one issue that can, and indeed should, be assessed empirically. And even if the possibility of withdrawal turns out to promote willingness to participate in research, one cannot jump to the conclusion that the right to withdraw is essential for this purpose. Willingness to participate can depend on a number of different factors [39, 40], and hence possibly be promoted in other ways too. Besides individual values, attitudes towards donation can also be influenced by (a) type of tissue being donated [39, 40], (b) the purpose for which donation is being sought, (c) the nature of the recipient of the donation [40], (d) procurement situation including who is asked to provide consent, (e) the biobank’s geographical, social and historical context, (f) the way different tissue types are portrayed

in the media, or (g) whose tissue that is being procured [39]. Obviously these other possible factors also need to be assessed empirically.

Moreover, one should bear in mind that the actual costs of allowing withdrawals from biobank research probably depend on what kind of research one has in mind, and on what is meant by withdrawal in that specific context – e.g. whether it is biological samples, data or products derived from these samples that are withdrawn. It is also important to consider which costs and whose costs have been included in the calculation, as well as how these costs have been estimated. Generally speaking, even if we should come up with evidence pointing in one direction or another, as to what effects the considered policy will have in a certain area, we must remind ourselves that it is total, or net, outcome of each policy that we ultimately should rely on.

In a similar fashion we need to find out whether the right to withdraw, in conjunction with other relevant facts, actually hampers scientific progress, undermines scientific integrity, and more.

The importance and implications of caution

Whenever policy depends on uncorroborated empirical assumptions, the way forward obviously involves filling the relevant knowledge gaps. Some empirical issues may be difficult to investigate, however, and even with regard to those issues that ultimately can be settled, some withdrawal policy has to be in place in the meantime. In addition to making use of evidence that suggests that some outcomes are more probable than others, considerations of *caution* need to take center stage. Those are assumptions about what empirical conjectures are safest for policy to depend on, if at the end of the day it turns out that those conjectures are wrong. Is it, for example, better to assume that denying people the right to withdrawal will negatively affect their trust in science when in fact it doesn't, than to assume that it doesn't have any such negative impact when in fact it does?

It may well be that cautionary thinking already underlies some of the principles stated in codes of research ethics, but the discussion about withdrawal would do well by explicitly putting the issue of caution on the table. Roughly, there are at least two kinds of factors to consider when trying to adopt a cautious approach. First, what the safest policy will be depends on what courses of action are reversible. In a theoretical sense, of course, no outcomes whatsoever are reversible, but in another sense, there are certainly differences between various measures and their potentially harmful outcomes. For example, if samples are destroyed or anonymized, those actions cannot be undone, and neither can any resulting damage. This might suggest that the safest thing to do, in the absence of evidence settling whether destruction or anonymization poses an actual serious threat to the reliability and informativeness of the scientific results, is to grant research subjects only a right to prohibit the use of their samples for research purposes (opening for the possibility that they may once again change their mind).

Caution might dictate that one adopts a certain amount of conservatism. As has been noted, the rules and practices regarding withdrawal are part of a larger regulatory framework, and the consequences of quick radical changes to this system can be difficult to predict. Favoring *status quo*, or at most small stepwise changes, could make sense if one worries that more radical changes lead to a significant loss of control and ability to make appropriate repairs, should such be necessary.

The second thing we need to ask ourselves when thinking about the most cautious way forward concerns underlying value assumptions, or moral assumptions, more broadly. The debate has identified many different values (interests, norms etc.) that could be at stake. It should be essential to one's approach, when there are uncertainties about what values will be realized in the relevant scenarios, that choices are made as to which values are the most important. For instance, had one known with greater certainty that no persistent significant psychological harm to donors could result from using their samples in research, this would perhaps suggest that one should not acknowledge any right to withdrawal. The gravity of such harm, however, should it nonetheless be inflicted upon donors, may decide in favor of such a right. Or in the other direction, had there been more reliable evidence that few people will ever withdraw their consent and endanger the quality of research, the right to withdrawal would perhaps be a no-brainer. But given the high cost that would have to be paid by many seriously ill patients who would not be able to benefit from research, should it after all turn out that its quality is endangered by the withdrawals that would be made, it might be better to err on the side of not acknowledging a right to withdraw. This leads us naturally to our last point, regarding the need to delve deeper into those ultimate values that seem to be at stake.

Deeper moral issues

What arguments regarding withdrawal ultimately boil down to are more fundamental assumptions about what is valuable, calling for respect, etc. On the surface there is broad agreement on what is at stake – autonomy, integrity, utility and harm, trust, etc. – but progress is doomed to be slow as long as the discussion allows itself to stick to unexplicated catch words, or mere hints as to what the deeper moral considerations might be. Moral philosophy is indeed hard, but the debate about the right to withdrawal, as many other debates in research ethics, makes few attempts to clarify the underlying normative premises. Let us give a few examples.

To evaluate the argument that withdrawal of consent ought to be allowed since it protects the autonomy of research participants, obviously it is necessary to determine how much weight the individual's autonomy to withdraw from biobank research should have in relation to other interests at stake. How much ought an individual's right to self-determination be limited for the sake of advancement of biomedical science or other interests of society and *vice versa* – how much effort ought to be required from researchers to enable research participants to exercise this right? But before any such

weighing of interests can meaningfully take place, we need to stop and ask ourselves exactly what we have in mind when we speak of autonomy and the research subject's interest in being granted autonomy. The many different senses of autonomy and their associated values are not merely of academic interest, but have immediate bearing on what the true moral costs, if any, of limiting the right to withdraw are.

If the right to autonomy is based on the assumption that if individuals are allowed to decide certain things themselves this by itself will positively affect their well-being, one might wonder whether such an interest is strong enough to warrant giving people a *right* to withdraw. If other possible instrumental values of self-determination are added, however, such as the broader effects on well-being that might result from the association between the possibility of self-determination and preserved trust, the benefits of allowing self-determination may, of course, be more significant. The source of the right to autonomy may, on the other hand, rather be the general assumption that no-one is better positioned than the individual herself, to determine what is a significant enough risk of personal harm, in which case the crucial issue will be whether or not this assumption is defeated in the case of biobank research. Yet other possibilities raise questions of their own. For example, as already touched upon, richer notions of autonomy may take the critical value to be the individual's possibility to lead a life that is in line with her deepest and most well-considered preferences, in which case one can imagine that long term autonomy may in fact be promoted when a person is denied a right to withdraw. Again, of course, this line of thought needs to be backed up by reasons for thinking that autonomy of this richer kind is especially worthy of respect or promotion.

The same goes for other moral concepts often invoked in the discussion about withdrawal. The notion of personal integrity (or privacy), for instance, often plays a significant role in the debate about biobank research, but is seldom explicated to any interesting extent. In order to know just what moral weight should be given to the protection of personal integrity, one first needs to know what exactly needs to be protected, and why. Is it a matter of giving special protection to that which is connected to an individual's body, and if so, what moral significance should this particular connection be given in the grander scheme of things? Or does the issue of personal integrity rather concern the individual's interest in controlling certain critical information about herself, and if so, just what information should be granted such special protection, and how strong should we take this interest to be?

Still other concerns are also underdeveloped in this context. As indicated, for example, the relationship between researchers and research subjects is sometimes portrayed as one where there is a significant power imbalance. Just what does this claim amount to, however, and what is the exact moral significance of the senses in which the claim might be true? Similarly, a serious discussion of the impact of withdrawal policies on trust has to pay close attention to the various things that one could have trust in, to the various senses of having trust in those things, and to the underlying values. Trusting specific

researchers is different from trusting researchers in general, which is different from trusting the scientific enterprise, or trusting the results in specific fields of research, etc. And are all the varieties of mistrust equally worrisome, or are there value distinctions worth paying attention to, when exploring the relationship between trust and withdrawal policies?

Finally, when values or interests at stake are better understood, the way they are balanced against one another obviously needs to be looked into in as well. Solid ethical conclusions regarding the possibility of withdrawal have to be based on a weighing of relevant concerns that is done not just based on gut reaction, but in as theoretically principled a manner as possible. One of the worries that have been expressed is that if public health concerns are allowed sometimes to trump the *prima facie* right not to participate in research if one doesn't want to, this amounts to a radical shift from the traditional view of research participation [41, 42]. If indeed it is claimed that biobank research should differ from clinical research in this central respect, this needs to be meticulously argued for.

4. Concluding remarks

Biobank research has posed new challenges to the important principle recognized in international legal documents and ethical guidelines concerning biomedical research on human subjects – the principle that research participants have the right to freely withdraw their participation at any time, without providing rationale for their decision. Despite the fact that some biobanks already have an unequivocal right to withdraw, various considerations have been put forward in favor of, or against, the right to withdraw consent to biobank research. However, we are still nowhere near a final verdict on this issue.

In this article, we have argued that the debate about whether, under what conditions, and to what extent withdrawal should be allowed is unlikely to make significant progress unless more attention is paid to a number of things. Distinctions between various ways of withdrawing need to be kept in mind, as does the distinction between having a right to withdraw and being allowed to withdraw without much friction. Further, to the extent that the debate makes assumptions about various empirical matters of fact (and it certainly does), more efforts have to be made to corroborate those assumptions, so that the debate doesn't rely on excessive speculation. The discussion would also profit from explicitly raising the issue of caution, allowing policy to be informed by considerations regarding what empirical mistakes might be easiest to live with, given that some empirical issues will remain unsettled. Also, certain fundamental moral questions need to be tackled head on, in spite of their complexity, in order for the final balancing of interests and concerns to be as well-founded as possible. Only after all these points have been addressed would it be possible to determine whether the arguments against

withdrawal justify a radical shift in the contemporary policy, outlined by research ethics guidelines.

It is our firm conviction that future work on the ethics of withdrawal would significantly benefit from paying close attention to these points. Finally, the points made in this article are relevant not only to the problem of withdrawal from biobank research, but can also be relevant in a wider context. Questions similar to those discussed in this paper arise also with regards to research on personal data – whether they are collected in connection with a research subject’s physical participation in a research project or collected from data registries. Although specific arguments in favor and against withdrawal may be different in that particular context, the fundamental moral questions to be tackled are likely to be similar.

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