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Research Ethics

Which Patient Groups Should Be Asked to Participate in First-in-Human Trials of Stem-Cell-Based Therapies?

Kristina Hug and Göran Hermerén

ABSTRACT

The aims of this article are to consider (1) whether there are medical and societal differences among diseases regarding which patient groups should be asked to participate in first-in-human (FIH) trials of stem-cell-based therapies; (2) any differences in the light of values generally endorsed by different types of ethical theories, since the question in the title of this article is value laden, and its answer depends on which values one wants to promote and protect, and how they are ranked in importance; (3) whether the answer to that 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 being translated from research to practice. This approach to the problem can be applied to decision making about similar problems raised by other diseases that exhibit the same types of differences.

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INTRODUCTION

In many research areas, healthy volunteers are not considered an appropriate population for Phase I or first-in-human trials, which are designed to test the safety of the experimental intervention. The contemporary standard is to involve the sickest patients, because they are less likely to be harmed by the intervention.[1] Dosages in Phase I studies are usually not tailored to maximize benefit for participants, since the primary goal is to determine the safety of the intervention.[2] It may not be considered appropriate to involve the sickest patients in Phase II studies, which typically test the efficacy of an experimental intervention, as it is thought that these patients would be least likely to benefit from the intervention,[3] and their involve-

ment might lead to a false conclusion that the intervention provides no benefit, when it actually might work in healthier patients.[4]

The designation "first-in-human" can mean different things; it can include interventions that are very similar to existing interventions, or interventions that are the first to use a particular type of mechanism, or new interventions that are significantly different from other, approved interventions.[5] In this article, we use the term to indicate the last type of intervention.

In the context of FIH clinical studies of stem-cell-based interventions, the likelihood that an intervention will lead to efficacy testing and subsequently to clinical use can't be known beforehand.[6] The risk-benefit ratio of cell replacement trials is therefore unlikely to be particularly favorable, and thus it would be difficult to justify the serious and potentially irreversible risks associated with such interventions.[7] For example, it has been argued that such studies should involve patients who suffer from diseases or conditions for which 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 less justification there is for patients to participate in Phase I studies, if the harm-benefit ratio is relatively poor.[9]

Should this always be the case regarding FIH experimental stem-cell-based interventions? The interventions may range from treatment of life-threatening diseases for which there are alternative therapies, to cosmetic therapies, thus involving different risk-benefit ratios.[10] Further, stem-cell therapies are based on different kinds of stem cells.[11]

The 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 that are common to several diseases? This seems like a technical question, but it is also value laden. The answer depends on which values one wants to promote and protect and how they are ranked in importance: the safety of patients, reliable and generalizable answers on choice of therapy and dosage, and so on. Although such questions are usually addressed during the ethical review process, the effects of FIH stem-cell-based interventions are more difficult to describe because there are many unknowns.

In the context of stem-cell-based interventions, the similarities and differences between diseases should be examined, and that is what we will do in this article. Two different scenarios become possible relevant to the preferred decision strategy. If comparative analysis provides relevant information on the differences between diseases, one type of decision-making strategy is called for. When there are considerable gaps in knowledge, and many identified unknowns, a different strategy suggests itself.

Three types of knowledge premises seem useful in such decision making. The first relates to the qualities of stem-cell-based therapies, especially to their safety and efficacy. The second relates to the characteristics of patients who are candidates for the therapies. We will discuss this premise in the next section. The third relates to the characteristics of the diseases that are intended to be treated by stem-cell-based therapies in FIH trials, including the existence or nonexistence of alternatives. These characteristics will be discussed in the section "Medical and Societal Differences between PD and HD." In the last section, we evaluate the ethical relevance of these knowledge premises for decision making about which patient groups should be asked to participate in FIH trials.

To analyze and concretize these general questions, we will use the examples of PD and HD. These diseases exemplify important medical and societal differences, and research on stem-cell-based therapies for the diseases is being translated from the laboratory to the clinic. The problems raised by FIH trials with stem-cell-based therapies will resemble in several ways FIH with therapies based in other new and emergent technologies. The problems of desperate patients will be similar, for example. But in this decision making, we must be more explicit about our knowledge premises and value assumptions. In the present article, we will focus on quality-of-life issues, discuss the role of health- and non-health related consequences,

the importance of alternative treatments (if any), early versus late-stage arguments, the role of changed facial expression and voice, the disparity of the feelings of patients, and inherent coercion. The approaches used in this article may be applied to similar decision making for other diseases.

WHEN CAN FIH TRIALS BEGIN AND WHAT PATIENT GROUPS SHOULD BE SELECTED?

To answer these questions, we will examine the requirements that stem-cell-based therapies must meet to be tested in FIH trials, and investigate which of these requirements are necessary to start FIH trials.

What Conditions Must Be Fulfilled Before FIH Trials May Begin?

Safety. A necessary condition is safety. Table 1 lists requirements concerning safety and risk management, in biomedical research in general and for stem-cell research in particular, from international guidelines and declarations and from European conventions, directives, and regulations.

Researchers emphasize the importance of safety in FIH trials. Sugarman has argued that it is only acceptable to move to an FIH trial for a cell-based intervention when there is scientific agreement about safety[12] based on preclinical studies. Safety and the possibility of benefit should be reasonably ensured.[13] Precision is important here. It would only be ethically acceptable to proceed with FIH trials if the scientific community agrees on the stability of the existing knowledge regarding safety. Should the scientific community agree that there are many gaps in knowledge regarding safety, the commencement of FIH trials would not be justified. Moreover, safety is not just a scientific issue; there should also be agreement regarding the acceptable level of risk, and such agreement involves value judgments. It is equally important to be precise regarding how many knowledge gaps are "too many." The distinction between "many" and "too many" is also value laden; it is not ethically neutral.

Sound research design is indispensable to ensure safety. Kimmelman and colleagues stress that designing preclinical studies to strengthen internal and external validity and executing them with scientific rigor are "a critical factor in assuring favorable benefit profiles—whether this involves direct, therapeutic benefits or knowledge benefits."[14] Research subjects should not be asked to participate in research of questionable safety; thus, safety is a necessary condition for FIH trials.

Efficacy. Prior to FIH trials, research involving animals must demonstrate proof-of-principle for desired therapeutic effect (that is, it must provide the first proof that the investigational product may work).[15] In this instance, animal research would have to demonstrate that a stem-cell-based approach has sufficient promise to provide substantial improvement in functional deficits that resemble patients' debilitating symptoms.[16] A *substantial improvement in functional deficits* is necessary to justify the risks when there are gaps in knowledge regarding the known and unknown risks of participating in research. In the future, should these gaps in knowledge be eliminated or reduced, less substantial improvement may be acceptable, depending on the given risks. And it is important to consider who decides whether an improvement is *substantial* or not.

Given current knowledge, animal models may not fully predict the safety or efficacy of stem-cell-based therapies. For example, animal models may not fully predict the toxicity of stem cells or their derivatives, the occurrence of immune and other biologic responses, the risk of tumors,[17] and other behavior after implantation in patients.[18] Further, animal models may not mimic all aspects of the pathology of the human condition, which may lead to a lack of efficacy of a stem-cell-derived product in a clinical trial.[19]

Clinical competitiveness. According to the *International Society for Stem Cell Research* (ISSCR) *Guidelines*, "a 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 particular disease, it

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 Clinical Practice;[1] Art. 2, Oviedo Convention[2]	Prevalence of the interests and welfare of the human being over the sole good 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, Oviedo Convention[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 in vitro studies and, when 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

NOTES

1. European Medicines Agency, *CPMP/ICH/135/95, ICH Topic E 6 (R1), Guideline for Good Clinical Practice: Note for Guidance on Good Clinical Practice* (July 2002), *http://www.emea.europa.eu/pdfs/human/ich/013595en.pdf,* accessed 15 March 2010.

2. Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV., 1997), *http://conventions.coe.int/Treaty/Commun/QueVoulezVous.asp?NT=164&CL=ENG*, accessed 12 March 2010

3. World Medical Association, *Declaration of Helsinki* (2008), *http://www.wma.net/e/ethicsunit/helsinki.htm,* accessed 14 March 2010

4. European Parliament and the Council of the European Union, *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use* (2001) *http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf*, accessed 12 March 2010.

5. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: 2002), *http://www.cioms.ch/publications/layout_guide2002.pdf,* accessed 15 March 2010.

6. See note 2 above.

7. International Society for Stem Cell Research, *ISSCR Guidelines for the Clinical Translation of Stem Cells* (3 December 2008), *http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf,* accessed 12 March 2010.

8. European Parliament, R*egulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004* (2007), *http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf,* accessed 14 March 2010.

is necessary to define the requirements for the stem-cell-based approach to be clinically competitive, and to determine what risks are acceptable.[21] For example, to be clinically competitive for 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, for PD patients, a 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 be more cost-effective,[25] or should counteract disease progression.[26]

The potential of stem-cell-based therapies to improve different areas of patients' health-related quality of life (HRQoL) should be taken into consideration when evaluating clinical competitiveness: these would include improvement of patients' emotional reactions, energy, and sleep; and decreased pain and social isolation.[27] Measurement of HRQoL can provide important information on the outcomes following transplantation that are not gained by traditional assessment protocols.[28]

If efficacious therapy is lacking, as in the case of HD, the severity of the disease may justify the potential risks of a stem-cell-based experimental intervention.[29] According to the *ISSCR Guidelines*, certain knowledge gaps may not be seen as a barrier to the 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. Obtaining free and informed consent is one—but not the only—requirement in the context of FIH trials. If scientific knowledge regarding the safety of stem-cell-based therapies is not stable, turning to an FIH trial as a last remedy may cause greater suffering for a patient, especially given the possible irreversibility of a cellular transplant. Similarly, if the scientific community does not agree that the efficacy of stem-cell-based therapy can be reasonably expected, consenting "hopeless" patients into an FIH trial may expose the patients to the additional burden of futile treatment.

Informed consent is essential to respect the values of potential research subjects. According to recommendation 28 (c) of the *ISSCR Guidelines*, subjects should be informed about the source of the cells, to fully respect their values.[31] What could this mean, in practice? For example, should subjects not be informed—if they expressly state that they do not want to know—whether the experimental intervention is based on human embryonic stem cells? On the one hand, one may imagine it might be easier for persons who object to the use of such cells to accept an intervention should they 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 participants' preferences for research-related information. But providing limited or partial information would not meet the requirements for informed consent, for example, the requirements of the U.S. Food and Drug Administration.

Which Patient Groups Should Be Selected to Participate in FIH Trials?

In the testing of most therapies or medications, FIH trials involve healthy volunteers. As mentioned above, the main aim of such trials is usually to test the safety of a treatment, and safety can be best evaluated when research involves healthy humans, 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, the safety of the research subjects must be considered. This 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 (for example, children, pregnant women, other adults), the disease, and the alternatives available.[32] The level of risk and safety of experimental stem-cell-based therapies can be judged by the aspect of risk[33] or by the goal of administering the therapy: that is, is the therapy meant to restore, maintain, or improve a patient's health and quality of life? These goals can be defined in many different ways[34] and are very important in deciding which categories of patients should be asked to participate in FIH trials. These goals will be considered in greater detail in the last section of this article.

Patients at early stages of their disease. Based on the *ISSCR Guidelines'* requirement that stem-cell-based clinical researchers "monitor research subjects for long-term health effects,"[35] the stage of disease is important in deciding which patient groups should be chosen to participate in FIH trials. For example, it is not possible to monitor for long-term health effects when patients who are close to death participate in FIH trials. As Sugarman points out, if healthier patients participate and the intervention proves to be harmful, the subjects may have shortened their lives or harmed their health.[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 could be monitored for long-term effects would be preferable for FIH trials. The efficacy of the administered stem-cell-based treatment may also depend on the stage of the disease, however, 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. Patients who are in the late or final stages of their disease may have the least to lose, but the scientific usefulness of FIH trials might be compromised if patients have a range of other health problems that confound study results.[38] If research is conducted in this population and the research is confounded by other illnesses, therapy that might aid patients who are in earlier stages of the illness may not be developed. 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] Therefore, having "the least to lose" should not be the decisive factor.

Can the stage of disease alone be a decisive factor in determining which groups of patients are selected? 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] These three requirements may pull in different directions. Various stages of a disease may meet the 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 judgment 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 existing alternatives (if any). 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 regarding which group of patients should be included in an FIH trial.

Desperate patients for whom alternative therapies do not work. Desperate patients for whom alternative therapies do not work, independent of the stage of their disease, are another group to consider. 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 *ISSCR 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 such alternatives are inaccessible. According to the *ISSCR 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 being different from the *Declaration of Helsinki's* requirement of comparison with the best proven therapy.

In summary: enrolling patients at earlier stages of their disease is preferable when more (or less) efficacious therapeutic alternatives do not exist or are not locally available, and/or when the successful administration of stem-cell transplants is likely to be in early stage patients. These statements will be re-examined in the last section of this article, in the light of the values that are endorsed by different ethical theories. The next section will outline the factual differences between PD and HD.

MEDICAL AND SOCIETAL DIFFERENCES

"Living with Parkinson's is like living with a thief," said one patient. "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 in the diseases in terms of their impact on the patient, on family caretakers, and on society, but there are also differences. The differences between PD and HD, outlined in this section, in many cases are not unique to the two diseases; other (neurodegenerative) diseases have such differences.

We will only outline the differences relevant to 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.

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 the last section of this article, particularly ethically relevant for deciding which patient groups should be asked 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 has side-effects.[47] Unlike PD, HD is a lethal, incurable disease, with an average duration of 16 years,[48] but this can vary greatly.

Availability of alternative therapies. Pharmaceutical and surgical interventions, as well as rehabilitation and medical nursing, are available to treat PD.[49] 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 assistance.[50] Provision of a full range of supportive medical nursing and social care can help improve a patient's quality of life.[51] Different treatments are available to reduce the severity of some HD symptoms.[52] For a summary of the parameters above, see table 2.

Chances of success of stem-cell-based therapies. This may, in practice, be a decisive factor in deciding whether such therapies should be tested clinically. The importance of proving chances for success is 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] The chances for the 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. 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 the safety of FIH studies, Kimmelman and colleagues argue 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 the efficacy of stem-cell-based therapies.

Even after FIH trials have started, many knowledge gaps will still exist regarding their safety and efficacy. In the course of the trials, it may turn out that stem-cell-based therapies are safe and efficacious, or safe but inefficacious, or 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 must consider all four of these scenarios.

Societal Differences

Psychological effects of the disease on the patient and the patient's family. PD and HD have similar effects on patients' social life, even though the causes of the effects may be 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 is affected by their inability to perform the social activities they formerly enjoyed. Patients' social life can be affected by possible misunderstandings caused by changed facial expression, an inability to express feelings through body language, changed voice for PD-affected patients,[58] and personality changes for HD-affected patients. In both cases, the progression of the disease and the extent of its symptoms can affect not only patients' ability to take an active role in everyday life, but also their desire to take an active role.[59] Patients face difficulties related to symptoms, treatment, and emotions.

For example, one study found that 76 percent of PD patients surveyed had difficulties walking outside their homes to a degree that affected their daily living, and 73 percent reported that maintaining their balance affected

TABLE 2. Examples of medical parameters for PD and HD

	Properties		
Disease	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)

their life (symptoms-related difficulty).[60] The same study found that 77 percent of PD patients planned their day around taking medication[61] (treatment-related difficulty), and that the greater frequency for taking medications caused greater inconvenience.[62] Another study reported that 78 percent of PD patients claimed that feelings of depression or misery affected their participation in life (emotionally related difficulty).[63] Of these, 76 percent experienced difficulty in remembering things, 64 percent had difficulty in getting to sleep, and 92 percent reported that tiredness during the day had an adverse effect on day-to-day living.[64] Feeling depressed or miserable and having difficulty remembering things and thinking things through affected all aspects of their life: social activity, leisure, and work.[65] Yet another factor that was found to contribute to their reduced social life was patients' physical appearance: about 79 percent rated the importance of their physical appearance as very important or moderately important.[66]

The social life of patients with PD may also be affected by communication difficulties in speech, facial expression, 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 lack of understanding.[69] Changes to the function of facial and 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 outbursts of anger, the 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, and dates, and an inability to organize themselves as they did previously; the long time required to perform simple tasks; making mistakes at work; and an inability to concentrate.[72] Before HD is diagnosed, all of these changes may be taken personally by others and may affect personal relationships negatively.[73]

Unlike the case of PD, the psychological effects of HD start *before* the disease manifests itself, and affect even 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 a child or a sibling of an HD patient carries the HD gene. Psychological effects may begin with anxiety regarding a decision to be tested for the HD gene. One HD-affected patient 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. The hereditary nature of HD may contribute to the breakdown of families, as the level of secrecy can become so great it is impossible to discuss the subject within the family.[75]

For those who test positive, fear about the future may lead to depression or to spending excessive time or money on things that one would otherwise focus on moderately. Fear of the future may also lead to self-restrictions; one study found that some people who tested positive for HD avoided getting into situations in which HD might express itself: for example, they gave up driving before they had to.[76]

For those who test negative, the psychological effects may take the form of feelings of guilt for not having inherited the HD gene when other family members test positive. Even HD-affected patients may experience feelings of guilt for having passed HD on to children, knowing that they have inherited the gene. These feelings of guilt may cause abnormal family relations.[77]

Impact of the disease on family caretakers. 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 from the time of diagnosis, and becoming a caretaker can lead to very mixed emotions.[78] At the later stages of PD and HD, patients may require a lot of care, resulting in great emotional and physical burdens for nonprofessional caretakers (such as spouses or children) and can lead to exhaustion,[79] the destruction of life or career plans, and negative effects on health (often due to lack of sleep and

constant stress). One Italian study of PD found that 60 percent of caretakers were spouses/partners, 21 percent were sons or daughters, and 19 percent "others"; 35 percent of the caretakers provided care 24 hours a day.[80]

Although the onset age of PD and HD may vary, HD usually affects individuals when they have many family responsibilities.[81] This means that partners who act as caretakers are often placed in a position of total responsibility, taking on the roles and responsibilities of their partners with their own.[82] Unlike PD, due to the hereditary nature of the disease, HD does not "disappear" with the death of an affected individual, and caretakers may end up caring for more than one generation of sufferers.[83]

Economic consequences of the disease for the patient and the family. PD, especially in the middle and advanced stages, may make it impossible for affected patients to keep their job. For example, one study found that only 17 percent of surveyed PD patients had a job.[84] HD-affected patients are in a similar situation. Families with PD or HD patients usually experience a drop in their standard of living after patients (especially if they had been "breadwinners") developed the disease.[85] Family members who became caretakers often had to give up their job, if they were employed, to provide care for an affected family member.[86] Families may struggle a great deal to make ends meet and may experience feelings of personal restriction that accompany involuntary unemployment.[87] It is important that financial difficulties do not prevent patients from accessing well-designed clinical trials, as emphasized by the *ISSCR Guidelines* (6.2.5) on fair subject selection. Patients' financial status, insurance coverage, or ability to pay should not hinder their access to such trials.

To sum up this section: the findings of the studies mentioned represent our current knowledge about PD and HD, collected in different countries, using different methodologies, at different times, with different levels of representativeness. There may be country-dependent or disease-dependent factors that influenced these findings. For instance, more extreme examples could have been found in the HD population because it is a smaller than the PD-affected population. These findings therefore should be considered as examples.

ETHICAL RELEVANCE OF MEDICAL AND SOCIETAL DIFFERENCES

We now analyze the ethical relevance of these differences. We deliberately refrain from mentioning names of ethical theorists because we are interested in exploring the differences that different ethical theories make in adopting—or arguing for—various decisions made in the described situations. We want to avoid, if possible, discussion of how the work of specific ethical theorists should be interpreted.

Although utilitarianism is not the only ethical theory that considers the consequences of an action as relevant to the ethical evaluation of the action, *only* the value of the consequences are considered in the classical forms of utilitarianism, of which there are several. From a utilitarian viewpoint, *the 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 that would alleviate the symptoms of the disease, for 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 the case of safe but ineffica-

cious experimental therapies. In the early stages of HD, patients may still be active professionally, and if an experimental therapy is administered rather than treatment for alleviation of symptoms, and it proves to be of limited efficacy, such patients may be harmed by the acceleration of their illness, for instance by losing their position 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 could be debated. In that case, an inability to use the usual treatment for alleviation of symptoms due to participation in a trial would be compensated by the efficacy of the stem-cell-based therapy, and the risks posed would need to be evaluated in the light of the risks, as well as in the light of the actual benefit to the patient.

If an experimental treatment turns out to be efficacious and safe for the patients participating in an FIH trial, it is not certain that HD patients in the later stages of their disease—as well as their family caretakers—would benefit from the treatment more than respective patients and family caretakers at an earlier stage of the patients' disease, if they were participating in such a trial. It is not certain because the magnitude of benefit would depend on how "benefit" is defined—for instance, in terms of prolonged life expectancy or in terms of improved life quality for the patient, or improved life quality for a patient's family caretakers. It would 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 patients in earlier or in later stages of HD should be asked to participate in FIH trials. If the limited alternative methods of alleviation of symptoms are not effective for particular patients, those patients could be seen as suitable candidates for FIH trials from a utilitarian perspective.

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

If experimental therapies turn out to be unsafe or efficacious (or both) for PD patients participating in an FIH trial, the therapies would have more negative consequences for PD patients than for HD patients, as PD patients have limited alternative treatments and alternative methods to alleviate symptoms. It could therefore be argued that FIH therapies for PD patients would be justifiable only in cases when alternative therapies are not efficacious for treatment or the alleviation of symptoms.

From a classical utilitarian viewpoint (and 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 the potential to reduce life expectancy. Therapies that turn out to be inefficacious but safe would not decrease the life expectancy of HD patients, as they have no alternative cure. The situation is less clear if such therapies turn out to be unsafe although efficacious, as the total amount of benefit for patients in terms of life expectancy would depend on how unsafe the treatment was, compared to its efficacy. Taking into consideration only the life expectancy of patients, it is not possible to estimate whether patients in earlier stages of HD or in later stages of HD should participate in FIH trials. Similarly, it is difficult to estimate whether patients for whom alternative methods of alleviation of symptoms are inefficacious should participate, as it is not certain that stem-cell-based therapies will increase their life expectancy.

Whether safe and efficacious stem-cell-based therapies would increase the life expectancy of PD patients would depend on how much

safer and more efficacious they would be, compared to other treatments. Considering the life expectancy of PD patients from a utilitarian viewpoint, the administration of such therapies would be acceptable only for PD patients for whom other therapies are not efficacious.

Another important factor, from a utilitarian viewpoint, are the *consequences of the disease for patients and patients' family members*. These consequences may differ, depending on how they are defined and measured; for example, in terms of lost income due to patients' unemployment, lost income due to the involuntary unemployment of family caretakers, expenses for patients' treatment, expenses for care or adaptation of facilities at home, and so on. Unless the definition and measurement problems are solved, it is not possible to estimate whether the administration of an experimental therapy, the safety and efficacy of which must be defined and measured, will reduce the economic consequences of the disease for patients and family members. Therefore it is not possible, given our 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. The economic situations of families of patients who have no efficacious treatment alternatives may improve if an experimental therapy, administered in the context of FIH trials, proves to be efficacious and safe. If the treatment proves to be inefficacious but safe, there could be no expected change in the families' economic situation.

It has to be mentioned, however, that research ethics committees (RECs) and institutional review boards (IRBs) usually do not include economic considerations when evaluating risk and benefit, but some economic aspects may be considered. For example, IRB guidelines intended to assist University of North Texas researchers include, in the risks that researchers must list in their application, the social and economic risks to prospective research subjects, including "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 on the consequences of FIH trials for PD and HD patients. Using a deontological way of thinking, the consequences of FIH trials do not determine their moral rightness. FIH trials are only morally right if they do not violate human rights or dignity.

The care of PD and HD patients often requires a lot of sacrifice on the part of family caretakers. It may be argued, therefore, that at least in some (or even many) cases, family members are "forced" to be caretakers because they have no choice. Their efforts to achieve good outcomes (the care of PD or HD patients) is provided without their consent; even though there is no "forced labor" in a literal sense, in many cases becoming a caretaker (24 hours, seven days a week) is not a matter of personal choice. We might consider that the consent of caretakers is not free if they make the choice because other forms of care are unavailable (too expensive, too far away, or both). It can be argued that advanced forms of PD or HD affect not only the autonomy of patients, but in some (or many) cases, affect the autonomy of family caretakers. Caretakers may have limited autonomy to make decisions that may be "dictated" by their situation. It must also be noted that the contributions to care of patients by their family members may be necessary to protect the patients' human rights, such as the right to life, and in this way the two rights come into conflict.

Successful application of stem-cell-based therapies may not only lead to improvement of the health and quality of life of PD- and HD-affected patients, but may also improve the quality of life (and indirectly, the health) of family caretakers. Efficacious therapies thus have the potential to enhance the autonomy of both patients and family caretakers. However, application of such therapies can only be morally acceptable if the free and informed consent of patients who receive the therapies is obtained. In the later stages of PD or HD, when patients' capacity to provide such consent is limited, an informed proxy decision maker must make the decision. The freedom of such proxy decision making may be questionable when the decision maker is a family member, especially when this

person is also a caretaker. There may be cases when exhausted caretakers see the enrollment of patients in a trial as the last hope for improvement—not only for patients, but also for themselves. In such cases, patients may be used as a means to improve caretakers' quality of life.

If patients' participation in FIH trials can enhance the autonomy of family caretakers, participation may be considered even more appropriate from a human rights perspective. Even if this 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 available, it cannot be argued from a human rights perspective that patients at later stages of their disease would be seen as more suitable candidates for participation in FIH trials.

Considering 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 disease may endanger the human dignity of PD and HD patients in terms of their loss of autonomy due to difficulty in communicating, physical appearance, difficulty of movement, and so on. From the perspective of human dignity-based theories, stem-cell-based therapies would be justified as means to achieve the goal of the least possible infringement of human dignity by the disease. In the case of HD, there are no therapies that prevent patients' eventual loss of autonomy. It could be argued that stem-cell-based therapies would be an acceptable means, in the absence of other more effective means, to prevent loss of autonomy. To sum up, from a human dignity perspective: such therapies would be acceptable in cases when patients' autonomy is lost or becomes very limited due to the psychological or physical (or both) effects of the disease. It should also be noted that, according to one interpretation of human dignity, the protection of dignity should extend also to human embryos and fertilized eggs, if one considers such entities worthy of the same level of protection as human beings who have been born. We have discussed this 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 patients' autonomy.

The psychological effects of the disease on patients and patients' family members, or the impact of the disease on patients' familial caretakers, would also be ethically relevant factors from a utilitarian viewpoint, but for different reasons. At least some forms of utilitarianism would consider these factors in terms of the happiness or unhappiness to which they contribute. However, the "amount" of unhappiness cannot be discussed until there is consensus regarding its definition and measurement.

CONCLUSIONS

The similarities and differences of PD and HD we describe 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 patients and families are important differences, from a utilitarian viewpoint. The difference concerning the impact of the disease on the patients' family caretakers may be particularly important from a human rights perspective. The psychological effects of the disease on patients are important from views based on human dignity, at least to the extent they affect patients' autonomy and human dignity. Despite the focus on different characteristics of the disease, the treatment, or the patients who would be asked to participate in FIH trials, all of 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 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 are (1) how we define and measure the safety of treatment, the efficacy of treatment, health, quality of life, or economic consequences of the disease on patients and patients'

families and the results of applying these definitions and methods of measurements to the diseases compared; and (2) how we define and measure the impact of the safety or efficacy of treatment on patients' health, quality of life, economic situation, life expectancy, or loss or re-acquisition of autonomy, and 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 of alternative methods to alleviate symptoms (in the case of HD) that are the determining factor regarding whether patients should participate in an FIH trial. Patients who have no efficacious alternatives are the most suitable candidates for FIH trials of stem-cell-based therapies, provided that the free and informed consent of the patients (or their legal representatives) has been obtained, and rigorous preclinical research has demonstrated the safety and the efficacy of the desired therapeutic effect of a stem-cell-based therapy.

Thirdly, the ethical guidelines reviewed in table 1 also indicate that it is not the stage of the disease, but rather the efficacy of the therapy that should be one of the factors in decisions regarding which group of patients should be included in an FIH trial. From the perspective of some of the reviewed ethical theories, a precise definition of "efficacy" is crucial to evaluate its importance.

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 for PD and HD. The ethical starting points also need to be made explicit, including positive and negative goals (what is to be achieved and avoided with the FIH trials of treatments for these diseases). Until this is clarified, it is difficult to determine whether the answer to the question analyzed in this article is disease-specific or whether it depends on factors that are common to several diseases.

Topics for further research include empirical and normative issues, for example, the probably considerable individual variations in how families' interests are weighed against patients' interests. This can be the subject of empirical study, 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 include the consideration of prioritizing treatment for those who are worst-off (in senses that need to be made more clear), as well as the lottery argument. That is, 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 could be justified, provided that other conditions in terms of information, consent, and safety are met. It is a different situation if we have reason to believe that patient selection makes a difference in outcome—that stem-cell-based therapies will be more efficacious for some patients than for others. In a lottery, every participant has a fair chance and an 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 for certain patients than others, a lottery would cause scarce resources (in terms of such interventions), to some extent, to be wasted. If we want to optimize the effects of stem-cell-based interventions, we cannot use a lottery approach, but must use these interventions in patient populations in which we have reason to believe that they will be efficacious; and behind "optimization" hides different value premises that must be spelled out, as the details may point to different conclusions.

An interesting possibility, worth an article of its own, would be to examine the history of medicine to see how similar cases in the past were handled, when treatments based on what were then new and emergent technologies were introduced. Which heuristic devices were used to think through these challenges? Analogies

should be used with caution, but something may be learned from them, if the similarities and differences between the examined cases are carefully spelled out.

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