

## Research Report

---

# Challenges to Informed Consent in First-In-Human Trials Involving Novel Treatments: A Case Study of Parkinson's Disease

Kristina Hug\* and Mats Johansson

*Medical Ethics, Department of Clinical Sciences Lund, Faculty of Medicine, Lund University, Lund, Sweden*

Accepted 2 October 2017

**Abstract.** Obtaining informed consent in clinical trials can be challenging both for researchers and for patients, albeit in different ways. The challenge concerns not only *how* to provide the needed information, but also *what* information to focus on when dealing with individual patients who have different goals, needs, histories, etc. This paper aims to contribute to a better informed consent process for Parkinson's patients taking part in first-in-human clinical trials of cell replacement therapies. It outlines a range of problems which patients and researchers may face in this process and provides practical advice to researchers engaged in such trials.

**Keywords:** Parkinson's disease, cell-based therapy, clinical trial, informed consent, autonomy, research ethics

## INTRODUCTION

Informed consent is an indispensable part of all clinical trials. Obtaining truly informed consent can be challenging both for researchers and for patients, albeit in different ways. In this article, we will explore some of the challenges raised by first-in-human trials of cell-based therapies for Parkinson's disease (PD). When such trials are offered to patients, the patients can become confused as they try to grasp information concerning the experimental nature of the treatment, the available alternative therapies, and the extent to which each option is suitable for tackling the problems that PD is causing in their

lives. In addition, cognitive aspects of PD itself potentially present impediments to informed consent [1, 2].

Patients typically considered for inclusion in first-in-human trials involving cell therapies are likely to have had PD and standard treatments for PD for a while, but to have now entered a stage of disease where responses are less predictable and sustained. Standard treatments for PD include levodopa and DA agonists, inhibitors of DA breakdown, which lengthen the duration of action of levodopa or specific anti-dyskinetic agents such as amantadine [3]. However, even with the addition and manipulation of these therapies, problems of adequate motor control still exist and thus patients are next considered for more invasive therapies such as apomorphine pumps, duodopa or deep brain stimulation. It is likely that patients for first-in-human studies involving cell

---

\*Correspondence to: Kristina Hug, Medical Ethics, BMC 112, 22184 Lund, Sweden. Tel.: +46 46 222 47 60; E-mail: Kristina.Hug@med.lu.se.

replacement therapies would be considered for these latter therapies.

The task of informing potential trial participants and ensuring they have understood the information is difficult. According to the Declaration of Helsinki the informed consent process should give special attention to the specific information needs of individual potential subjects (Art. 26) [4]. Hence, the scientist/clinician must consider not only *how* to provide the information so that understanding is improved, but also *what* information to focus on. There are a large number of licensed therapies available for PD and so the rationale and value of experimental therapies has to be explicitly explained and justified.

In this article we outline a range of problems which PD patients and researchers may face in the informed consent process and provide practical advice to those engaged in such trials. Our aim is to identify ways to improve the informed consent process for PD patients taking part in first-in-human clinical trials of cell replacement therapies, although many of the principles explored here are relevant for other novel treatments.

## THE PROBLEM

There are many ways in which *informed* consent can fail. For instance, the patient may underestimate or overestimate the therapeutic options that are *suitable* and *available* in his/her particular case. Patients may also misjudge the *therapeutic potential* or misunderstand scientific evidence available regarding the likely safety and/or efficacy of therapies, and in particular the unknown risks that are implicit in any first-in-human study. Obviously, the recruiting scientist is not accountable for the patient's level of mental competence, but he or she is nonetheless obliged to accurately communicate to the patient the information relevant to the patient's decision-making. A patient who lacks sufficient *capacity* to understand such information cannot provide valid informed consent. In more complicated cases, where the cognitive performance of patients has been impaired, e.g. as a result of extensive medication side effects, but the trial design requires their inclusion, the informed consent procedure needs strong tools to validate that such patients understand and are fully cognizant of the risks and responsibilities associated with participation in a trial.

Ethical guidelines, such as the Declaration of Helsinki [4], the ICH Guideline for Good Clinical

Practice [5] and the CIOMS Ethical Guideline [6], are fairly clear about what information should be given to the patient – namely, the purpose of the trial, what it means to take part in it, the risks of harm, and the chance of benefit, and so on. The real question is not about what *types* of information should be communicated to the patient, but rather about what the information-giving process should focus on, and how to assess that the necessary information has been appropriately and accurately communicated.

It is not easy to cover the particular issues that the patient considers to be especially harmful or beneficial. First, as a result of space limitations in participant information sheets and time constraints during recruitment, some less likely harms or benefits may not even get mentioned. Secondly, one can expect national or even regional differences over what issues consent forms need to address. It is not only that there are differences in national legislation governing consent; the requirements of informed consent are also influenced by the ways in which ethics committees, reviewing research protocols, balance ethical principles. Ethics committees typically apply principles of autonomy, non-maleficence, beneficence and justice when considering research protocols [7]. For instance, it has been argued that “in many countries ethics committees have increasingly focused on the principles of autonomy and non-maleficence” intending “to ensure that research participants are freely choosing to participate and are not harmed by their experience”, and that in view of this the principle of beneficence might be under-valued [7]. In many westernized countries, autonomy has tended to override and devalue the other principles, particularly justice and the needs of the community [8].

Besides these national differences in the law governing informed consent forms, and differing cultures and values at play in ethics committees, there can be differences even at the level of protocol. Depending on the nature of the clinical trial, protocols may differ in the issues they particularly underline or (alternatively) devote less attention to. Discussion of particular clinical trials and particular protocols, however, falls outside the scope of this paper, which addresses first-in-human trials involving irreversible therapies, and which takes cell-based therapies for Parkinson's disease as an illustrative case.

An example will help us to explain the way in which risks and benefits can be individualized. Consider therefore an orchestra conductor who uses one

of his hands for expression and turning the pages of the musical score, while the other hand beats the rhythm. He needs unimpaired dexterity to be able to function as a conductor. He may be less concerned about certain problems with his legs, for instance, as these will not impact on his ability to do his job. So, in this case, even a small and distant risk of losing sensitivity or ability in one of his hands may be a major issue for the patient. (Of course, there may be other significant concerns, unconnected with the patient's work as a conductor; we are using the hand example to illustrate our point.)

The researcher recruiting this patient will not know the details of the conductor's case unless he is told, and needless to say, it is not the researcher's job to decide what goals and preferences are to be taken seriously, since that would amount to unwarranted paternalism. The patient, however, may not always know what questions to ask, especially if he or she is overwhelmed by the amount of information to consider. So we may face a situation where, from a formal perspective, the researcher has provided written information about a clinical trial and answered the questions posed by the patient, but where a discussion about hand function never took place because the focus was on other, much more likely (but for the patient, less important) implications of participation in the trial.

To prevent such problems, or reduce the chance of them arising, clinical studies involving high risk and a high level of medical complexity could combine several different approaches. First, in the recruitment process, researchers could attempt to ensure that recruited patients not only meet the formal requirements for capacity to consent, but also demonstrate the ability to assess harm-benefit ratios in the proposed study. As long as this does not introduce a bias in the study, the informed consent process could be adapted accordingly to a patient's educational level and/or accumulated experience of medical treatment, for instance. In other words, the informed consent process should involve making sure the patient has interpreted the information provided correctly. There exists abundant literature on how to enhance understanding in the consent process.

Second, we suggest that those obtaining informed consent from potential research candidates consider focusing on what *types* of information should be particularly stressed for the patient they are recruiting. For this, we suggest researchers take the steps outlined below.

## HELPING PATIENTS TO MAKE AN INFORMED CHOICE: STEPS TO CONSIDER

Our argument is that the steps below (not necessarily in the presented order) can help PD patients make informed choices about participation in first-in-human clinical trials.

### *Step 1. What are the patient's goals?*

This is a core question to be addressed in the recruitment process. Clearly, the mere fact that a patient fits the trial's inclusion criteria does not mean that the intervention will serve his or her interests. If the orchestra conductor in our example focuses on managing a work situation as one of his main goals, he is likely to attach importance to therapies able to reduce or retard PD symptoms affecting hand dexterity, facial expressions and speech – functions which he needs in his work. To him it also matters how the suggested intervention compares with other alternatives, with respect to the expected effect on these symptoms. Work-related goals are, of course, only a part of what can reasonably be expected to be relevant. Other goals might relate to family-life, spare time activities, etc. However, the conductor's unusual (but to him, significant) work-related needs highlight the importance of unravelling what really matters to the individual patient.

Researchers, clinicians, patients and their relatives may have different perspectives on which harms and benefits are significant and rank their importance differently, whereas it is the patient who is directly concerned by the decision made. One questionnaire study found that while researchers and ethicists focus on the physical aspects of risk, PD patients' understanding of risk went beyond the physical [10]. This research showed that patients were concerned about how their decisions would impact on their family. Indeed, in the context of broader "family network" or financial responsibilities, patients' expectations of symptom relief can have a considerable impact on their decisions to enter the study, or to remain in the study.

It also needs to be recognized that patients receiving novel therapies often find themselves in new roles and new environments. This requires some adjustment on the part of the professionals with whom they are interacting, such as researchers and clinicians [9]. Finding oneself new to both a role and a situation can become an important factor in decision-making.

Patient's goals are what matter primarily in the informed consent process. Obviously, the participant

information texts cannot be sensitive to individual patients' goals, but researchers can and should take up this issue in verbal discussion. Researchers could try applying different strategies to enhance patient's decision-making, such as using decision dashboards [11] or providing a "degree of confidence" scale wherever possible, bearing in mind the knowledge gaps that typify first-in-human trials. These decision-making aids will be especially helpful if they are also applied to alternative treatments, if such are available. Prospective participants can make a more educated decision on the harms and benefits involved in participation in the trial if the same parameters are presented for both experimental and alternative therapies.

Researchers are at risk of being excessively paternalistic in yet another sense, i.e. by focusing too much on the information which they consider to be relevant for the patient's decision-making. Here it should be noted that what goals the patient acknowledges will depend on the information they possess. Had the patient received other pieces of information – information which the researcher now judges as irrelevant considering this patient's goals – he may even have modified or changed his goals. The orchestra conductor may have told the recruiting doctor of his wish to preserve refined use of his hands as much as possible, and so, considering this, the doctor may have focused on risks related to his hands, not mentioning, say, the equally significant risks of reduced walking capacity following the intervention. The latter may be as important to an orchestra conductor as risks to his hands. But he may simply be unaware of such risks and not take this issue up as a consequence. The researcher therefore should not be deciding which information is relevant, and which irrelevant, for the patient. One needs as complete a set of information as one can assemble in order to enable an *informed* choice. Of course, the researcher cannot be expected to fully cover all imaginable risks. Instead, he or she can indicate possible but remote risks and check with the patient if any of these are of special concern, in which case a more detailed discussion of this can be had. Where possible, bearing in mind the knowledge gaps in first-in-human trials, scaling the probability of risk factors could enhance the informedness of the consent.

Finally, it may be important to take up the temporal aspect of risks and benefits in the decision-making process: some PD patients may be less interested in long-term disease modifications and side-effects, and instead want immediate access to the therapeutic benefits. The latter, of course, are not usually a

goal of first-in-human trials [12], as typically such trials focus on the feasibility and tolerability (safety) of the experimental intervention rather than its efficacy. In other words, the goals of the trial and the patient's goals may point in completely different directions, without patients necessarily being aware of this. In a properly performed informed consent process such discrepancies will be captured by recruiting researchers – provided they are aware of patients' goals. The recruiting researcher should be clear about timing, whenever that can be more or less reliably predicted, and communicate his or her understanding of that to the patient. When prediction is not possible, the researcher should at least consider how timing issues are perceived by the patient (or the patient's representatives, if it is from them that consent is being sought) and correct any unrealistic expectations. Misunderstandings about the timing of "end points" or the timing of symptom relief can lead to legal action.

PD patients may not always be familiar with the specific risks of harm potentially involved in invasive first-in-human PD trials targeting the brain. The brain as an organ is very closely related to our personhood [13] and thus "adverse events have the potential to disrupt those features that make us who we are: language, memory, cognition, and identity." [14] Depending on the type of intervention into the brain, as well as the location of intervention, some of these features can be affected, more or less seriously. Such risks can be higher or lower depending on the specific details of each particular trial, and they should be explained by the researchers where relevant.

It is therefore worth asking the patient whether there is something else, besides the already mentioned types of harm and benefit, which the patient would consider potentially harmful or beneficial. For instance, researchers could ask the patient about his or her hobbies, or try to get a sense of the patient's priorities in other ways.

*Step 2. What aspects of therapy does the patient consider important for their decision-making?*

Therapy can have many different aspects – and here we refer not only to cell therapies, but also any other therapies where the questions listed below could be relevant. Some of these aspects are more likely than others to be perceived by patients as advantages or disadvantages. Examples are:

- (a) *Does it matter if the therapy involves an active substance/device?* Some therapies involve the

administration of an active substance (such as a pharmaceutical or cells) or use of a device (such as a tube in the intestine or wires in the brain). Others (such as physiotherapy, speech therapy or occupational therapy) will involve training alone. Devices are more “material” than pharmaceuticals and cells, and they may therefore be perceived as more “invasive”. Some patients will have strong opinions as to “invasive” and “non-invasive” therapies. Discussing this issue may help in decision-making for those who consider that the degree of “invasiveness” matters.

(b) *If cells are used, does their source matter?*

Patients may have strong opinions about which sources of cells used for their treatment are acceptable to them. Some may hold views on the use of embryonic stem cells or fetal cells, or pig xenogeneic tissue; some may prefer autologous cells, where possible, to donor cells. It has been demonstrated in a questionnaire-based study, for instance, that autologous cells were the preferred choice of cell for patients suffering from various diseases, including Parkinson’s [15]. This study showed that “patients have a hierarchy of preferred source of cells for use in tissue-engineered products” and that attitudes toward stem cell therapy “may be influenced by the patient’s disease state”.

(c) *Does the method of administration of the treatment matter?*

If several medical therapies suit a particular patient’s needs, the method of their administration, if different, may be an important factor to consider. Electrodes implanted in the patient’s brain (deep brain stimulation or DBS), fetal cells injected into the brain, and regular infusions of pharmaceutical treatment, may all address the same PD symptoms. However, although the method of administration may not be the only difference between these therapies (e.g. their side-effects may also differ), the route by which they are given could be a major issue for some patients. Some may prefer cell therapy, perceiving it as a “single-event fix” rather than taking tablets regularly or having wires in the brain. Others may prefer wires to “foreign” cells in their brains. Still others may prefer to organize their daily activities around taking pills, rather than have “foreign” objects in their bodies. Preferences may depend on, among other

things, the patient’s goals, lifestyle or beliefs. In studies addressing xenotransplantation, for instance, patients perceived living cells as more natural than mechanical implants, but they also feared that transplants “could transmit nonmaterial substances such as other living beings’ identity or characteristics” [16]. Discussion of the method of administration should therefore form part of the informed consent process, especially when it comes to therapies involving more invasive or complicated methods of administration than just taking a pill.

(d) *Does the reversibility of therapy matter?*

Some therapeutic approaches, such as injecting cells or making lesions in patients’ brains are irreversible. This means that a patient, having once consented to participate in a clinical trial, cannot withdraw from it in the sense of reversing the treatment. Some researchers suggest that “potentially harmful and difficult to reverse interventions should be undertaken only where there is a reasonably high degree of confidence that they offer therapeutic benefit” [14]. It is therefore crucial that the patient, consenting to an irreversible procedure is fully aware of the permanent effect of injected cells or lesions, especially in view of the possibility that this permanent effect will close the door to participation in other clinical trials in the future. In this way, the patient subjected to an irreversible therapy may lose the “chance” of benefiting from future trials of potential interest to him or her. Moreover, irreversible cell therapy would usually imply a long-term follow-up to protect the safety of trial participants and to study the safety and efficacy of the treatment itself. Patients’ compliance with such follow-ups is of the utmost importance for both the patient’s safety and the quality of the trial itself. The patient should be made aware of such potential consequences, and this discussion should definitely be part of the consent process, where relevant. With the research participant’s right to withdraw from the study at any time, on the one hand, and the utmost importance of compliance with the long-term follow-up, on the other, this is a complicated issue. It merits closer examination and thorough analysis. We have addressed the issues in another paper [17], and therefore will not take them up here.

*Step 3. How proven is the experimental treatment in this trial?*

Invasive first-in-human trials to treat PD “present significant surgical risks, and high degrees of uncertainty about intervention risks and biological effects” [14]. Uncertainty can relate to the investigational agent, the delivery process or both. Uncertainties and knowledge gaps in first-in-human clinical trials make it difficult to assess risks and benefits in these trials, which in turn complicates the consent process. It is difficult to be precise about safety or possible efficacy; about the magnitude and/or likelihood of potential risks associated with the experimental treatment; about the time needed to reach the desired outcome; and about the extent to which the therapy is clinically competitive with existing alternatives. When precision is not possible, researchers tend to use terms such as “likely” or “unlikely”, “great” or “low”. However, these terms can be interpreted by patients in all manner of ways. Instead of using such general terms, researchers could instead focus on issues such as:

- What endpoints of a given therapy have been studied in animals? Some things, such as higher brain functions including cognition are difficult to model preclinically [14]. The high uncertainty present in invasive first-in-human trials for PD, some researchers suggest, has led to a presumption that risks in these trials exceed the numeric “best-estimates” provided by preclinical studies [14].
- What endpoints of this therapy have been studied in humans (if any) in previous trials of a similar nature?
- What were the results in those studies?
- Is there something that researchers wish they knew, but they do not yet know today?
- What exactly is experimental about the administered treatment?

In the face of uncertainty, coverage of these and similar points may give patients a better understanding of the experimental therapy and thus help them to make informed decisions. For those patients who wish to receive more extensive information, researchers can make a full disclosure of all pre-study data. If a particular patient lacks the competence to review and understand such data, a third party, approved by the patient, could help to review the relevant data available from preclinical studies. Realistically, in many cases difficulties will probably arise: patients will be unable to review the data them-

selves or find it hard to obtain help from a third party who is competent to undertake the necessary review. Alternatively, therefore, researchers could make a summary of pre-clinical data which is adapted for public outreach and thus more accessible to patients and/or their representatives.

*Step 4. What are the alternatives for this particular patient?*

Consent cannot be informed unless the patient understands how the experimental therapy compares with the therapeutic alternatives available now as well as those that will be available in the foreseeable future. One should also bear in mind that certain patients may also benefit from physiotherapy, occupational therapy or speech therapy in addition to the standard pre-existing treatments such as therapies they are being offered in the trial. The patient should know what these other types of therapy can do for them, and that participation in a clinical trial may prevent them from using such therapies for the duration of the trial. It is not certain, however, that every patient is being made aware of all relevant alternatives at the moment he or she is considering participation in a first-in-human trial. The researcher could therefore obtain a statement from the patient’s treating neurologist covering relevant alternative treatments and their future availability if the patient participates in the trial. That statement could be a routine part of informed consent process.

*Step 5. What does withdrawal from the study imply in practice?*

According to standard requirements set out in most ethical guidelines, research participants can withdraw from a study at any time, for any reason and without fear of that compromising their medical care. In connection with this right to withdraw, certain practical issues need to be communicated during the consent process. If the effect of the administered therapy is irreversible, the patient needs to know what withdrawal from the study will imply in practice. For instance, what will happen to data collected about this patient during the study? Will it be destroyed? Will it be made untraceable? If biological samples have been collected for research purposes, what will happen to them? At what point are the data (or biological samples) collected during the trial destroyed or made unidentifiable – e.g. after researchers have used them in an aggregated analysis, or in a report? What is the “point of no return” regarding biological samples? This information would not only enable patients

to make an informed decision, but also help to avoid misunderstandings in case of actual withdrawal.

## CONCLUSIONS

Attention to the steps suggested in this paper ought to help researchers to offer a more fully informed choice to patients enrolling in first-in-human experimental trials. In particular, understanding patients' motives and goals, as well as preferences vis-à-vis the method of administration and the level of evidence available about a particular treatment, should ensure that a better-informed consent procedure is undertaken. Throughout the paper, in referring to informed consent, we have in principle meant written information handed out for trial participants (participant information sheets) and verbal discussions with the recruiting researchers or trial doctors and nurses. However, some of the issues mentioned in the five steps presented above could also be taken up in the study homepage – for instance, the information on how proven the treatment is, what exact substances or procedures it entails, and similar information of more general nature.

There are limitations to our study. First, it may not be relevant to all PD patients, or applicable at all stages of PD. However, it is hoped it can nonetheless facilitate decision-making in many cases. Secondly, it may not be an issue for some first-in-human trials. Thirdly, we have conducted a prospective study of these issues in first-in-human trials using cell transplants in PD, so we cannot validate what we have proposed. Finally, our analysis has addressed cases where it is possible to obtain informed consent, i.e. cases where potential participants in a trial possess decision-making capacity. In this sense, the analysis harmonizes with many contemporary guidelines, which suggest that whenever research can be conducted by enrolling persons capable of giving informed consent, potential participants who lack such a capacity should not be enrolled. Of course, the line between individuals with decision-making capacity and those without it is not always clear. Grey zones can be complex – for example, when medicines taken by a patient with capacity will affect their perception of risk. Further research is needed to address these important issues, especially in the context of informed consent.

The suggestions made in this paper explore *additional* aspects of informed consent that are of particular importance for PD patients consider-

ing participation in first-in-human trials involving cell replacement therapies. As such they should not be regarded as replacements for the standard requirements on research participant information outlined in various regulatory and ethical guidelines.

## ACKNOWLEDGMENTS

This work has been supported by funding through Swedish Research Council-financed research projects K2012-99X-22324-01-5 and Dnr 2012-723. The authors express their gratitude to G Hermerén and R Barker as well as two anonymous referees for valuable comments.

## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

## REFERENCES

- [1] Ford PJ (2009) Vulnerable brains: Research ethics and neurosurgical patients. *J Law Med Ethics*, **37**, 73-82.
- [2] Kubu CS, & Ford PJ (2007) Ethics in the clinical application of neural implants. *Camb Q Healthc Ethics*, **16**, 317-321.
- [3] Buttery PC, & Barker RA (2014) Treating Parkinson's disease in the 21st century: Can stem cell transplantation compete? *J Comp Neurol*, **522**, 2802-2816.
- [4] World Medical Association (2013) Declaration of Helsinki. <http://www.wma.net/en/30publications/10policies/b3/>, Accessed March 24, 2017.
- [5] International Conference of Harmonization. ICH Guideline for Good Clinical Practice E6 (R1). 1996. [https://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf), Accessed July 13, 2017.
- [6] The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) – International Ethical Guideline for Biomedical Research Involving Human Subjects. 2002. [https://cioms.ch/wp-content/uploads/2016/08/International\\_Ethical\\_Guidelines\\_for\\_Biomedical\\_Research\\_Involving\\_Human\\_Subjects.pdf](https://cioms.ch/wp-content/uploads/2016/08/International_Ethical_Guidelines_for_Biomedical_Research_Involving_Human_Subjects.pdf), Accessed July 13, 2017.
- [7] Goodyear-Smith F, Lobb B, Davies G, Nachson I, & See-lau SM (2002) International variation in ethics committee requirements: Comparisons across five Westernised nations. *BMC Med Ethics*, **3**, 2.
- [8] Childress J (1990) The place of autonomy in bioethics. *Hastings Cent Rep*, **20**, 12-17.
- [9] King IM (1999) A theory of goal attainment: Philosophical and ethical implications. *Nurs Sci Q*, **12**, 292-296.
- [10] Finder SG, Bliton MJ, Gill CE, Davis TL, Konrad PE, & Charles PD (2012) Potential subjects' responses to an ethics questionnaire in a phase I study of deep brain stimulation in early Parkinson's disease. *J Clin Ethics*, **23**, 207-216.
- [11] Dolan JG, & Veazie PJ (2015) Balance sheets versus decision dashboards to support patient treatment choices: A comparative analysis. *Patient*, **8**, 499-505.

- [12] Yee KM, & Ford PJ (2012) Regulatory misconception muddies the ethical waters: Challenges to a qualitative study. *J Clin Ethics*, **23**, 217-220.
- [13] Echarte LE, & Garcia-Valdecasas M (2014) Identity and conflicts in the ethics of neural implants. *Cuad Bioet*, **25**, 415-425.
- [14] Kimmelman J, London AJ, Ravina B, Ramsay T, Bernstein M, Fine A, Stahnisch FW, & Emborg ME (2009) Launching invasive, first-in-human trials against Parkinson's disease: Ethical considerations. *Mov Disord*, **24**, 1893-1901.
- [15] Clover AJP, Lane O'Neill B, & Kumar AHS (2012) Analysis of attitudes toward the source of progenitor cells in tissue-engineered products for use in burns compared with other states. *Wound Repair Regen*, **20**, 311-316.
- [16] Lundin S, & Widner H (2000) Attitudes to xenotransplantation: Interviews with patients suffering from Parkinson's disease focusing on the conception of risk. *Transplant Proc*, **32**, 1175-1176.
- [17] Hug K, & Johansson M (2017) The ethics of withdrawal: The case of follow-up from first-in-human clinical trials. *Regen Med*, **12**, 25-36.