Towards guidelines for informed consent for prospective stem cell research

J Greenberg,[1] PhD; **D C Smith**,[1] PhD; **R J Burman**,[2] BSc Hons; **R Ballo**,[3] PhD; **S H Kidson**,[3] PhD

[1] *Division of Human Genetics, Department of Pathology, Faculty of Health Sciences, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa*
[2] *MRC/UCT Receptor Biology Unit, Division of Medical Biochemistry, Department of Integrated Biomedical Sciences, Faculty of Health Sciences, University of Cape Town, South Africa*
[3] *Division of Cell Biology, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa*

Corresponding author: *J Greenberg (Jacquie.greenberg@uct.ac.za)*

Stem cell science is advancing at an unprecedented rate, with thousands of research papers being published every year and many clinical trials for a wide range of conditions underway as registered on ClinicalTrials.gov. This rapidly expanding and alluring field has brought with it ever more complex and multifaceted ethical issues, many of which require new guidelines, consent protocols and even change in legislation, since they do not fit comfortably in the existing bioethical regulations and protocols. Keeping up with the ethical implications of stem cell research is daunting to the expert and non-expert. We review the various types of stem cells and then focus on multipotent and pluripotent cell types, since it is these cell types that bring with them the greatest research and therapeutic potential, while concurrently delivering novel ethical conundrums. Certain key considerations are currently lacking and what is needed is how to obtain permission from individuals who donate their biological material for both scientific inquiry and eventually, for their potential therapeutic utility.

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Stem cells have been classified broadly into three categories:

- Adult stem cells
- Multipotent mesenchymal stem cells
- Pluripotent stem cells, including embryonic stem (ES) cells and induced pluripotent stem cells (iPSCs).

Skin epidermal cells (keratinocytes) are a typical example of adult stem cells; they can be harvested from donor skin samples, cultured *in vitro* and used for research or for treatment, such as for burns. These unipotent adult cells can only be grown into skin cells and are covered in current consent protocols. In contrast, mesenchymal stem cells can be obtained from a variety of tissues, including bone marrow, umbilical cord, fetal and adipose tissues. Bone marrow cells have been used for treating haematological conditions for over 70 years. The transplanted cells home into and populate the recipient's bone marrow and when successful, differentiate into all the blood cell types. Many studies have shown these cells to differentiate into several different cells types in culture, including adipocytes, chondrocytes and osteoblasts.[1] Mesenchyme stem cells also seem to have the ability to modulate inflammatory reactions, and are being used in treatment trials for pathologies resulting from, for example, lung injury, myocardial infarction, diabetes, sepsis and stroke.[2]

Pluripotent stem cells are capable, at least *in vitro*, of differentiating into all the types of cells in the body. However, the ability of pluripotent cells to become a part of a fully functional normal tissue remains to be proven, though many animal studies and some human studies provide exciting prospects.[3] Human embryonic stem (hES) cells obtained from the inner cell mass of the blastocyst can be considered as the 'gold standard' of pluripotency, but because embryos must be destroyed to obtain these cells, the harvesting and use of hES cells is limited by their availability and is constrained and regulated by complex ethical and moral issues.[4] The stem cell community was therefore greatly excited when, in 2006, Takahashi and Yamanaka showed that it was possible to 'reprogramme' fully mature differentiated cells back into pluripotency by the addition of genes that reactivate the embryonic genetic programme.[5,6] We, and many groups around the world, immediately saw the potential of these cells to study development and have established 'disease-in-the-dish' models to help elucidate the cellular aetiology of diseases and for patient-specific drug-testing studies.[7] With the rapid exploration of iPSC technology and the burgeoning research output, it is not surprising that the first trial of iPSC for the treatment of age-related macular degeneration is underway.[8] However, the rise of iPSC technology has brought into focus many new ethical questions that must be addressed and resolved.

Ethics

Medical research involving human subjects or human biological material should be designed to promote the best interests of the study participants. Disclosure of research protocols which affect the participant directly and in some instances, indirectly, is non-negotiable and should be communicated to participants in such a manner that they have no uncertainties about their rights in the study. The methods of conveying this information to participants are open to much debate and the World Medical Association (WMA) has developed the declaration of Helsinki (DoH) as a statement of ethical principles which should govern medical research on human subjects and identifiable human biological material.[9] Although primarily addressing physicians, the DoH policy is widely used by scientific

researchers and underpins the informed consent (IC) requirement for ethical approval by Human Research Ethics Committees (HRECs) at academic institutions.

In South Africa (SA), we propose that IC guidelines for stem cell research should attempt to cover all the aspects in the DoH. This should take into account the local challenges resulting from the diversity of culture, religion and socioeconomic status of the subjects in SA and in Africa. However, regardless of how carefully the IC is worded, the implementation of the recommendations of the DoH relies on the researchers' truthfulness, humanity, respect for others and sensitivity to social and cultural issues. Without a continuous audit of the study progress and of the researchers' adherence to the IC commitment, ethical deviations may escalate.

Consent guidelines

Whether or not one agrees that individual consent is warranted for any cell type derived from a patient's sample, a more fundamental issue revolves around the patient's competency in making the decision to allow for the use of their biological material. Stem cells pose challenges that the standardised IC documents for collection of blood and DNA often do not address. A case in point is the generation of iPSCs with their potential to become any cell type in the body and therefore the long-term potential use for these cells in clinical translational studies in the future.[5,6] It is almost impossible to provide accurate information about the path that iPSCs will traverse in their lifetime, given the rapid advances in this field.[10] However, when conveying information to study participants, efforts should be made to be explicit regarding current controversial issues in this regard. For example, it should be stated that germ line cell derivatives and reproductive applications will not be attempted or developed with the generated iPSCs, and one should provide the reassurance that current legislation prohibits certain uses of biological samples, such as the reproductive cloning of humans (National Health Act 61/2003: 57(1)). In SA, with its social challenges and significant rate of illiteracy, how does one convey information to a layperson about the reprogramming of somatic cells back to their embryonic state? We believe that the emphasis must be on ensuring that the relevant information is imparted in a clear and simple manner and in the appropriate language. Innovative ways of communication may be required. Moreover, it is noteworthy that in Japan, the Japanese Minister of Health, Labour and Welfare has initiated a 'new five-year clinical trial activation plan' running role-play workshops on IC to boost public understanding of clinical trials with stem cells (see Kusenose *et al*. in this edition).

The University of Cape Town (UCT), Human Research Ethics Committee (HREC) has the following recommendations for IC during the collection and storage of biological material from human subjects and recommends the use of videotapes, photographs or diagrams of research procedures, pre-visits to the research site to see equipment, group discussions, web sites and comics that explain the nature of the research where applicable; as well as brochures and guidance on participants' rights in research (see the UCT FHS HREC website re human ethics standard operating procedures).

As stem cell research is so complex, it may be difficult for patients to comprehend what exactly scientists are attempting to

Table 1. Issues to address when compiling informed consent forms for stem cell related research (based on recommendations by Lowenthal *et al*.[13] 2012)

Point	Details
Purpose of the study	Give a description of the study. This may be detailed if the samples are intended for a specific project, or broader in the case of a larger undefined study.
What are iPSCs/ mesenchymal stem cells/haematopoietic stem cells/adult stem cells?	Provide a simple explanation of the type of cell that will be obtained, and a description of the potential uses of the cell type (for example, disease modelling and drug testing).
Details of participation	Describe what type of donation will be required (skin biopsy, blood sample, hair sample, cord blood).
Collection of medical/ clinical information	Outline what medical information will be requested from the individual, such as age, sex, family history of disease.
Number and frequency of visits required	State whether a single sample will be donated in one visit, or if multiple samples will be collected over a period.
Re-contact	State whether the participant may be re-contacted in the future to obtain additional consent for future projects, to update the participant on the progress of the research, or to obtain additional health-related information.
Limitations on use of cells	Describe the limitations of the use of the donated cells. It may be useful to state that all research will comply with applicable federal and institutional laws and policies.
Risks	Outline any risks associated with the applicable medical procedure (skin biopsy or blood donation, etc).
Confidentiality	Describe the plans and policies in place to protect the confidentiality of the donor, such as password-protected databases, coding, and restricted access to lab areas.
Benefits	Will there be direct benefit to the donor or their family, or simply to the scientific community?
Options	State that participation is voluntary.
Amendments to consent	Describe what options the donors have if they change their mind. Can the sample be withdrawn? Can the material be de-linked from the donor?
Payment	State whether the participant will be compensated for their participation. You may wish to include a clause about financial compensation regarding any future commercial products.
Problems or questions	Provide the details of a person and/or group whom the donor may contact if they have any further questions or concerns.

do with a developing technology, which is still often in the unknown. Therefore, there is now an urgent need for professionally trained staff in SA, who are able to objectively explain the risks and benefits of stem cell research to study participants and highlight the value of their possible future participation in clinical trials. These trained experts could be described as stem cell counsellors who could help potential participants navigate through trials; explain risks, benefits, and therapeutic alternatives; and provide information about unproven transplants offered outside the bounds of good clinical practice and ethical research. They would also need to work closely with patients enrolled in clinical trials and serve as a public resource for patient education, advocacy and outreach efforts.[11]

The reason is that despite the dramatic development of gene- and stem cell-based therapies in ophthalmology, for example, there are still major concerns that need to be addressed concerning the promise and pitfalls of communicating these facts to patients as the clinical research progresses. At present they could, at best, represent a treatment but not a cure and are, as yet, certainly not 'risk-free'.[12]

The generation of iPSCs has great potential for future research and the scope and extent of their use is limitless. However, it is impossible to anticipate the full range of their future application. Therefore, regarding prospective collection of biological material for future research of this nature, we propose that the consent form should be used prudently to assure participants of the ethical use and governance of their specimens in SA, as was proposed by Lowenthal *et al*.[13] Some guidelines should be formulated for an ethical approach to obtaining comprehensive IC for the collection of biological material for the generation of iPSCs for prospective research purposes. Broadly, the recommended issues to be addressed in IC forms, incorporating requirements for stem cell research, are given in Table 1.

The approach to obtaining IC for stem cell research may be considered as a spectrum. On the one end, consent may be obtained for a broad, open-ended study, which requires a single interaction with the research participant. While this type of consent may be facilitative for future research purposes, it can be questioned whether this truly embodies 'informed' consent, since the full extent of future stem cell research potential cannot be predicted. The narrow approach to IC can be considered to lie on the other end of the spectrum, where participants give consent for their material to be used for a very specific purpose. Lowenthal et al[13] suggest that an IC 'middle ground' can be reached, which allows for broad aims, but with clear boundaries with regard to future research. This approach relies on a constant dialogue with participants, and re-consenting may be required in some cases. Institutions may also consider a tiered approach to consent, which uses an opt-in or -out system that allows participants to tailor their consent, but would require added oversight and monitoring regarding the use of individual cell lines. There is the also the question of unlimited use of de-identified samples for research purposes that needs to be considered.[14] The issue of privacy and confidentiality is a major area of concern to potential research participants, given that true de-identification of biological material and/or data is not always possible, since a small number of genetic variants can uniquely identify the donor. The protection and respect of research participants' privacy is of paramount importance.[14]

In 2009 Aalto-Setälä and colleagues discussed that the development of iPSCs had reshaped and revolutionised the scientific and political arenas of stem cell research.[15] They proposed that iPSCs had provided many novel scientific opportunities to study the pathophysiology of diseases that had hitherto been impossible. iPSCs have enabled scientists to understand more about stem cell biology, identify new therapeutic targets and facilitated the testing of novel therapies *in vitro*. Therefore a wait-and-see approach to the therapeutic use of iPSCs is proposed. In SA the focus should fall on the use of iPSCs as disease-in-a-dish models, and that for now we must determine their efficacy and safety by using them as pre-clinical cellular models. This time should be used constructively and productively to possibly develop prospective policies for the use of iPSCs for therapeutic transplantation in the future and also to address the scientific, legal and ethical implications of establishing and using iPSCs in the laboratory.[10]

For SA to continue to develop the capacity to incorporate new biomedical technologies, it must become proactive in formulating clear guidelines for the oversight of IC for future anticipated and as yet, unanticipated use of multipotent and pluripotent stem cells in research.

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