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Guidelines for the Clinical Translation of Stem Cells

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Preface

The Guidelines for the Clinical Translation of Stem Cells (hereafter Guidelines) highlight the scientific, clinical, regulatory, ethical, and social issues that should be addressed so that basic stem cell research is responsibly translated into appropriate clinical applications for treating patients. The Guidelines offer recommendations founded on general principles for scientific, clinical, and ethical conduct that should be followed by all translational stem cell researchers, clinician-scientists, and regulators in the international community.

The Guidelines pertain to clinical translational research involving products from human embryonic or other pluripotent stem cells, novel applications of fetal or somatic (adult) stem cells, and hematopoietic or other stem cells used for applications outside established standards of care. The Guidelines address three major areas of translational stem cell research: (a) cell processing and manufacture; (b) preclinical studies; and (c) clinical research. The Guidelines also address issues of social justice as they relate to translational stem cell research and access to such research and clinically established stem cell-based therapies. Detailed technical information and links to resources are available for scientists, regulators, policy makers, and patients in the Appendices.

The Guidelines were developed by the Task Force for the Clinical Translation of Stem Cells, a multidisciplinary group of stem cell researchers, clinicians, ethicists, and regulatory officials from 13 countries.

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1. Introduction

Stem cell research holds tremendous promise for the development of novel therapies for many serious diseases and injuries. While stem cell-based treatments have been established as a clinical standard of care for some conditions, such as hematopoietic stem cell transplants for leukemia and epithelial stem cell-based treatments for burns and corneal disorders, the scope of potential stem cell-based therapies has expanded in recent years due to advances in stem cell research.

At the same time, the scale of media coverage for early-stage stem cell research has raised the hopes of many patients afflicted with currently incurable diseases and disabling conditions. Those involved with testing novel stem cell-based interventions should be keenly aware that patients may bring unrealistic expectations to clinical trials of experimental therapies.

The public, too, should recognize that in all areas of medicine, the maturation of an early-phase, experimental intervention into an accepted standard of medical practice is a long and complex process usually involving many years of rigorous preclinical and clinical testing and many setbacks and failures. Only with time and experience do most new clinical treatments come to be accepted by medical professionals.

Attempts to develop a stem cell-based intervention into an accepted standard of medical practice are particularly difficult processes for the following reasons.

- Stem cells and their direct derivatives represent, in most cases, an entirely novel product, requiring that investigators assist in the design and development of both the manufacturing process and the assays that assure the safety, purity, stability, and potency of the final product.

- Stem cell self-renewal and differentiation are difficult to control, leading to long experiments with unavoidable heterogeneity in results.

- Animal models of many diseases do not accurately reflect the human disease and toxicological studies in animals are sometimes poor at predicting toxicity in humans.

- Transplantation studies where human cells are implanted in animals cannot provide full prediction of immune or other biologic responses to human cells in patients.

- Stem cells and their derivatives may act on several targets and exert both beneficial and detrimental effects, most notably, the risk of ectopic tissue and tumor formation. Thus, preclinical evidence of safety is of utmost importance.

- Cellular transplants may persist for many years in patients, or their actions may be irreversible, thus necessitating careful patient monitoring and extended follow-up.

- Stem cells may be harvested from donors of different ages, sexes, and ethnicities, bearing different molecular signatures. The standardization of donation procedures and the establishment of rigorous quality control for harvested somatic (adult) stem cells have only just commenced.

Such considerations underscore the need for independent expert peer review prior to clinical investigation to ensure the integrity of the research and informed consent processes.

2. Position on Unproven Commercial Stem Cell Interventions

The ISSCR recognizes an urgent need to address the problem of unproven stem cell interventions being marketed directly to patients. Numerous clinics around the world are exploiting patients' hopes by purporting to offer new and effective stem cell therapies for seriously ill patients, typically for large sums of money and without credible scientific rationale, transparency, oversight, or patient protections. The ISSCR is deeply concerned about the potential physical, psychological, and financial harm to patients who pursue unproven stem cell-based "therapies" and the general lack of scientific transparency and professional accountability of those engaged in these activities.

The marketing of unproven stem cell interventions is especially worrisome in cases where patients with severe diseases or injuries travel across borders to seek treatments purported to be stem cell-based "therapies" or "cures" that fall outside the realm of standard medical practice. Patients seeking medical services abroad may be especially vulnerable because of insufficient local regulation and oversight of host clinics. Some locales may further lack a system for medical negligence claims, and there may be less accountability for the continued care of foreign patients. To help address some of these concerns, the

ISSCR offers a patient guide in Appendix 1 to help individuals and their doctors make informed choices when contemplating a stem cell-based intervention either locally or abroad.

The ISSCR recognizes a distinction between the commercial purveyance of unproven stem cell interventions and legitimate attempts at medical innovation outside the context of a formal clinical trial. Responsible clinician-scientists may have an interest in providing medically innovative care to a few patients using stem cells or their derivatives prior to proceeding to a formal clinical trial. In these circumstances, the ISSCR strongly recommends that clinician-scientists follow the policy outlined below in Section 7, Stem Cell-Based Medical Innovation.

In all other circumstances, the ISSCR condemns the administration of unproven uses of stem cells or their direct derivatives to a large series of patients outside of a clinical trial, particularly when patients are charged for such services. Scientists and clinicians should not participate in such activities as a matter of professional ethics. Health care institutions and research institutions should not participate in such activities. Regulators in countries where such illegitimate therapies are offered have a responsibility to prevent exploitation of patients and, if necessary, to close fraudulent clinics and to take disciplinary action against the clinicians involved.

The ISSCR recognizes the value of having separate jurisdictions provide their own regulations covering medical innovations using stem cells or their direct derivatives and strongly recommends the creation of such regulations through consultation with expert scientists, clinicians, and ethicists. Clinician-scientists and their institutions have a duty to follow local regulations or laws, whenever they exist.

3. Responsibility for Conduct

Given the wide variety of stem cell-based interventions that may be developed, the Guidelines cannot address in detail each conceivable research proposal. Researchers, regulators, and members of institutional bodies reviewing stem cell-based translational research proposals must therefore use their best professional judgment about how to apply the Guidelines to specific protocols. What follows are core principles identified by the ISSCR Task Force for the Clinical Translation of Stem Cells and offered in the form of recommendations.

Recommendation 1: Institutions where preclinical or clinical research involving stem cells or their direct derivatives is performed should take efforts to ensure that investigators are aware of these Guidelines and other relevant policies and regulations and put them into practice.

While there is a need for meticulous oversight of all varieties of clinical research, clinical investigations using stem cell-based products raise unique issues that require specialized scientific expertise and a rigorous scientific and ethical review. Supplementary expertise in the scientific or ethical issues pertinent to stem cells might, for example, be accessed through consultation with stem cell research oversight (SCRO) committees.

Recommendation 2: Human subjects review committees must review clinical research involving (a) products from human embryonic or other pluripotent stem cells; (b) novel applications of fetal or somatic (adult) stem cells; and (c) hematopoietic or other stem cells used for applications outside established standards of care. The human subjects review of stem cell-based clinical protocols must enlist stem cell-specific scientific and ethical expertise. The ISSCR does not anticipate that stem cell research oversight committees will be required to conduct a separate review, although some members of stem cell research oversight committees may be used as consultants to the human subjects review process.

Given the novelty and unpredictability of early stem cell-based clinical research, it is of utmost importance that the peer review process be conducted with the highest possible rigor and integrity. Institutional human subjects review committees are ultimately responsible for review of clinical trials with stem cell-based products, and thus to ensure the highest degree of scientific rigor in the review, should enlist experts in the review process, and where applicable, work in conjunction with stem cell research oversight committees (or their independent equivalents), animal care and use committees, biosafety boards, and any other relevant regulatory bodies to conduct a coordinated review of all aspects of the proposed research. In locales without stem cell expertise, the ISSCR will help identify appropriate domain experts to assist in the human subjects review process.

Regardless of the recommendations encompassed in this document, scientists and clinicians should comply with local policies and adhere to local, national, and

international guidelines relevant to research. Scientists and clinicians must also be guided by principles articulated in documents that have become part of the international heritage of research ethics (Appendix 2.1).

4. Cell Processing and Manufacture

The majority of stem cells and their derivatives represent novel products with which scientists and clinicians have little experience in human patients. Cell-based products present new and potentially unknown challenges in their processing and manufacture. Given the variety of different potential cell products, these Guidelines emphasize that cell processing and manufacture of any product be conducted under scrupulous, expert, and independent review and oversight, to ensure as much as possible the quality and safety of the cells. All of the possible standard operating procedures for cell processing are not yet delineated. In addition, distinct principles pertain depending upon the extent of manipulation of the cells prior to use in patients. Typically, minimally manipulated products (commonly defined as cells maintained in culture under non-proliferating conditions for short periods of time, normally less than 48 hours) require less burdensome characterization and control than cell products subjected to extensive manipulations *ex vivo.* Also, distinct principles pertain depending upon the source of cells (autologous versus allogeneic), their differentiation potential (unipotent versus multipotent), their intended use (for homologous versus non-homologous functions), their persistence in the patient, and the integration of cells into tissues or organs (versus, for example, encapsulation).

Many countries have established regulations that govern the transfer of cells into patients (Appendix 2.2). Given the unique proliferative and regenerative nature of stem cells and their progeny and the uncertainties inherent in the use of this therapeutic modality, stem cell-based therapies present regulatory authorities with unique challenges that may not have been anticipated within the existing framework or regulations. The following recommendations involve general considerations for cell processing and manufacture. Technical details pertaining to cell sourcing, manufacture, standardization, storage, and tracking can be found in Appendix 3.

4.1 Sourcing Material

Scientists and clinicians conducting human stem cell research must ensure that human biological materials are procured in a manner according to globally accepted principles of research ethics. Cells for therapy should be procured under guidelines regulating the procurement of human blood, tissues, and organs with additional considerations specific to the derivation of human embryonic stem cells (hESCs) (Appendix 2.3). Especially pertinent are the considerations outlined in the following recommendation.

Recommendation 3: In the case of donation for allogeneic use, the donor should give written informed consent that covers, where applicable, the following issues:

(a) that cells and/or cell lines may be subject to storage. If possible, duration of storage should be specified;

(b) that the donor may (or may not) be approached in the future to seek additional consent for new uses, or to request additional material (blood or other clinical samples) or information;

(c) that the donor will be screened for infectious and possibly genetic diseases;

(d) that the donated cells may be subject to genetic modification by the investigator;

(e) that with the exception of directed altruistic donation, the donation is made without restrictions regarding the choice of the recipient of the transplanted cells;

(f) disclosure of medical and other relevant information that will be retained, and the specific steps that will be taken to protect donor privacy and confidentiality of retained information, including the date at which donor information will be destroyed, if applicable;

(g) explanation of what types of genomic analyses (if any) will be performed and how genomic information will be handled; and

(h) disclosure that any resulting cells, lines or other stem cell-derived products may have commercial potential, and whether any commercial and intellectual property rights will reside with the institution conducting the research.

The initial procurement of tissue from a human donor may not require Good Manufacturing Practice (GMP) certification, depending on the jurisdiction (Appendix 2.4), but should always be conducted using sterile techniques and universal precautions to minimize the risks of contamination, infection, and pathogen transmission.

Recommendation 4: Donors must be screened for infectious diseases, as is done for blood and solid organ donation, and for genetic diseases as appropriate.

4.1.1 Variability in Source. Unlike chemicals or recombinant protein products that can be manufactured to high degrees of homogeneity, manufactured cells or those harvested and processed from different anatomic sites or unrelated individuals present significant challenges of biological variability. In the case of allogeneic therapies, the establishment of a single master cell source may mitigate variability. In autologous therapies, cell supply may be limited, thereby precluding extensive tests of product quality. Given the general lack of experience of investigators with the manufacture, culture, or use of stem cells and their derivatives, definitions of identity and potency remain to be determined during the course of future research. These unique aspects of cell manufacture motivate the next recommendation.

Recommendation 5: In the course of development of stem cell-based products, it is imperative to validate surrogate markers of the identity and potency of cell products.

4.1.2 Production. Inclusion of animal materials in the cell manufacturing process does not preclude human use, as stipulated in existing guidelines for medicinal products (Appendix 2.2), but raises unique concerns that must be addressed by additional testing to minimize the risk of transmission of animal pathogens and reaction to the animal proteins. Thus it is essential to maintain detailed documentation to track all materials used in cell production.

Recommendation 6: Where possible, components of animal origin used in the culture or preservation of cells should be replaced with human components or with chemically defined components to reduce the risk of accidental transfer to patients of unwanted chemical or biological material or pathogens.

4.2 Manufacture

The variety of distinct cell types, tissue sources, and modes of manufacture and use necessitate individualized approaches to cell processing and manufacture. (For an expanded discussion of the manufacturing process, see Appendix 3.) The maintenance of cells in culture for any period of time places different selective pressures on the cells than when they exist *in vivo*. Cells in culture age and may accumulate both genetic and epigenetic changes, as well as changes in behavior. Unfortunately, scientific understanding of genomic stability during cell culture is primitive at best and assays of genetic and epigenetic status of cultured cells are still evolving.

Recommendation 7: Acknowledging the limitations in current assays, scientists and regulators must work together to develop common reference standards for minimally acceptable changes during cell culture, to ensure quality and safety of cell therapy, and to facilitate comparisons across studies.

Recommendation 8: The level of regulation and oversight should be proportional to the degree of risk raised by the particular cell product and intended use (autologous versus allogeneic use, minimally versus highly manipulated cell products, use for homologous versus non-homologous functions).

When adequate cellular material is available, assays that might be required include mRNA, microRNA, and protein expression and activity, rates of proliferation, global patterns of methylation and chromatin modification, and in the logical extreme, complete sequencing of the genome, as determined after rigorous review by a panel of independent experts. Defining optimal quality control for cultured cell products remains a key goal of current stem cell research.

Recommendation 9: To facilitate international collaboration and universal access to stem cell-based treatments (both during clinical trials and when established as standards of clinical care), there is a need to develop appropriate quality management systems for donation, procurement, testing, coding, processing, preservation of stem cell potency, storage, and distribution of the cells. For extensively manipulated stem cells (either autologous or

allogeneic) destined to clinical application, the ISSCR recommends adherence to GMP procedures, which includes minimizing risks to patients from unwanted cell products.

Recommendation 10: Cellular therapeutics that incorporate gene repair or genetic modification must adhere to regulatory guidelines set forth for both gene therapy and cell therapy.

These recommendations are not meant to supervene the current established practice standards for the therapeutic use of cells (for example, for bone marrow stem cells). However, consistent with evolving standards of regulation, future cell therapy products may be regulated under more stringent guidelines than currently applied.

4.2.1 Cell Banking. Some stem cell products entail minimal manipulation and immediate use, whereas other stem cell products are intended for future use and thus necessitate storage, sometimes long-term. Precedents exist for two types of stem cell banks: (a) private banks where cells are harvested from an individual and stored for future use by that individual or designated family members; and (b) public banks that procure, process, store, and deliver cells to matched recipients on a need-based priority list, in a model akin to blood banking. The development of banks may be in the public interest once stem cell-based treatments are proven effective and become the standard of care. The composition of the bank must be constituted with adequate genetic diversity to ensure wide access.

4.2.2 Developing Uniformity in Standards. Given that universal standards have emerged governing blood transfusion and hematopoietic transplantation therapies, uniform standards should likewise emerge relating to identification of donors, consent and procurement, manufacturing regulations, method of delivery, and selection of recipients for novel stem cell-based therapies. Several non-profit organizations have taken the lead in providing accreditation services for cellular therapies. For example, the Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA), a collective of professional organizations (see Appendix 4), is developing a minimum set of standards for the collection and use of hematopoietic stem and progenitor cells, including cord blood, that include minimal required testing of the donor, a donor identification number, and an identification of the process of obtaining tissue, along with tracking and tracing requirements and product labeling nomenclature including information on split number and clinical expiry date. Other efforts include the International Stem Cell Forum's initiatives to develop recommendations for the storage, deposit, and analysis of hESCs. Further initiatives include proposals for the collection of a minimal amount of information on the human embryos used to derive hESC lines. Models for obtaining appropriate information on the different available hESC and other pluripotent cell lines and Web-based registries should be put in place. The ISSCR is committed to playing a role in helping to organize the stem cell therapy sector to ensure as much uniformity in preclinical and clinical practice as possible.

5. Preclinical Studies

The purpose of preclinical studies is to (a) provide evidence of product safety and (b) establish proof-of-principle for the desired therapeutic effect. Before initiation of clinical studies with stem cells in humans, persuasive evidence in an appropriate *in vitro* and/or animal model must support the likelihood of a relevant positive clinical outcome. A fundamental operative principle here is that preclinical studies must be subject to rigorous and independent peer review and regulatory oversight prior to initiation of clinical trials, in order to ensure that the performance of clinical studies is scientifically and medically warranted.

Recommendation 11: Sufficient preclinical studies in relevant animal models – whenever possible for the clinical condition and the tissue physiology to be studied – are necessary to make proposed stem cell-based clinical research ethical, unless approved, controlled, and conclusive humans studies are already available with the same cell source. Investigators should develop preclinical cell therapy protocols in small animal models, as well as in large animal models when deemed necessary by independent peer review or regulatory review.

Preclinical testing in animal models, whenever feasible, is especially important for stem cell-based approaches because stem cells can act through multiple mechanisms, and because it is difficult to predict behavior in an animal from cell culture studies alone. Physiological integration and long-lived tissue reconstitution are hallmarks of stem cell-based therapeutics for many disease applications. Animal models will be relevant to assessing possible adverse effects of implanted cellular products. The need for animal models is especially strong in the case of extensive *ex vivo* manipulation of cells and/or when the cells have been derived from pluripotent stem cells.

It should be acknowledged, however, that preclinical assays including studies in animal models may provide limited insight into how transplanted human cells will behave in human recipients due to the context-dependent nature of cell behavior and the recipient's immune response. These uncertainties must be borne in mind during the independent peer review of preclinical data. Only when compelling preclinical data are available is careful and incremental testing in patients justified, and then always subject to rigorous and independent scientific and ethical oversight.

Recommendation 12: Because new and unforeseen safety concerns may arise with clinical translation, frequent interaction between preclinical and clinical investigators is strongly encouraged.

5.1 Efficacy

Given the goals of stem cell-based therapy in tissue repair or disease eradication, preclinical studies should demonstrate proof-of-principle for a desired therapeutic effect in a relevant animal model whenever possible for the clinical condition and the tissue physiology to be studied. Mechanistic studies utilizing cells isolated and/or cultured from animal models or diseased human tissues are desirable for defining the underlying biology of the cellular therapy. The Guidelines recognize that a 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 and/or in approved and conclusive human studies with the same cell source.

Recommendation 13: Small animal models should be used to test the transplantation of wild-type and/or diseased and genetically-corrected stem cells, to assess the morphological and functional recovery caused by cell therapy, and to investigate the biological mechanisms of tissue restoration or repair. Small animal studies should also assess the dosage and route of administration of potential cell therapies, the optimal age and disease stage for therapeutic efficacy, and the cellular distribution, survival, and tissue integration.

Immune-deficient rodents can be especially useful to assess human cell transplantation outcomes, engraftment *in vivo*, stability of differentiated cells, and cancer risk. Many small animal models of disease (for example rodents) can faithfully reproduce aspects of human diseases, although there are considerable limitations. Large animal models may be more informative than small animal models with respect to several factors, such as disease complexity, effective cell dosage, response, cell survival after transplantation, and tissue-related inflammatory and immunologic barriers to long-term cellular engraftment. Furthermore, for many therapeutic applications, large animal models may be essential to evaluate issues of scale-up, physiology (such as cardiac physiology), migration, and feasibility.

Recommendation 14: Large animal models should be used for stem cell research related to diseases that cannot be sufficiently addressed using small animal models or where structural tissue such as bone, cartilage, or tendon need to be tested in a load-bearing model. The selected large animal model must offer an appropriate context for studying the human disease and conditions of specific interest.

However, it should be recognized that while genetically immunocompromised small animal models are available for testing, large animals need adjunctive immunosuppressive drug therapy to accept human cell transplants. The side effects of the drugs may interfere with any long-term evaluation of experimental success.

Recommendation 15: The need for studies in non-human primates should be evaluated on a case-by-case basis, and performed only if the studies promise to provide necessary and otherwise unobtainable information for experimental therapeutic application of stem cells or their progeny in patients. All studies involving the use of non-human primates must be conducted under the close supervision of qualified veterinary personnel with expertise in their care and their unique environmental needs.

International codes of research ethics, such as the Declaration of Helsinki and the Nuremberg Code, strongly encourage the performance of preclinical animal studies prior to clinical trials in humans. Efforts should be made to point out that diseased animals are not provided *ad hoc* but selected to try a new experimental therapy using stem cells that may, in the long term, benefit many patients with similar conditions and injuries. Responsible animal research adheres to the principles of the three Rs– Reduce numbers, Refine

protocols, and Replace animals with *in vitro* or non-animal experimental platforms whenever possible. Investigators planning to conduct animal studies using human stem cells and their direct derivatives should refer to applicable ethical considerations described by the ISSCR Ethics and Public Policy Committee (Appendix 3) and the ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research.

5.2 Toxicity

Human cells will need to be produced under the conditions discussed in Section 4, Cell Processing and Manufacture. Special attention should be paid to the characterization of the cell population, including possible contamination by irrelevant cell types and when necessary to the appropriate safeguards for controlling the unrestricted proliferation and/or aberrant differentiation of the cellular product and its progeny.

Recommendation 16: Cells to be employed in clinical trials must first be rigorously characterized to assess potential toxicities through *in vitro* studies and (where possible for the clinical condition and tissue physiology to be examined) in animal studies.

Outside of the hematopoietic and stratified epithelia systems there is little clinical experience with the toxicities associated with infusion or transplantation of stem cells or their derivatives. In addition to the known and anticipated potential risks, including acute infusional toxicity, deleterious immune responses, unexpected behavior of the cellular product, and tumorigenesis, there are likely to be unanticipated toxicities that will only be learned with experience. Animal models may not replicate the full range of human toxicities; therefore, particular vigilance must be applied in preclinical analysis of the toxicities of cell-based interventions. This section will define toxicities that are likely to be unique to stem cells or their progeny.

Cells grown in culture, particularly for long periods or under stressful conditions, may become aneuploid or have DNA rearrangements, deletions, and other genetic or epigenetic abnormalities that could predispose them to cause serious pathologies such as cancer.

Recommendation 17: Criteria for release of cells for transfer to patients must be designed to minimize risk from culture-acquired abnormalities.

Given the nature of pluripotent cells and their innate capacity to form teratomas, there is a particular concern for the potential tumorigenicity of hESCs and induced pluripotent stem cells or their differentiated derivatives.

Recommendation 18: Risks for tumorigenicity must be assessed for any stem cell-based product, especially when extensively manipulated in culture or when genetically modified. A clear plan to assess the risks of tumorigenicity for any cell product must be implemented under the direction of an independent review body prior to approval for human clinical use.

Cell preparations that show a high risk or incidence of abnormal tissue formation or tumorigenesis might entail design of a "suicide strategy" involving genetic modification of the cells to render them susceptible to cell killing with an exogenous drug (for example, incorporation of the thymidine kinase gene into cells, thereby rendering them sensitive to gancyclovir). It should be noted, however, that once a cellular therapy has undergone genetic modification, the use of the genetically modified cells will be considered a gene transfer intervention that may involve an additional layer of regulatory oversight pertinent to gene transfer research. The relative risks and benefits of such mechanisms should be addressed by an independent review body during the regulatory oversight process.

Route of cell administration – local or systemic – may lead to different adverse events. Local, intramuscular or subcutaneous injection of cells is unlikely to produce acute systemic adverse events (unless antigen-presenting cells are transplanted) but may eventually result in local destruction of donor cells. Similarly, local application of engineered skin grafts may result in destruction of the graft and consequent tissue damage and inflammation, but are unlikely to elicit systemic adverse events. On the other hand, even local transplantation into organs like the heart or the brain may lead to life-threatening adverse events related to the transplantation itself or to the damage that transplanted cells may cause to vital structures. Especially in cases where cell preparations are infused at anatomic sites distinct from the tissue of origin (for example, for non-homologous use), great care must be exercised in assessing the possibility of local and systemic toxicities.

Because of the potential for cells to persist or expand in the body, systemic delivery of cells raises additional toxicity questions. The long-term consequences of fusion of delivered cells to host cells are not known. Given the dissimilarities of animal and human physiology, preclinical models may not faithfully anticipate all potential deleterious events. In particular, animal models are inadequate for assessing pain and its exacerbation by cell therapies, and many anticipated disease targets are associated with pain.

While rodents or other small animal models are a necessary step in the development of stem cell-based therapies, they are likely to reveal only major toxic events. The similarity of many crucial physiological functions between large mammals and humans may favor testing the toxicity of a novel cell therapy in at least one large animal model. Moreover, consideration should be given to long-term monitoring of animals as a source of information on the late effects of cell therapies.

Recommendation 19: Cell cultures and animal models should be used to test the interaction of cells with drugs to which recipients will be exposed. These include the immunosuppressants planned for recipients, as well as other drugs that might be used to treat their underlying disease process.

6. Clinical Research

As with all clinical research, clinical trials of stem cell-based interventions must follow internationally accepted principles governing ethical conduct of clinical research and the protection of human subjects. Key requirements include regulatory oversight, peer review by an expert panel independent of the investigators and sponsors, fair subject selection, informed consent, and patient monitoring. However, there are a number of important stem cell-related issues that merit special attention.

Recommendation 20: Stem cell-based clinical researchers should:

(a) cooperate with and share scientific expertise to assist other investigators and human subjects research review committees in assessing:

i. the biological characteristics of the cells to be used in clinical trials;

ii. whether these cells have been developed with appropriate manufacturing standards;

iii. preclinical data on their use in animal and/or other models for evaluating their safety and efficacy; and

iv. any early clinical data, if available, which address safety issues in the short and medium term and continued observation for long term effects;

(b) address the risks of stem cell-based interventions including, for example, cell proliferation and/or tumor development, exposure to animal source materials, risks associated with viral vectors, and risks as yet unknown;

(c) provide the utmost clarity regarding the potential benefits of participating in the trial with stem cells, since patients may have recourse to reasonable therapeutic alternatives; the informed consent process must emphasize the novel and experimental aspects of cell based interventions. It is important to minimize misconceptions patients may have about the potential for therapeutic efficacy;

(d) disclose any financial and non-financial conflicts of interest among the investigators, sponsors, and institutions in which the stem cell research is being conducted;

(e) monitor research subjects for long-term health effects and protection of the confidentiality of their health data;

(f) provide a clear, timely, and effective plan for adverse event reporting;

(g) offer a clinical plan to provide treatment for toxicity, including treatment of tumors that might arise. This plan might include compensation for research-related injuries; and

(h) ensure that insurance coverage or other appropriate financial or medical resources are available to patients to cover potential complications arising from their research participation.

6.1 Regulatory Oversight

The goal of regulatory review and oversight is to ensure that the stem cell-based clinical trial is likely to be safe, has scientific merit, and that it is designed and carried out in a manner that will yield credible data that will be of value to the biomedical research community.

Recommendation 21: All studies involving clinical applications of stem cells, whether publicly or privately sponsored, must be subject to independent review, approval, and ongoing monitoring by human subjects research oversight bodies with supplemental appropriate expertise to evaluate the unique aspects of stem cell research and its application in a variety of clinical disciplines. This review and oversight process must be independent of the investigators regardless of whether it occurs at the institutional, regional, or national level, and regardless of whether investigators employ the services of a contract research organization.

Independent review and informed consent are required in stem cell-based clinical trials to minimize the possibility of conflict of interest which may prejudice the research design by investigators, to maximize the coincidence of the goals of the research with the subjects' interests, and to maximize respect for the voluntary nature of the subjects' participation.

Independent evaluation of stem cell research projects occurs through multiple groups, including granting agencies, local peer review, and data and safety monitoring boards. To initiate stem cell-based clinical trials, it is critical that investigators follow and comply with a local and national regulatory approvals process.

Recommendation 22: In countries where there is no official national regulatory body, the ISSCR strongly encourages governments to develop a regulatory competence at the national, regional, or local level to monitor clinical interventions with stem cell-based products. The ISSCR will strive to provide professional advice to those governing bodies interested in building their own capacities for regulatory oversight.

In many countries, the regulatory approval process requires a statement from the investigator outlining well-defined goals of the clinical trial, detailed research protocols, manufacturing guidelines, and toxicology information.

6.2 Standards for Peer Review

6.2.1 Elements of the Peer Review Process. Assessment of clinical protocols for stem cell-based interventions, especially those using novel preparations of stem cells, requires unique expertise.

Recommendation 23: The peer review process for stem cell-based clinical trials should have appropriate expertise to evaluate (a) the *in vitro* and *in vivo* preclinical studies that form the basis for proceeding to a clinical trial and (b) the scientific underpinnings of the trial protocol, the adequacy of planned end-points of analysis, statistical considerations, and disease-specific issues related to human subject protection.

Peer review should also judge whether the proposed stem cell-based clinical study is likely to lead to improvement in health or may generate important new knowledge. Comparing the relative value of a new stem cell intervention to established modes of therapy is integral to the review process.

6.2.2 Risk-Benefit Analysis. As discussed in Section 5, Preclinical Studies, there should be persuasive preclinical evidence of safety and benefit for the stem cell-based intervention to justify proceeding to clinical trials in humans.

Recommendation 24: Risks should be identified and reduced, and potential benefits to subjects must be realistically delineated but not overemphasized. Subject selection can affect the risks and benefits of the study and subjects should be selected to minimize risks, maximize the ability to analyze results, and enhance the benefits to individual subjects and society.

6.2.3 Comparison with Existing Therapy. Genetic and acquired diseases differ widely in their degree of disability, morbidity, and their available therapeutic options. These facts have a crucial impact on the decision to proceed to clinical application with a novel stem cell-based approach, which is itself experimental and potentially risky.

Recommendation 25: As a general principle, a stem cell-based approach must aim at being clinically competitive or superior to existing therapies. If an efficacious therapy already exists, the risks associated with a stem cell-based

approach must be low and the stem cell-based approach must offer a potential advantage (for example, better functional outcome; single procedure (cell administration) versus life-long drug therapy with associated side effects; reduction in long-term cost). 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. Maximum effort should be made to minimize the risks for all possible adverse events associated with stem cell-based approaches. Care must also be taken to not take advantage of the hopes of patients with poor short-term prognoses.

6.2.4 Standard of Care. The ISSCR recognizes that stem cell research is an international endeavor where local standards of care differ dramatically. Due consideration should be given to achieve best optimal care in a given locale, taking into consideration legitimate factors that impact the quality of care available locally. The ISSCR strongly discourages conduct of trials in a foreign country solely to benefit patients in the home country of the sponsoring agency. The test therapy, if approved, should realistically be expected to become available to the population participating in the clinical trial through existing health systems or those developed on a permanent basis in connection with the trial. For a trial with comparison arms, it may be justified to perform a study comparing the stem cell-based approach with the best locally achievable treatment and follow-up, if the local risk-benefit consideration allows.

Recommendation 26: Clinical research should compare new stem cell-based therapies against the best medical therapy currently available to the local population.

6.2.5 Fair Subject Selection. The ISSCR supports the ideal of fair access to well-designed clinical trials and effective stem cell-based therapies without regard to patients' financial status, insurance coverage, or ability to pay. In stem cell-based clinical trials, the sponsor and principal investigator have an ethical responsibility to make good faith, reasonable efforts whenever possible to secure sufficient funding so that no person who meets eligibility criteria is prevented from being considered for enrollment because of his or her inability to cover the costs of the experimental treatment.

Recommendation 27: As far as possible, groups or individuals who participate in clinical stem cell research should be in a position to benefit from the results of this research. Groups or individuals must not be excluded from the opportunity to participate in clinical stem cell research without rational justification.

6.2.6 Standards for Voluntary Informed Consent. Culturally-sensitive voluntary informed consent is a necessary component in the ethical conduct of clinical research and protection of human subjects. With respect to stem cell-based interventions, for which desperate patients might unrealistically expect therapeutic benefit, the informed consent process must clearly state the experimental and preliminary nature of the clinical intervention. Investigators involved in clinical research must carefully assess whether participants understand the essential aspects of the study – specifically, that this may be the first time the experimentally-derived cells have been administered to humans, that animal studies may not predict effects of cell therapies in humans, that the aim of the study may simply be to assess safety, that the risks are unknown, and that, historically, some human participants in early drug trials have experienced serious adverse effects, including death. Subjects should be made aware that their participation is entirely voluntary and not necessary for their continued clinical care, and that participation or non-participation will not interfere with their ongoing clinical care.

Recommendation 28: Informed consent is particularly challenging for clinical trials involving highly innovative interventions.

(a) Patients need to be informed when novel stem cell-derived products have never been tested before in humans and that researchers do not know whether they will work as hoped.

(b) Cell-based interventions, unlike many pharmacological products or even many implantable medical devices, may not leave the body and may continue to generate adverse effects for the lifetime of the patient. The possible irreversibility of a cellular transplant should be explained clearly.

(c) Subjects should be informed about the source of the cells so that their values are respected.

(d) Ensuring subject comprehension must be done at each phase of the clinical trials process. Ideally, the subject's comprehension of information should be assessed through a written test or an oral quiz during the time of obtaining consent.

(e) Human subjects research committees should ensure that informed consent documents accurately portray these uncertainties and potential risks, and clearly explain the experimental nature of the clinical study.

Recognizing the potential value of stem cell-based therapies for subjects who are cognitively impaired, procedures should be developed and employed allowing authorized representatives to be placed in decision-making roles and to monitor participation on behalf of potential subjects. It is important that such subjects and their conditions are not excluded from biomedical advances involving stem cells. At the same time, such subjects should be recognized as especially vulnerable, and steps should be taken to involve guardians or surrogates who are appropriately qualified and informed to make surrogate research judgments and to provide other protections.

6.3 Patient Monitoring and Adverse Event Reporting

Recommendation 29: A data monitoring plan, which may involve an independent data safety and monitoring process, is required for all clinical studies, and aggregate updates should be provided to peer review committees on demand, complete with adverse event reporting and ongoing statistical analysis.

The welfare of subjects should be carefully monitored throughout the duration of stem cell-based clinical trials, privacy must be respected, and subjects must be free to withdraw without penalty, as new information about the effect(s) of the intervention or the subject's clinical condition may change in the course of research.

Recommendation 30: Subject withdrawal from the research should be done in an orderly fashion to promote physical and psychological safety. Given the potential for transplanted cellular products to persist long-term, and depending on the nature of the experimental stem cell-based intervention, patients may have to undergo long-term health monitoring, and additional safeguards for ongoing patient privacy should be provided.

Recommendation 31: To advance scientific understanding, research subjects should be asked, in the event of death, for consent to the performance of a partial or complete autopsy to obtain information about the extent of cellular implantation and its morphological and functional consequences. Any request for an autopsy must consider cultural and familial sensitivities.

This is a delicate issue, but without access to post mortem material, the information coming out the trial will be substantially reduced to the detriment of future product/delivery refinements in the indication.

Recommendation 32: Researchers should facilitate the gathering of empirical data about socio-demographic characteristics of participants in clinical trials, financial compensation levels (if applicable), and the nature and extent of any benefit and harm resulting from research participation. Such data are crucial for health services researchers and policy-makers to improve the conduct of future clinical trials and to assess the utility of the information obtained in these trials for informing policy decisions such as approval and insurance coverage for cell-based interventions.

6.4 Publication of Research Results

Publication of both positive and negative results and adverse events is strongly encouraged to promote transparency in the clinical translation of cell-based therapies, to ensure development of clinically effective and competitive stem cell-based therapies, and to prevent participants in future clinical trials from being subjected to unnecessary risk.

Recommendation 33: Researchers should publish both positive and negative results and adverse events. To ensure the integrity of scientific information and to promote the highest standards of professional conduct, researchers should present their results at professional scientific conferences or in peer-reviewed scientific journals before reporting their research to the lay media or to patient advocacy groups and associations.

7. Stem Cell-Based Medical Innovation

Historically, many medical innovations have been introduced into clinical practice without a formal clinical trials process. Some innovations have resulted in significant and long-lasting improvements in clinical care, while others have been ineffective or harmful. In contrast to the commercial purveyance of unproven stem cell interventions noted in Section 2, the ISSCR acknowledges that in some very limited cases, clinicians may be justified in attempting medically innovative stem-cell based interventions in a small number of their seriously ill patients.

In the case of medical innovations using stem cells and their direct derivatives, unique considerations justify a heightened level of caution. The diseases which potentially could be targeted by stem cell-based interventions are some of the most intractable diseases confronting clinicians – and interest in stem cell research has resulted in the organization of patient communities with high hopes for the prospect of future stem cell treatments. Due to their relative novelty in science, stem cells and their direct derivatives could behave more unpredictably when delivered to patients than either drugs used off-label or modified surgical techniques. Some attempts at medical innovation using stem cells and their direct derivatives may inadvertently violate physicians' ethical obligation to "do no harm," by producing more injury than benefit.

Innovative medical care and clinical research aim at different goals. The mere fact that a procedure is medically innovative does not qualify it as clinical research. Clinical research aims to produce generalizable knowledge about new cellular or drug treatments, or new approaches to surgery. Notably, the individual patient's benefit is not the focus of clinical research, nor is the individual patient's benefit the primary focus of the human subjects research committees overseeing clinical research. In contrast, medical innovations do not aim to produce generalizable knowledge but are aimed primarily at providing new forms of clinical care that have a reasonable chance of success for individual patients with few or no acceptable medical alternatives. Unlike clinical research, then, the main goal of innovative care is to improve an individual patient's condition.

Although attempting medically innovative care is not research *per se*, it should still be subject to scientific and ethical review and proper patient protections. This is especially true for stem cell-based medical innovation.

Given the many uncertainties surrounding the infusion of cells in ectopic locations and the significant challenges to the processing and manufacture of cellular products, only in exceptional circumstances does the ISSCR believe it would be acceptable to attempt medical innovations involving stem cells and their direct derivatives. The ISSCR anticipates that the following recommendation will be applicable primarily for seriously ill patients who lack good medical alternatives.

Recommendation 34: Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial, provided that:

(a) there is a written plan for the procedure that includes:

i. scientific rationale and justification explaining why the procedure has a reasonable chance of success, including any preclinical evidence of proof-of-principle for efficacy and safety;

ii. explanation of why the proposed stem cell-based intervention should be attempted compared to existing treatments;

iii. full characterization of the types of cells being transplanted and their characteristics as discussed in Section 4, Cell Processing and Manufacture;

iv. description of how the cells will be administered, including adjuvant drugs, agents, and surgical procedures; and

v. plan for clinical follow-up and data collection to assess the effectiveness and adverse effects of the cell therapy;

(b) the written plan is approved through a peer review process by appropriate experts who have no vested interest in the proposed procedure;

(c) the clinical and administrative leadership supports the decision to attempt the medical innovation and the institution is held accountable for the innovative procedure;

(d) all personnel have appropriate qualifications and the institution where the procedure will be carried out has appropriate facilities and processes of peer review and clinical quality control monitoring;

(e) voluntary informed consent is provided by patients who appreciate that the intervention is unproven and who demonstrate their understanding of the risks and benefits of the procedure;

(f) there is an action plan for adverse events that includes timely and adequate medical care and if necessary psychological support services;

(g) insurance coverage or other appropriate financial or medical resources are available to patients to cover any complications arising from the procedure; and

(h) there is a commitment by clinician-scientists to use their experience with individual patients to contribute to generalizable knowledge. This includes:

- **i. ascertaining outcomes in a systematic and objective manner;**
- **ii. a plan for communicating outcomes, including negative outcomes and adverse events, to the scientific community to enable critical review (for example, as abstracts to professional meetings or publications in peer-reviewed journals); and**
- **iii. moving to a formal clinical trial in a timely manner after experience with at most a few patients.**

Not following such standards may exploit desperate patients, undermine public trust in stem cell research, and unnecessarily delay better designed clinical trials. Many who provide stem cell-based therapies may claim that they offer innovative medical care not available in other medical institutions because of the conservative nature of medical care. Strict application of the above criteria to many clinical interventions offered outside of a formal clinical trial will identify significant shortcomings that should call into question the legitimacy of the purported attempts at medical innovation.

8. Considerations of Social Justice

While all research should be responsive to issues of justice, there are additional reasons to consider justice in the context of stem cell translational research. First, ethical arguments in support of stem cell research depend in part on its potential for advancing scientific knowledge that may result in therapies or cures for disease, other health benefits associated with advances in scientific knowledge, or associated technological or methodological developments. As such, governments, institutions, researchers, and providers have a responsibility to attend to issues of public benefit and specifically to ensure that the anticipated benefits are genuinely and justly available. Second, stem cell research offers the potential to develop therapies that could be widely shared internationally. Choosing which applications to address for clinical development, and how, will necessarily require special attention to issues of social justice.

Addressing issues of social justice at each stage of research and involving various entities – researchers, institutions, companies, funders, review bodies, ethicists, and policy-makers – will require carefully and locally adapted procedures.

Recommendation 35: Regulatory and oversight agencies, (local, national and international) must explicitly include the consideration of social justice principles into their evaluations. Mechanisms include (a) involvement of community and patient advocates in public discussions, committee representation, and oversight board evaluation procedures; (b) opportunity for open discussions about ethical issues; (c) enforcement of social justice considerations by appropriate agencies.

Researchers ought not to raise false hopes and must deal honestly with serious issues of risk, harm, and chance. Similarly, opponents of research ought not to raise unfounded alarms. Discussion must be transparent, accurate, inclusive, interactive, critical, and fair.

Recommendation 36: Reporting on stem cell research must be based in scientifically-grounded research. Frank disclosure of failures in research, adverse incidents, and lack of significant change in the status of treated patients will need to be made. Patient advocates must follow the same standards of discourse.

Recommendation 37: There should be public engagement in the policy making of individual governmental agencies. Such consultation should aim to be inclusive and interactive.

Recommendation 38: The ISSCR seeks to maximize social good, which leads to the following considerations:

(a) Stem cell collections with genetically diverse sources of cell lines should be established.

(b) Collaborations among researchers and institutions should be structured to maximize the fairness of the parties' roles, and to increase joint capacity and social benefit.

(c) Fair access is important. Access will depend on financial terms and business models that are perceived as fair by all stakeholders, including patients, providers, payers, companies, and governments. The ISSCR therefore:

i. encourages open stakeholder discussion to identify and evaluate alternative models and terms; and

ii. encourages development and assessment of alternative models of intellectual property, licensing, product development, and public funding to promote fair and broad access to stem cell-based diagnostics and therapies.

Recommendation 39: As an aspirational ethical goal – provided that a stem cell-based therapy is proven to offer a major therapeutic benefit – commercial companies, subject to their financial capability, should offer affordable therapeutic interventions to persons living in resource-poor countries who would otherwise be wholly excluded from benefiting from that stem cell-based therapy. Academic and other institutions that are licensing stem cell therapeutics and diagnostic inventions should incorporate this requirement in their intellectual property license.

The ISSCR will continue to play a leadership role, in dialogue with policy-makers, the public, and the research community, in establishing specific norms of social justice in this research.

9. Ongoing Review of Guidelines

Recommendation 40: These guidelines will be reviewed and revised as needed to accommodate new scientific advances and to address specific translational research issues.

10. Acknowledgments

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11. Appendices

Appendix 1: Patient Handbook on Stem Cell Therapies

The ISSCR receives many questions regarding clinical therapies using stem cells. In the *Patient Handbook on Stem Cell Therapies* we seek to address some of the important elements that underlie these questions and outline key criteria, warning signs, and things to ask when considering a stem cell therapy.

Patient Handbook on Stem Cell Therapies: http://www.isscr.org/clinical_trans/patienthandbook.pdf

Appendix 2: International, National and Local Regulations, Guidelines and Resources

Links to regulations, guidelines, professional bodies and other resources: http://www.isscr.org/clinical_trans/app2.cfm

A2.1 Codes of Conduct for Research Involving Human Subjects

A2.2 Existing International Regulations and Regulatory Bodies and Professional Organizations Governing Cell-Based Therapies

A2.3 Existing International Regulations and Guidelines Governing Procurement of Tissues or Organs for Cell Therapies and Research Involving Human Subjects

A2.4 Existing International Regulations Governing Good Manufacturing Practice

Appendix 3: Related Articles

Ährlund-Richter, L., De Luca, M., Marshak, D.R., Munsie, M., Veiga, A., and Rao, M. (2009). Isolation and production of cells suitable for human therapy: Challenges Ahead. *Cell Stem Cell 4*, in press. Published online December 4, 2008.

Daley, G. Q., Hyun, I., and Lindvall, O. (2008). Mapping the Road to the Clinical Translation of Stem Cells. *Cell Stem Cell 2*, 139-140. http://download.cell.com/cell-stem-cell/pdf/PIIS193459090800012X.pdf

Hyun, I., Taylor, P., Testa, G., Dickens, B., Jung, K. W., McNab, A., Robertson, J., Skene, L., and Zoloth, L. (2007). Ethical Standards for Human-to-Animal Chimera Experiments in Stem Cell Research. *Cell Stem Cell 1*, 159-163. http://download.cell.com/cell-stem-cell/pdf/PIIS193459090700080X.pdf

Hyun, I., Lindvall, O., Ährlund-Richter, L., Cattaneo, E., Cavazzana-Calvo, M., Cossu, G., De Luca, M., Fox, I. J., Gerstle, C., Goldstein, R. A., Hermerén, G., High, K. A., Kim, H. O., Lee, H. P., Levy-Lahad, E., Li, L., Lo, B., Marshak, D. R., McNab, M., Munsie, M., Nakauchi, H., Rao, M., Rooke, H. M., Simon Valles, C., Srivastava, A., Sugarman, J., Taylor, P. L., Veiga, A., Wong, A. L., Zoloth, L. and Daley, G. Q. (2008). New ISSCR Guidelines Underscore Major Principles for Responsible Translational Stem Cell Research. *Cell Stem Cell 3*, 607-610.

Appendix 4: Acronyms and Definitions

Allogeneic transplantation: refers to the transplantation of cells from a donor to another person.

Autologous transplantation: refers to the transplantation to a patient of his/her own cells.

Ectopic tissue: foreign tissue of one type that forms in a distinct tissue or non-native location, as a result of the transfer of cellular products.

Ex vivo: (Latin, outside the living) refers to the manipulation of cells, tissues or organs outside of the body with the intent to return to a living body.

Homologous use: refers to intended therapeutic use of cells within their native physiological context, for example, the transplantation of hematopoietic stem cells to regenerate the blood.

In vivo: (Latin, inside the living) occurring within the body.

In vitro: (Latin, in the glass) occurring outside of the body.

Non-homologous use: refers to intended therapeutic use of cells outside their native physiological context, for example, the transplantation of hematopoietic stem cells into the heart for repair or regeneration of myocardial tissue.

Teratoma: a benign, encapsulated mass of complex differentiated tissues comprising elements of all three embryonic germ layers: ectoderm, endoderm, and mesoderm. Used to assess the pluripotency of stem cells (their capacity to form all tissues in the body).

Tumorigenicity: the property of cells that describes their potential for forming tumors, or abnormal growths of cells.

AHCTA, Alliance for Harmonisation of Cellular Therapy Accreditation. AHCTA represents the American Association of Blood Banks (AABB), American Society for Blood & Marrow Transplantation (ASBMT), European Federation for Immunogenetics (EFI), European Group for Blood & Marrow Transplantation (EBMT), Foundation for the Accreditation of Cellular Therapy (FACT), International Society for Cellular Therapy (ISCT) (Europe), Joint Accreditation Committee ISCT-EBMT (JACIE), International NETCORD Foundation, and the World Marrow Donor Association (WMDA).
For more information: www.ahcta.org

ISCF, International Stem Cell Forum. The ISCF represents 21 funders of stem cell research from around the world and has undertaken several international projects that address key issues for stem cell scientists and funders.
For more information: www.stemcellforum.org