



International Society for Stem Cell Research

Guidelines for the Conduct of Human Embryonic Stem Cell Research

Version I: December 21, 2006

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1) Justification for stem cell research and goals

1.1) Stem cell research, with foundations in the fields of cell and developmental biology and genetics, seeks to answer basic questions about the nature of tissue formation and maintenance. The first stem cells to be isolated were from developed tissues and organs, and are now used in tissue and organ regeneration experimentally and clinically.

1.2) The rapid growth of the field of stem cell research follows numerous recent seminal discoveries, including the isolation of human embryonic stem cells and stem cells of various types that have the potential to generate many different cells and tissues.

1.3) Stem cell research encompasses new approaches for the elucidation of disease mechanisms, offers promise for discovery of novel drugs that act on stem cells, and may yield cell replacement therapies for a multitude of devastating and widespread genetic, malignant, and degenerative diseases that are currently untreatable. Stem cell research is certain to advance fundamental knowledge and to have a profound impact on medicine. The goals of stem cell research are widely accepted in the biomedical research community and endorsed by diverse scientific societies worldwide. Long-term goals include improvements in human health and the relief of disease, infirmity, and human suffering through advances in knowledge and new clinical tools that can be made available and affordable throughout the world.

1.4) The International Society for Stem Cell Research (ISSCR) endorses the goals of stem cell scientists and exists to promote innovation in research, education, and the free exchange of scientific ideas and research materials.

2) Mission of task force

2.1) Scientific, cultural, religious, ethical, and legal differences across international borders affect how early stages of human development are viewed, and how research on human embryos and embryonic stem cells is conducted. ISSCR calls for due consideration and appropriate oversight of human stem cell research to ensure transparent, ethical, and responsible performance of scientific experiments.

2.2) The ISSCR Task Force is charged with formulating guidelines that articulate ethical principles and rules of behavior for the performance of human stem cell research.

2.3) These Guidelines are meant to emphasize the responsibility of scientists to ensure that human stem cell research is carried out according to rigorous standards of research ethics, and to encourage uniform research practices that should be followed by all human stem cell scientists globally.

3) Comment on scientific terminology

3.1) The ISSCR is dedicated to the use of precise and accurate terminology in stem cell research, and to educating researchers and the public on the meaning of terms and their proper usage in the discourse on stem cell research. Discussion of the merits of stem cell research requires that the discussants share a common understanding about the meaning and usage of specific terms, and the biological implications of the terminology. We also acknowledge the limitations of descriptive terminology in the practice of a fast-moving field of science, and endeavor to apply the most precise terms in the proper context. We have endeavored to employ the most accurate terms throughout the document, as defined in an appended glossary.

4) Scope of Guidelines

4.1) Fundamental ethical requirements in research include review and approval of projects by a panel that is independent of the investigators, and voluntary and informed consent from any human participants. Well-established guidelines and regulations governing the use of human subjects are already in place throughout the world. These principles have been articulated in internationally recognized research ethics guidelines including, but not limited to, the Nuremberg Code of 1947, the Declaration of Helsinki of 1964 and amendments, the Belmont Report of 1979, the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects of 2002, and the UNESCO Universal Declaration on Bioethics and Human Rights of 2005. Regulations for use of animals and hazardous materials in research have also been well established and are in wide use. This Guideline document focuses on issues unique to stem cell research that involves pre-implantation stages of human development, research on the derivation or use of human pluripotent stem cell lines, and on the range of experiments whereby such cells might be incorporated into animal hosts.

4.2) These Guidelines pertain to the procurement, derivation, banking, distribution, and use of cells and tissues taken from pre-implantation stages of human development; to procurements of gametes and somatic tissues for stem cell research; and to the use of human totipotent or pluripotent cells or human pluripotent stem cell lines.

4.3) These Guidelines assert that researchers involved in human stem cell research must adhere to ethical and transparent practices for performing research and sharing research materials.

4.4) These Guidelines assign criteria for defining categories of research that are non-permissible, that are permissible under currently mandated review processes, and research that is permissible yet should be subjected to an added level of oversight. These Guidelines prescribe the nature of regulatory

review and oversight for each of the permissible research categories.

4.5) These Guidelines do not pertain to research on animal stem cells, or on classes of human somatic stem cells that remain restricted in tissue potential and are not known to possess totipotent or pluripotent potential. Research pertaining to these classes of stem cells does not raise the same sets of issues as dealt with in these Guidelines.

4.6) In their current form, these Guidelines are incomplete in their potential application to various types of fetal stem cells, which raise a unique set of issues around their procurement. Future revised versions of the Guidelines may incorporate more specific information pertinent to fetal stem cells.

5) Responsibility for conduct

5.1) International scientific collaboration and mutual trust among researchers are vital to the success and advancement of science and should be encouraged. Collaborations between scientists in different jurisdictions will raise issues due to the differences in the laws and regulations that govern stem cell research. An underlying principle of these guidelines is that any and all stem cell research shall be conducted in accordance with any applicable laws and regulations of the country or region where such research takes place, recognizing and respecting that certain laws and regulations may be applicable to individual researchers, regardless of where the research will take place.

5.2) Researchers must assume the responsibility for compliance with local statutes and adherence to guidelines. Institutions sponsoring stem cell research must take steps to ensure that education and appropriate training takes place to make researchers aware of regulations and professional guidelines. If warranted, institutions should obtain legal opinions on any issues of concern on behalf of their researchers.

5.3) Scientists and clinicians must be transparent and truthful about issues relating to human stem cell research and its potential to advance medicine. To guard against the creation of unrealistic expectations of success and to safeguard patients from serving prematurely as experimental subjects in human stem cell research, scientists and clinicians must clearly articulate the distinct goals of basic research, preclinical studies, and clinical trials. Investigators must assume the responsibility to educate the public about the many steps required to garner the scientific and clinical evidence to establish treatments as safe and effective.

5.4) Scientific trainees and technical staff who have a conscientious objection to aspects of stem cell research should not be required to participate in research, and should be free of retribution or undue discrimination in assessments of professional performance. Clinical personnel who have a

conscientious objection to stem cell research should not be required to participate in providing donor information or securing donor consent for research use of embryos, gametes, or somatic cells; that privilege should not extend to the clinical care of a donor.

6) Statement on reproductive cloning

6.1) Human reproductive cloning is defined as the act of seeking to establish either a pregnancy or the birth of a child by gestating or transferring into a uterus human embryos that have been derived in vitro by nuclear transfer or nuclear reprogramming. Given current scientific and medical safety concerns, attempts at human reproductive cloning should be prohibited.

7) Issues pertinent to international collaborations and the role of ISSCR

7.1) In the context of international collaborations, issues will arise that relate to ownership and custodianship of intellectual property. As a general principle, the ISSCR stands for the open exchange of scientific ideas and materials to maximize exploration, to promote innovation and to increase the probability of public benefit through affordable advances made possible by human stem cell research. Given the need to respect the varying laws and regulations of different jurisdictions that may apply to any international collaboration, intellectual property issues are best left to be negotiated among the collaborating parties, taking into consideration the protection regimes or other relevant laws and regulations of their respective jurisdictions. Nonetheless, we endorse in the strongest possible terms the principle that research with human materials is valuable to all, and that the proper practice of science requires unhindered distribution of research materials to all qualified investigators engaged in non-commercial research and the dissemination of its benefits to humanity at large on just and reasonable terms.

7.2) Pluripotent human stem cell lines are important tools for research and replication of experimental data and scientific collaboration are vital to scientific advancement. The ISSCR recommends that institutions engaged in human stem cell research, whether public or private, academic or otherwise, develop procedures whereby research scientists are granted, without undue financial constraints or bureaucratic impediment, unhindered access to these research materials for scientifically sound and ethical purposes, as determined under these Guidelines and applicable laws. The ISSCR urges such institutions, when arranging for disposition of intellectual property to commercial entities, to take all possible care to preserve nonexclusive access for the research community, and to promote public benefit as their primary objective. The ISSCR endorses the principle that as a prerequisite for being granted the privilege of engaging in human stem cell research, researchers must agree to make the materials readily accessible to the biomedical research

community for non-commercial research. Administrative costs such as shipping and handling should be borne by the receiving party so as not to pose a severe financial burden on the researcher providing the cells.

7.3) The ISSCR encourages scientists conducting human stem cell research to submit any human stem cell lines they derive to national or international depositories that allow open distribution in order to facilitate the wider dissemination of these valuable research tools across national boundaries. Scientists and stem cell bio-banks should endeavor to work together to harmonize standard operating procedures to facilitate international collaboration.

7.4) The process of identifying international ethical standards and practices for the conduct of human stem cell research should include concerted efforts to engage people throughout the world in honest and realistic conversations about the science and ethics of stem cell research and its emerging applications.

8) Recommendations for oversight

8.1) All experiments pertinent to human embryonic stem cell research that involve pre-implantation stages of human development, human embryos or embryonic cells, or that entail incorporating human totipotent or pluripotent cells into animal chimeras, shall be subject to review, approval and ongoing monitoring by a special oversight mechanism or body equipped to evaluate the unique aspects of the science. Investigators should seek approval through a process of Stem Cell Research Oversight (SCRO).

8.2) Review can be performed by an oversight mechanism or body at the institutional, local, regional, national, or international level, or by some coordinated combination of those elements provided that the review as a whole occurs effectively, impartially and rigorously. Multi-institutional arrangements for coordinated review, which involve delegation of specific parts of this review, shall be permitted as long as they meet that standard. A single review rather than redundant review is preferable as long as the review is thorough and pertains to the uniquely sensitive elements of human stem cell research. Unless the review is specifically designed to be comprehensive, the SCRO process shall not replace other mandated reviews such as institutional reviews that assess the participation of human subjects in research, or the oversight for animal care, biosafety, or the like. Institutions engaged in stem cell research must establish procedures to ensure that research conducted under their auspices have been subject to appropriate review.

8.3) Review must include assessment of:

i) *Scientific rationale and merit of proposal.* Research with human embryonic material, or totipotent or pluripotent cells requires that scientific goals and methods be scrutinized to ensure scientific rigor. Appropriate scientific justification for performing the research using the specified materials is required.

ii) *Relevant expertise of investigators.* Appropriate expertise and/or training of the investigators to perform the stated experiments must be ascertained in order to ensure the optimal use of precious research materials. For derivation of new human cell lines or experiments that involve use of human embryonic materials, relevant expertise would include prior experience with embryonic stem cell derivation in animal systems and competence in the culture and maintenance of human embryonic stem cells.

iii) *Ethical permissibility and justification.* Research goals must be assessed within an ethical framework to ensure that research proceeds in a transparent and responsible manner. The project proposal should include a discussion of alternative methods, and provide a rationale for employing the requested human materials, the proposed methodology and for performing the experiments in a human rather than animal model system.

8.4) The mechanism or body that provides SCRO function is responsible for interpreting Guidelines, defining research practices, and monitoring compliance.

8.4a) The SCRO function should assume responsibility for monitoring and periodic review and re-approval of ongoing research proposals.

8.4b) The SCRO function has the responsibility for defining whether a research proposal constitutes permissible or non-permissible research.

8.5) Recommendations for composition of participants to be engaged in providing SCRO function; appropriate expertise, objectivity and responsibility.

8.5a) Scientists and/or physicians with relevant expertise, including representation from scientists that are not directly engaged in the research under consideration. Relevant expertise includes areas of stem cell biology, assisted reproduction, developmental biology, and clinical medicine.

8.5b) Ethicists with ability to interpret the moral justifications and implications of the research under consideration.

8.5c) Members or advisors familiar with relevant local legal statutes governing the research.

8.5d) Community members, unaffiliated with the institution through employment or other remunerative relationships, who are impartial and reasonably familiar with the views and needs of research subjects, patients and patient communities who could be benefited by stem cell research, and community standards.

8.5e) Those responsible for formulating the mechanism or body to provide SCRO function must be cognizant of the potential for conflicts of interest that might compromise the integrity of the review process, and attempt to eliminate such conflicts. Potential participants in the SCRO process should be selected based on the capacity for impartiality and freedom from political influence.

8.6) Each institution, academic or commercial, that engages in human stem cell research shall determine an appropriate SCRO procedure, either internal or external, by which their researchers will be subject to review, approval, and monitoring of their human stem cell research activities.

9) Mechanisms for enforcement

9.1) The development of consensus in ethical standards and practices in human stem cell research through thoughtful and transparent dialogue is a critical catalyst for international collaboration to proceed with confidence, and for research from anywhere in the world to be accepted as valid by the scientific community. These standards and practices should be incorporated in a comprehensive code of conduct applicable to all researchers in the field. Senior or corresponding authors of scientific publications should specifically be charged with the responsibility of ensuring that the code of conduct is adhered to in the course of conducting human stem cell research and of supervising junior investigators that work in their respective organizations or projects. Institutions where such research is undertaken shall strive to provide to researchers working on any such projects under their auspices, particularly junior investigators, with up-to-date information on such standards and practices on an ongoing basis.

9.2) Journal editors should require a statement of compliance with the ISSCR 'Guidelines for the Conduct of Human Embryonic Stem Cell Research' or adherence to an equivalent set of guidelines or applicable regulations, and a statement that the research was performed after obtaining approvals following a suitable SCRO process.

9.3) Grant applicants, in particular the individual scientists undertaking the research, should undertake to provide funding bodies with sufficient documentation to demonstrate that the research for which funding is requested is ethically and legally in accordance with relevant local and national regulations and also in compliance with the ISSCR 'Guidelines for the Conduct of

Human Embryonic Stem Cell Research.' Funding organizations should pledge to comply with these Guidelines or their equivalent and require entities whose research is funded by such organizations to do the same.

9.4) In order to facilitate the adoption of uniform standards and practice of human stem cell research, the ISSCR will make available for download on the ISSCR website examples of informed consent documents for obtaining human materials for stem cell research (gametes, embryos, somatic tissues), and a Material Transfer Agreement for the sharing and distribution of materials (see appendix).

10) Categories of research

To ensure that stem cell research is proceeding with due consideration, to ensure consistency of research practices among scientists globally and to specify the nature of scientific projects that should be subject to SCRO review, we propose specific categories of research.

10.1) Category 1: Experiments that are permissible after review under existing mandates and by existing local committees, and are determined to be exempt from full SCRO review. These will include experiments with pre-existing human embryonic stem cell lines that are confined to cell culture or involve routine and standard research practice, such as assays of teratoma formation in immune-deficient mice. We recommend that all institutions pursuing such research establish a mechanism capable of determining that a) these projects can be adequately reviewed by committees with jurisdiction over research on human tissues, animals, biosafety, radiation, etc. and b) that full review by a SCRO mechanism or body is not required. This mechanism should include a determination that the provenance of the human embryonic stem cell lines to be used has been scrutinized and deemed acceptable according to the principles outlined in this document, and that such research is in compliance with scientific, legal and ethical norms.

10.2) Category 2: Forms of research that are permissible only after additional and comprehensive review by a specialized mechanism or body established to address the issues pertinent to stem cell research (i.e., the SCRO function). Such forms of research will require provision of greater levels of scientific justification, consideration of social and ethical aspects of the research and justification for not pursuing alternative methods to address the same experimental goals. If the research requires obtaining informed consent from human subjects, the research will require review to ensure that treatment of human subjects is consistent with international norms and local laws, and any other applicable regulations or guidelines. Review of such forms of research should consider the protection of genetic and medical privacy of donors; such a review is typically done by a local institutional review board or its equivalent, but could also be

performed as part of the SCRO process, with the SCRO exercising due regard for the authority of the institutional review board and avoiding duplication of its functions.

10.2a) Forms of research that involve the derivation of new human pluripotent cell lines by any means.

10.2b) Forms of research in which the identity of the donors of blastocysts, gametes, or somatic cells from which totipotent or pluripotent cells are derived is readily ascertainable or might become known to the investigator.

10.2c) Forms of research in which human totipotent cells or pluripotent stem cells are mixed with pre-implantation human embryos. In no case shall such experiments be allowed to progress for more than 14 days of development *in vitro*, or past the point of primitive streak formation, whichever is first.

10.2d) Clinical research in which cells of totipotent or pluripotent human origin are transplanted into living human subjects.

10.2e) Forms of research that generate chimeric animals using human cells. Examples of such forms of research include, but are not limited to introducing totipotent or pluripotent human stem cells into non-human animals at any stage of post-fertilization, fetal, or postnatal development.

- i) We note that chimeric animal research has a long history and has been a scientifically essential and valid procedure for understanding cellular, tissue, and organ function, and has also served as a key pre-clinical stage of research in the evaluation of therapeutics.
- ii) There are two main points of concern with chimeric animals containing human cells: the degree of the resulting chimerism and the type of tissues that are chimerized. The earlier that human cells are introduced during animal development, the greater the potential for their widespread integration during development. Introduction of a greater number of cells later in development may have an equivalent effect. In general, chimerism of the cerebral cortex or the germ-line are of greatest concern.
- iii) In reviewing forms of research of this type, the SCRO mechanism or body should communicate with the appropriate mechanism or body that oversees research involving animal subjects, and give special attention to a number of issues including: A) the probable pattern and effects of differentiation and integration of the human cells into the non-human animal tissues; and B) the species of the animal, with particular scrutiny given to experiments involving non-human primates. Experiments that generate chimerism of the cerebral cortex or germ-line should be subjected

to especially careful review. Although it is highly unlikely that any viable fertilization event of an animal gamete by a human gamete generated in an animal would occur, chimeric animals should typically not be allowed to produce offspring, whether by natural or artificial means. If there is a very strong scientific rationale for deriving offspring from such animals, then review committees should consider whether such an experiment might be appropriate to pursue. In any case, interbreeding of such chimeras should not be allowed, to preclude the possibility of inadvertent human-human fertilization events.

10.3) Category 3: Research that should not be pursued at this time because of broad international consensus that such experiments lack a compelling scientific rationale or raise strong ethical concerns. Such forms of research include:

10.3a) *In vitro* culture of any post-fertilization human embryos or organized cellular structures that might manifest human organismal potential, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.

10.3b) Research in which any products of research involving human totipotent or pluripotent cells are implanted into a human or non-human primate uterus.

10.3c) Research in which animal chimeras incorporating human cells with the potential to form gametes are bred to each other.

II) Procurement of materials

The procurement of human gametes, pre-implantation embryos, and somatic cells are integral to the conduct of human stem cell research. The international community of professional scientists conducting human stem cell research must ensure that human biological materials are procured in a manner according to globally accepted principles of research ethics. Chief among the ethical principles applicable to the conduct of human stem cell research are that persons should be empowered to make voluntary and informed decisions to participate or to refuse to participate in research. In the case of human embryonic stem cell research, the public participates by providing necessary human biological materials. Persons should be afforded a fair opportunity to participate in research, and they must be treated justly and equitably. Furthermore, privacy and confidentiality of personal information should be protected with the utmost care. Caution must also be taken to ensure that persons are not exploited during the procurement process, especially individuals who are vulnerable due to their dependent status or their compromised ability to offer fully voluntary consent. Consistent with well-established principles of justice in human subject research, there

must be a reasonable relationship between those from whom such materials are received and the populations most likely to benefit from the research. Finally, the voluntary nature of the consent process must not be undermined by undue inducements or other undue influences to participate in research.

11.1) Institutional review for procurement of materials:

Rigorous review, whether at the local institutional, regional, or national level, must be performed prior to the procurement of all gametes, embryos, or somatic cells that are destined for use in stem cell research. This will include the procurement of oocytes and embryos in excess of clinical need from infertility clinics, fertilized oocytes and embryos generated by IVF specifically for research purposes, and oocytes, sperm, or somatic cells donated for development of totipotent cells or pluripotent stem cell lines by parthenogenesis, androgenesis, nuclear transfer or other means of somatic cell reprogramming. Review at all levels must ensure that vulnerable populations are not exploited due to their dependent status or their compromised ability to offer fully voluntary consent, and that consent is voluntary and informed, and that there are no undue inducements or other undue influences for the provision of human materials.

11.2) Contemporaneous consent for donation:

Consent for donation of materials for research should be obtained at the time of proposed transfer of materials to the research team. Only after a rigorous review by a SCRO mechanism or body can permission be granted to use materials for which prior consent exists but for which re-consent is prohibitively difficult. Consent must be obtained from all gamete donors for use of embryos in research. Donors should be informed that they retain the right to withdraw consent until the materials are actually used in research.

11.3) Informed consent:

Researchers should exercise care in communicating the concept of “informed consent” to ensure that such consent has actually been obtained. The informed consent process should take into account language barriers and the educational level of the subjects themselves. In order to facilitate the adoption of sound and uniform standards of informed consent for the procurement of materials for human stem cell research, the ISSCR has made sample documents available to researchers by download from the ISSCR website (<http://www.isscr.org>). The samples will need to be customized for use in specific research studies.

11.3a) The informed consent document and process should cover, at a minimum, the following statements (adapted to the particular research project):

- i) that the materials will be used in the derivation of totipotent or pluripotent cells for research.
- ii) that the materials will be destroyed during the process of deriving totipotent or pluripotent cells for research (unless the specific research protocol aims to

preserve the integrity of the research material, as in the case of embryo biopsy for procurement of blastomeres for human embryonic stem cell generation. In this circumstance, disclosure that the materials “may be destroyed” rather than “will be destroyed” would be appropriate).

iii) that derived cells and/or cell lines might be kept for many years and used for future studies, many of which may not be predictable at this time.

iv) that cells and/or cell lines might be used in research involving genetic manipulation of the cells or the generation of human-animal chimeras (resulting from the mixing of human and non-human cells in animal models).

v) that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous transplantation.

vi) whether the donation is limited to specific research purposes and not others or is for broadly stated purposes, including research not presently anticipated, in which case the consent shall notify donors, if applicable under governing law, of the possibility that permission for broader uses may later be granted and consent waived under appropriate circumstances by an ethical or institutional review board. The consent process should explore whether donors have objections to the specific forms of research outlined in the research protocol.

vii) disclosure of what donor medical or other information and what potential donor identifiers will be retained; specific steps taken to protect donor privacy and the confidentiality of retained information; and whether the identity of the donor will be readily ascertainable to those who derive or work with the resulting stem cell lines, or any other entity or person, including specifically any oversight bodies and government agencies.

viii) disclosure of the possibility that any resulting cells or cell lines may have commercial potential, and whether the donor will or will not receive financial benefits from any future commercial development.

ix) disclosure of any present or potential future financial benefits to the investigator and the institution related to or arising from proposed research

x) that the research is not intended to provide direct medical benefit to anyone including the donor, except in the sense that research advances may benefit everyone.

xi) that neither consenting nor refusing to donate materials for research will affect the quality of care provided to potential donors.

xii) that there are alternatives to donating human materials for research, and an explanation of what these alternatives are (e.g. donation for fertility treatment, discard, etc.).

xiii) (for donation of embryos) that the embryos will not be used to produce a pregnancy, and will not be allowed to develop in culture in vitro for longer than 14 days from conception.

xiv) (for experiments in embryonic stem cell derivation, somatic cell nuclear transfer, somatic cell reprogramming, parthenogenesis, or androgenesis) that the resulting cells or stem cell lines derived would carry some or all of the DNA of the donor and therefore be partially or completely genetically matched to the donor.

11.4) Separation of informed consent for research donation from clinical treatment. To facilitate free and voluntary choice, decisions related to the donation of gametes or creation of embryos for fertility treatment should be free of the influence of investigators who propose to derive or use human embryonic stem cells in research. Wherever possible, the treating physician or infertility clinician should not also be the investigator who is proposing to perform research on the donated materials.

11.5) Additional guidelines for procurement of specific research materials:

11.5a) *For donating embryos or gametes generated in the course of clinical treatment.* Except when specifically authorized by the SCRO process, no reimbursement of direct expenses or financial considerations of any kind may be provided for donating embryos or gametes that have been generated in the course of clinical treatment and are in excess of clinical need or deemed of insufficient quality for clinical use. Researchers may not request that members of the infertility treatment team generate more embryos or harvest more oocytes than necessary for the optimal chance of reproductive success. People who elect to donate stored materials for research should not be reimbursed for the costs of storage prior to the decision to donate. Reimbursement for direct expenses incurred by donors as a consequence of the consent process may be determined during the SCRO process.

11.5b) *For provision of oocytes for research, when oocytes are collected outside the course of clinical treatment.* In locales where oocyte donation for stem cell research is allowed, the SCRO mechanism or body is responsible for conducting rigorous review of any protocol to ensure the safety and the free and informed choice of oocyte providers, according to the following principles:

i) There must be monitoring of recruitment practices to ensure that no vulnerable populations, for example, economically disadvantaged women, are disproportionately encouraged to participate as oocyte providers for research.

ii) In locales where reimbursement for research participation is allowed, there must be a detailed and rigorous review to ensure that reimbursement of direct expenses or financial considerations of any kind do not constitute an undue inducement.

iii) At no time should financial considerations of any kind be given for the number or quality of the oocytes themselves that are to be provided for research.

iv) Oocyte procurement must be performed only by medically qualified and experienced physicians, and non-aggressive hormone stimulation cycles and frequent monitoring must be used to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

v) Due to the unknown long-term effects of ovulation induction, women should not undergo an excessive number of hormonally induced ovarian stimulation cycles in a lifetime, regardless of whether they are induced for research or assisted reproduction. The limits should be determined by thoughtful review during the SCRO process, which should be informed by the latest available scientific information about the health risks.

vi) There should be a provision to pay for the cost of any medical care required as a direct and proximate result of a woman's provision of oocytes for research.

vii) An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be paid specifically for the material obtained, but rather for specifically defined cost-based reimbursements and payments for professional services.

11.5c) *For provision of sperm for research.* Reimbursement for direct expenses incurred by donors as a consequence of the consent process may be determined during the SCRO process.

11.5d) *For provision of somatic cells for research.* Reimbursement for direct expenses incurred by donors as a consequence of the consent process may be determined during the SCRO process.

i) In the case that the somatic cell donor is a child or a decisionally incapacitated adult, consent must be provided by a legal parent or guardian or other person authorized under applicable law.

ii) Contemporaneous consent is not necessary if researchers procure somatic cells from a tissue bank. However, somatic cells may be procured from a tissue bank only if the tissue bank's informed consent documents specifically designate nuclear transfer or other reprogramming methods for stem cell research as one of the possible uses of the donor's tissues, and only if researchers use somatic cells from tissue samples whose donors have clearly consented to this possible use.

11.6) Steps to enhance the procurement process:

Attempts should be made to improve the informed consent process for human materials procurement. The informed consent document is but one aspect of this process. The purpose of the informed consent document is to record that all the ethically relevant information has been discussed. The informed consent document alone can never take the place of an interactive dialogue between research staff and providers of human materials. Researchers are thus encouraged to focus on enriching the informed consent process itself, in addition to ensuring that the informed consent document includes all of the ethically relevant information. The informed consent process can be enhanced in the following ways:

- i) Whenever possible, the person conducting the informed consent dialogue should have no vested interest in the research protocol. If members of the research team participate in the informed consent process, their role must be disclosed and care must be taken to ensure that information is provided in a transparent and accurate manner.
- ii) Empirical research has shown that informed consent is most effective as a dynamic, interactive, and evolving process as opposed to a static, one-time disclosure event. Thus, researchers should provide ample opportunities for providers of human materials to discuss their involvement in the research protocol.
- iii) Counseling services should be made available upon request to any providers of human materials prior to procurement.
- iv) Procurement procedures should be revised in light of a) ongoing studies of the long-term risks associated with oocyte retrieval; and b) research on informed consent for all types of human biological materials procurement.
- v) Researchers should consider on a regular basis, subject to annual review, the possible use of alternatives to hormonally induced oocytes procured solely for stem cell research, such as oocytes derived from pluripotent stem cells, *in vitro* maturation of oocytes from ovariectomy samples, and egg sharing programs offered through infertility clinics.

12) Principles for derivation, banking, and distribution of human pluripotent stem cell lines

Proposals for derivations of new human pluripotent stem cell lines should be scientifically justified and executed by scientists with appropriate expertise. Hand-in-hand with the privilege to perform derivations is the obligation to distribute the cell lines to the research community. A clear, detailed outline for banking and open access to the new lines should be incorporated into derivation proposals. New pluripotent stem cell lines should be

made generally available as soon as possible following derivation and first publication. The ISSCR encourages researchers to deposit lines early into centralized repositories where the lines will be held for release and distribution upon publication.

12.1) Derivation of new lines

12.1a) Proposals to attempt derivation of new totipotent cells or pluripotent stem cell lines from donated pre-implantation human embryos, embryonic cells, or via nuclear reprogramming must be approved by a SCRO process. New derivations by necessity involve procurement of materials from human subjects and, therefore, will need to be approved by institutional oversight bodies with specific responsibility for protection of human subjects, as well as by the SCRO process. In some jurisdictions, the SCRO process will be formulated in a manner that encompasses all human subjects and stem cell oversight responsibilities.

12.1b) The scientific rationale for the need to derive new totipotent cells or pluripotent stem cell lines must be provided by the researcher, with justification of the numbers of pre-implantation embryos to be used. For proposals that incorporate nuclear transfer or reprogramming, an explicit scientific justification is needed and the numbers of trials to be attempted must be justified.

12.1c) Researchers must demonstrate appropriate expertise or training in the culture and maintenance of existing human embryonic stem cell lines and expertise or training in the derivation of pluripotent non-human stem cell lines before being granted permission for attempts at derivations of new human stem cell lines.

12.1d) Investigators performing derivations should have a detailed, documented plan for characterization, storage, banking and distribution of new lines.

12.1e) Embryos made via nuclear transfer, parthenogenesis, androgenesis, or other *in vitro* means of embryo production shall not be transferred to a human or non-human uterus or cultured *in vitro* intact as embryos for longer than 14 days or until formation of the primitive streak, whichever occurs first.

12.1f) Investigators performing derivations should propose a plan to safeguard the privacy of donor information.

12.2) Banking of stem cell lines: The ISSCR encourages the establishment of national and international repositories, which are expected to accept deposits of newly derived stem cell lines and to distribute them on an international scale. In order to facilitate easy exchange and dissemination of stem cell lines, repositories should strive to form and adhere to common

methods and standards; at a minimum, each repository must establish its own clear guidelines and make those available to the public. Repositories must have a clear, easily accessible material transfer agreement (MTA) [a sample MTA is available as an appendix and can be downloaded from the ISSCR website]. Each repository may have its own criteria for distribution. The repository has right of refusal if a cell line does not meet its standards.

12.2a) Repository must have clear, publicly available protocols for deposit, storage and distribution of hESC lines and related materials.

12.2b) For deposits, repository must receive documentation pertinent to the depositor's SCRO process. These documents should be kept on file at the repository. This will include, but is not limited to, proof of institutional and/or SCRO approval of the process for procurement of research materials according to ethical and legal principles of procurement as outlined in these Guidelines, approval of protocols for derivation of new lines, copies of the donor informed consent documents and what, if any, reimbursement of direct expenses or financial considerations of any kind were provided to the donors.

12.2c) Repository should obtain all technical information from depositor. For example, methods used in the derivation of lines, culture conditions, infectious disease testing, passage number and characterization data. Repository will make this information publicly available. If repository modifies depositor's protocols or obtains additional data this will also be made available.

12.2d) Repository should engage in, but is not limited to, the following:

- i) Reviewing and accepting deposit applications
- ii) Assigning unique identifiers (catalogue number) to deposits
- iii) Characterizing cell lines
- iv) Human pathogen testing
- v) Expansion, maintenance and storage of hESC lines
- vi) Quality assurance and quality control of all procedures
- vii) Maintenance of website with pertinent characterization data, protocols and availability of hESC lines
- viii) Tracking distributed cell lines
- ix) Posting a clear cost schedule for distribution of materials. Repositories should distribute internationally and charge only the necessary costs, which include shipping and handling.

12.3) Provenance of stem cell lines: Owing to the nature of the materials involved in the generation of human stem cell lines, appropriate safeguards should be used to protect the privacy of donors and donor information. In order for the stem cell lines to be as useful as possible and so as not to preclude future potential therapeutic applications, as much donor information as possible should be maintained along with the cell line, including, but not limited to: ethnic background, medical history, and infectious disease screening. Subject to local laws, donor samples and cell lines should be de-identified (anonymized) and coded using internationally accepted standards for maintaining privacy. Informed consent and donor information will be gathered and maintained by the repository, including whatever reimbursement of direct expenses or financial considerations of any kind were provided in the course of the procurement. Documentation of the provenance of the cell lines is critical if the cell lines are to be widely employed in the research community, and the provenance must be easily verified by access to the relevant documents.

12.4) Maintenance of a database of human stem cell lines and verification of provenance: The ISSCR will curate and maintain a website listing of human stem cell lines that testifies to independent validation of the provenance of the cell lines. It will become the responsibility of the ISSCR Standards Committee to scrutinize the documents relevant to the derivation of stem cell lines to vouch for the provenance of the cell lines, according to the principles laid out in these Guidelines.

13) Dispute resolution

Any conflicts of interest or other conflicts or disputes that may arise in the course of any international collaboration, for example, disagreements or difference of opinions between researchers from different countries involved in common projects, may be resolved in accordance with an agreed-upon dispute resolution mechanism in a forum with international representation from countries doing research and clinical trials in human stem cells. Members of the forum will, as appropriate, seek guidance from experts in the fields of science, ethics, law and medicine from different national, social and religious backgrounds. It is recommended that all international collaboration agreements incorporate a dispute resolution provision providing that any disputes or differences shall be settled through mediation or arbitration by international forum, and this provision shall stipulate whether or not any decision made by the forum will be binding on the relevant parties.

14) Ongoing review of Guidelines: call for formation of a new International Guidelines Committee of the ISSCR

14.1) These guidelines should be revised and updated on a regular basis to accommodate scientific advances and to address specific scientific issues in the order of priority based on the degree of urgency. These guidelines should be applicable to stem cell research internationally and should continue to address the challenges of international collaboration.

14.2) New ethical challenges in the conduct of stem cell research that are on the horizon must be addressed in a timely manner to ensure that our science proceeds in a socially responsible and ethically acceptable fashion. To enhance the likelihood that the international scientific research community will be bound together by a common set of principles governing the performance of stem cell research, we recommend the creation, under the auspices of the ISSCR, of a committee that includes members with expertise in various aspects of stem cell biology, including but not limited to the scientific issues pertinent to human embryo and pluripotent stem cell research and the ethical considerations of such research, supplemented by external contributors with supplemental and complementary expertise as needed. This committee will evaluate the Guidelines on a yearly basis, updating and revising, and providing guidance and counsel on the ethical, social and legal aspects as stem cell science evolves. The committee will coordinate with other national and international efforts to promote a uniform set of governing principles for the field.

15) Acknowledgments

The establishment of these Guidelines represent the fruits of a global conversation among researchers, ethicists, and legal experts from 14 countries and a diversity of scientific and intellectual perspectives. No such document stands independent of documents and discussions that preceded it. Indeed, these Guidelines borrow extensively from the principles and the language established by the Committee on Guidelines for Human Embryonic Stem Cell Research (2005) of the National Research Council and Institute of Medicine of the National Academy of Sciences of the USA. Other important source materials include the Medical and Ethical Standards Regulations of the California Institute for Regenerative Medicine and the Hinxton Group's Consensus Statement (2006). The thoughtful deliberations that characterized these earlier efforts provided a sound foundation upon which to launch our own inquiry into the subject. The ISSCR wishes to acknowledge the financial support of The Genetics and Public Policy Center of John Hopkins University (Director: Kathy Hudson, PhD), the Norwegian Research Council, Sung Chull Junn Esq., and WilmerHale.

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16) Appendices

16.1) Definitions and discussion of scientific terminology as used in these Guidelines

16.1a) *The term 'embryo' and other terms used to describe early stages of development*

Embryo: The term 'embryo' has been defined and used differently in various biological contexts as discussed below.

In this document, the term 'embryo' is used generically to describe all stages of development from the first cleavage of the fertilized ovum to nine weeks of gestation in the human (and to term in the mouse). More precise terms have been used to describe specific stages of embryogenesis; for example, the two, four and eight cell stages, the compacting morula and the blastocyst all describe particular stages of early pre-implantation embryonic development.

Prior to implantation, the embryo represents a simple cellular structure with minimal cellular specialization, but soon after implantation a defined axis of development called the primitive streak begins to form. After this time twinning of the embryo can no longer occur as there is irreversible commitment to the development of more complex and specialized tissues and organs.

Classical embryology used the term embryo to connote different stages of post-implantation stages of development (e.g. the primitive streak and onwards to fetal stages). Indeed, Dorland's Illustrated Medical Dictionary (27th edition, 1988 edition, W. B. Saunders Company) provides the definition "in animals, those derivatives of the fertilized ovum that eventually become the offspring, during their period of most rapid development, i.e., after the long axis appears until all major structures are represented. In man, the developing organism is an embryo from about 2 weeks after fertilization to the end of seventh or eighth week." An entry in Random House Webster's College Dictionary reads "in humans, the stage approximately from attachment of the fertilized egg to the uterine wall until about the eighth week of pregnancy." However, the nomenclature is often extended by modern embryologists for the human to include the stages from first cleavage of the fertilized ovum onwards to seven to nine weeks of gestation, after which the term fetus is used.

Zygote: The fertilized single cell pronuclear ovum (egg), typically observed in humans between 20 to 35 hours after insemination with sperm.

Cleavage Stage Embryo (pre-implantation stage): The cleaving or dividing zygote; precise terms include the 2-cell, 4-cell, 8-cell and 16-cell embryo. In humans, each cleavage division consumes around 18 to 24 hours.

Morula: The compacting grape-like cluster of 16-cells, typically formed 4 days after fertilization.

Blastocyst: The embryonic stage formed from 64 cells onward, defined by the pumping of fluid into an internal space. The blastocyst is surrounded by a ring of differentiated trophectoderm cells, and encloses a nest of 10 to 25 cells termed the Inner Cell Mass (ICM). The trophectoderm cells attach the embryo to the uterine wall, and the ICM forms the embryo proper. The blastocyst forms 5 to 7 days after fertilization. The blastocyst hatches from the zona pellucida (glycoprotein shell) around days 6 to 7 after fertilization. Thereafter, and coupled to implantation, which provides requisite signals for the maturation of the embryo, the ICM of the blastocyst begins to organize itself into a long axis with anterior and posterior orientation. If isolated from the trophectoderm, the ICM never adopts an axis, and after this time it is not possible for the cultured ICM to form an organism, but instead will form a teratoma (disorganized differentiating cell body) when transplanted.

Gastrula: The embryonic stage of formation of the trilaminar embryonic disc, leading to the specification of ectoderm, endoderm, and mesoderm.

Neurula: The embryonic stage when the neural plate is closing to form the neural tube.

Parthenogenetic embryo: Activation of the unfertilized mammalian ovum can result in embryonic development, and embryonic stem cells can be derived from the ICMs of parthenogenetic blastocysts. After uterine transfer, parthenogenetic embryos can progress to a fetal stage, but further development is compromised by an underdeveloped placental system that prevents normal gestation.

Gynogenesis: A particular form of parthenogenesis in which an embryo is created from the genetic contributions (female pronuclei) of two different fertilized oocytes.

Androgenesis: The creation of an embryo that incorporates the male pronuclei from two different fertilized oocytes.

Nuclear Transfer: The insertion of a nucleus of a cell into an ovum from which the nuclear material (chromosomes) has been removed. The ovum will reprogram (incompletely) the cell nucleus to begin development again. Embryos created by nuclear transfer are typically abnormal and often die during development, but rarely are capable of development to term. ICMs from blastocysts derived by nuclear transfer will form apparently normal embryonic stem cells.

Altered Nuclear Transfer: A process whereby the genetic material of the donor cell is altered prior to nuclear transfer, such that implantation and subsequent development of an embryo is not possible. Pluripotent stem cells can be derived following the process of altered nuclear transfer.

This technique was employed in the mouse by knock-down of expression of the *cdx2* gene. The *cdx2* gene product is critical for the formation of the trophoblast which is critical for post-implantation development. When expression of *cdx2* was knocked-down by short hairpin RNAs in the donor cell nucleus prior to nuclear transfer, the developmental potential of the nuclear transfer embryo was compromised; the trophoblast was unable to develop and support post-implantation development. However, ICM structures formed, and embryonic stem cells were successfully generated.

Meissner, A., and Jaenisch, R. (2006). Generation of nuclear transfer-derived pluripotent ES cells from cloned *Cdx2*-deficient blastocysts. *Nature* 439, 212-215.

Fetus: In this document, the term 'fetus' is used to describe post-embryonic stages of prenatal development, after major structures have formed. In humans, this period is from seven to nine weeks after fertilization until birth.

16.1b) Terminology relating to developmental potential

Totipotent: The state of a cell that is capable of giving rise to all types of differentiated cells found in an organism, as well as the supporting extra-embryonic structures of the placenta. A single totipotent cell could, by division in utero, reproduce the whole organism.

Pluripotent: The state of a single cell that is capable of differentiating into all tissues of an organism, but not alone capable of sustaining full organismal development, because for instance, it lacks competency to generate the supporting extra-embryonic structures of the placenta.

16.1c) The term 'chimera' in stem cell research

Trace Chimeras: The simplest form of chimera is one in which a limited number of human cells are introduced at any stage of pre- or post-natal development, and where incorporation into any lineage or tissue is likely to be minimal. An example is the use of an immuno-deficient mouse as a host to study tumor formation from a human cancer cell line. Such chimeras require oversight appropriate to animal use and biosafety (among others as deemed appropriate by local regulatory bodies), and typically will not raise significant concerns unique to human stem cells. Any trace human/animal chimera that carries human germ-lineage cells bears special concern.

Interspecies Chimeras: Interspecies chimeras are those animals containing extensive and integrated cellular contributions from another species. There are two types of true human/animal chimeras bearing special concern: those formed at the earliest stages of development and those formed later but contributing a significant degree of chimerism to the central nervous system and/or germline. Human/non-human primate chimeras formed at any stage of development warrant particular attention. Human/non-human chimeras bearing central nervous system chimerism also warrant particular attention.

Hybrids: Animals formed in which each of the individual cells carry roughly equal genetic contributions from two distinct species resulting from inter-breeding of species or fusion of genetic material. Examples include the mule (horse bred to a donkey). Hybrids are only likely to survive if the genetic contributions derive from closely related species. The greatest concern would be for experiments that entail creation of hybrids between humans and closely related non-human primates.

16.2) Weblinks: international, national and local regulations and reports pertinent to stem cell research

Belmont Report (1979)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research
<http://ohsr.od.nih.gov/guidelines/belmont.html>

Council for International Organizations for Biomedical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

http://www.cioms.ch/frame_guidelines_nov_2002.htm

Guidelines for Human Embryonic Stem Cell Research

Authored by the Committee on Guidelines for Human Embryonic Stem Cell Research, NATIONAL RESEARCH COUNCIL AND INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES (USA)
<http://www.nap.edu/books/0309096537/html>

Hinxton Group's Consensus Statement (2006)

<http://hinxtongroup.org/consensus/consensus.html>

Human Fertilisation and Embryology Authority (HFEA)

Home Page
<http://www.hfea.gov.uk/cps/rde/xchg/hfea>
Code of Practice
<http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-F6DA3CC3/hfea/hs.xsl/411.html>
Research licence application
<http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-F6DA3CC3/hfea/hs.xsl/376.html>
EU Tissues and Cells Directives
<http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-F6DA3CC3/hfea/hs.xsl/493.html>

Nuremberg Code (1947)

<http://www.nihtraining.com/ohsr/site/guidelines/nuremberg.html>

Regulations of the California Institute for Regenerative Medicine

Medical and Ethical Standards Regulations
<http://www.cirm.ca.gov/laws/default.asp>

UNESCO Universal Declaration on Bioethics and Human Rights (2005)

http://portal.unesco.org/shs/en/ev.php-URL_ID=1883&URL_DO=DO_TOPIC&URL_SECTION=201.html

World Medical Association Declaration of Helsinki (1964 and updates)

Ethical Principles for Medical Research Involving Human Subjects

<http://www.wma.net/e/policy/b3.htm>

16.3) Sample consent documents for procurement of human biological research materials for stem cell research

Egg donation for stem cell research; provided directly and solely for stem cell research

<http://www.isscr.org/guidelines/CFeggresearch.doc>

Egg donation for stem cell research; collected during the course of fertility treatment and in excess of clinical need

<http://www.isscr.org/guidelines/CFeggsexcessofclinical.doc>

Embryo donation for stem cell research; created for fertility purposes and in excess of clinical need

<http://www.isscr.org/guidelines/CFembryos.doc>

Somatic cell donation for stem cell research

<http://www.isscr.org/guidelines/CFsomatic.doc>

Sperm donation for stem cell research

<http://www.isscr.org/guidelines/CFsperm.doc>

Acknowledgments. The sample informed consent documents were compiled by task force member **Insoo Hyun, Ph.D.** The ISSCR also wishes to acknowledge the following individuals for reviewing the documents and providing feedback on their content (this acknowledgment does not imply that the individuals listed fully endorse the design and content of the documents, as these exist as samples that must be modified according to individual research protocols and ultimately approved through a process of Stem Cell Research Oversight): Melinda Abelman, Jessica Berg, Bernard Dickens, Kate Heffernan, Jeffrey Jones, Kyu Won Jung, Eng Hin Lee, Bernard Lo, Patricia Marshall, Alan Meisel, Jonathan Moreno, Ralph Nachman, Pearl O'Rourke, John Robertson, Jeremy Sugarman, and Patrick Taylor.

16.4) Sample Material Transfer Agreement (MTA)

[Adapted and modified from the uniform biological material transfer agreement published in the Federal Register, February 18, 1995]

Sample Material Transfer Agreement (MTA) document

<http://www.isscr.org/guidelines/mta.doc>

Acknowledgment. The sample material transfer agreement document was prepared by task force member **Patrick Taylor, JD.**